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April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to notify participating sites that the **S1400** Pathology Webinar Documents, Sample Documents for Site Use, New Investigator's Brochures, Site Coordinators Committee Application are now available.

1. The **S1400** Pathology Webinar Documents are now available on the **S1400** Abstract Page under **S1400** Resources on the SWOG website (http://swog.org).
   The documents include:
   - Pathology Slide Deck
   - Pathology Webinar Recording
   - Questions and Answers

2. The Sample Documents for Site use are now available on the **S1400** Abstract Page under **S1400** Resources on the SWOG website (https://swog.org/Visitors/S1400/S1400SampleDocs.asp).

3. New Investigator's Brochures are available for the following investigational agents:

Sub-Study: **S1400C**	Agent: Palbociclib Palbociclib_Mar2017 Palbociclib_Mar2017_with Summary of Changes
Sub-Study: **S1400I**	Agent: Ipilimumab ipilimumab_9Mar2017_Ver 20 ipilimumab_15Mar2017_Ver 20 Erratum 01

SWOG's standard procedures will be followed in updating the drug information sections based on the most recent Investigator's Brochure versions. Sites should seek updated Investigator's Brochures as required by the site's IRB of record.

The Investigator's Brochures are available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms. Complete and return to ctsucontact@westat.com.

4. The Site Coordinators Committee is seeking new members. For more information about the committee contact: LungmapSCC@crab.org

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
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( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to notify the CIRB and participating sites of a correction in the **S1400I** Treatment Consent Form.

1. In the **S1400I** Treatment Consent Form, Page 110, the asterisk footnote underneath the RARE, AND SERIOUS category of the Ipilimumab condensed drug table is no longer applicable.

   *This is applicable for patients who have undergone a stem cell transplant. (Added 3/3/16)

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This will be removed in a subsequent revision. In the meantime, sites may update their respective Informed Consents.

Patients need not be informed of the changes unless required by the local IRB.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Feb. 28, 2017 Mfr Rpt #BMS2017010889
S1404 Melanoma	Mar. 01, 2017 Mfr Rpt #BMS2016085259 FU
S1609 Early Therapeutic	Mar. 02, 2017 Mfr Rpt #BMS2016085054 FU
	Mar. 24, 2017 AE-2921421
	Mar. 28, 2017 Mfr Rpt #BMS2017020499 FU
	Apr. 03, 2017 Mfr Rpt #BMS2017021208 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by

your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reporst via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:

S1400I Lung
S1609 Early Therapeutics

Reports:

Feb. 28, 2017 Mfr Rpt #BMS2017010889
Mar. 01, 2017 Mfr Rpt #BMS2016085259 FU
Mar. 02, 2017 Mfr Rpt #BMS2016085054 FU
Mar. 03, 2017 Mfr Rpt #BMS2017006152
Mar. 03, 2017 Mfr Rpt #BMS2017014298
Mar. 21, 2017 Mfr Rpt #BMS2016101248 FU
Mar. 23, 2017 Mfr Rpt #BMS2017019724
Mar. 28, 2017 Mfr Rpt #BMS2017020499 FU
Apr. 03, 2017 Mfr Rpt #BMS2017021208 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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Distribution Date: April 15, 2017
E-mailed Date: April 11, 2017
Version Date: March 14, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

REVISION #8

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required: Patients currently on **S1400G** may continue on study provided they are informed of the new and/or modified risk information. Please see details below.
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

CTEP's Action Letters require immediate suspension of accrual to the active sub-study (**S1400G**) until the revision incorporating the changes outlined in the Action Letter have been incorporated into the protocol/consent and approved by both CTEP and the IRB of record. CTEP and CIRB have approved this revision (Revision #8) for this study.
Sites whose IRBs of record have already reviewed and approved Revision #8 (including sites utilizing CIRB as the IRB of record) DO NOT need to suspend local accrual.

Any site not utilizing CIRB and whose IRB of record has not approved Revision #8 MUST suspend local accrual to sub-study S1400G until the IRB of record has approved Revision #8.

NOTE: Patients who have already signed an S1400G consent form may be registered.

REVISION #8

This revision has been prepared in response to the Request for Rapid Amendment (RRA) received on March 13, 2017 from Dr. Richard Piekarz (piekarzr@mail.nih.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov). The associate Action Letter is attached.

The above-referenced study has been updated as follows:

1. The Version Date of the protocol and Model Consent Forms has been updated.

2. Table of Contents: The page numbers have been updated.

S1400G

1. **Section 3.1c.1, Talazoparib (BMN 673) (NSC 771561) (IND-119672):** The talazoparib adverse effects section has been replaced with Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.1, December 29, 2016. The section has been updated as follows:

   Added New Risk:
   - Less Likely: Dyspepsia; Epistaxis; Pain
   - Rare but Serious: Typhlitis
   - Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal distension; Dry skin; Dysgeusia; Hepatic failure; Insomnia; Neck pain; Non-cardiac chest pain; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Small intestinal obstruction; Weight loss

   Increase in Risk Attribution:
   - Changed to Likely from Less Likely: Anemia; Diarrhea; Platelet count decreased
   - Changed to Less Likely from Rare but Serious: Febrile neutropenia
   - Changed to Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal pain
   - Changed to Less Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Anorexia; Fever; Headache; Hypokalemia; Infection; Nervous system disorders - Other (neuropathy peripheral); Rash maculo-papular; White blood cell decreased

   Provided Further Clarification:
   - Peripheral sensory neuropathy (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Nervous system disorders - Other (neuropathy peripheral) (under Less Likely).
   - Lung infection and Sepsis (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Infection (under Less Likely).
   - A new footnote #2 has been added as follows: “Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.”
   - A new footnote #3 has been added as follows: “Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOURS SYSTEM DISORDERS.”

Model Consent Forms Changes

The following section refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. **Pages 119-120 [S1400G], "What possible risks…":** Patients currently receiving talazoparib **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, patients must be notified at their next visit and this conversation must be documented in the patient chart. The following changes have been made to the talazoparib side effects information:

   Added New Risk:
   - **Occasional: Heartburn; Nose bleed**
   - **Rare but Serious: Swelling of the bowels which may require surgery**

   Increase in Risk Attribution:
   - **Changed to Common from Occasional: Anemia which may require blood transfusion; Diarrhea; Bruising, bleeding**
   - **Changed to Occasional from Rare: Infection, especially when white blood cell count is low**
   - **Changed to Common from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain**
   - **Changed to Occasional from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Loss of appetite; Fever; Headache; Muscle weakness; Numbness, tingling or pain of the arms and legs; Rash**

[Note: Sites should seek an updated investigator brochure as required by site's IRB of record. The Investigator's brochure is available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms or by clicking on the study link. Complete and return to ctsucontact@westat.com].

An entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of **S1400**.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Hossein Borghaei, D.O.
Corey J. Langer, M.D.
James L. Wade III, M.D.
Martin J. Edelman, M.D.
Kathy S. Albain, M.D.
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Louise Highleyman
Krystle Pagarigan
Sarah Basse
MedImmune, LLC./ AstraZeneca
Genentech, Inc.
Pfizer, Inc.
Bristol Myers Squib
Medivation, Inc. / Pfizer
Foundation Medicine Inc.
TRIAD
Nationwide

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **April 7, 2017**

FROM: Richard Piekarz, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Talazoparib (BMN 673, NSC 771561)

TO: Investigators for CTEP-supported Studies Involving Talazoparib (BMN 673, NSC 771561)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with talazoparib, and to request all trials with talazoparib be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes talazoparib. See the accompanying list of CTEP trials with talazoparib.

In response to the new/modified risk information CTEP is requiring that all trials with talazoparib be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on April 21, 2017** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Richard Piekarz (piekarzr@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since talazoparib is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with talazoparib.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.1, December 29, 2016):___
   Page Number(s): ____

- Added New Risk:
  - Less Likely: Dyspepsia; Epistaxis; Pain
  - Rare but Serious: Typhlitis
  - Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal distension; Dry skin; Dysgeusia; Hepatic failure; Insomnia; Neck pain; Non-cardiac chest pain; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Small intestinal obstruction; Weight loss

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Anemia; Diarrhea; Platelet count decreased
  - Changed to Less Likely from Rare but Serious: Febrile neutropenia
  - Changed to Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal pain
  - Changed to Less Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Anorexia; Fever; Headache; Hypokalemia; Infection; Nervous system disorders - Other (neuropathy peripheral); Rash maculo-papular; White blood cell decreased

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Abdominal pain; Alopecia; Anorexia; Dizziness; Fever; Headache; Infection; Pain; Vomiting

- Provided Further Clarification:
  - Peripheral sensory neuropathy (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Nervous system disorders - Other (neuropathy peripheral) (under Less Likely).
  - Lung infection and Sepsis (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Infection (under Less Likely).

- A new footnote #2 has been added as follows: "Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC."

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.1, and associated risk information for the ICD, to the most recent CAEPR Version 2.0. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.0), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Occasional: Heartburn; Nose bleed
  - Rare but Serious: Swelling of the bowels which may require surgery

- Increase in Risk Attribution:
  - Changed to Common from Occasional: Anemia which may require blood transfusion; Diarrhea; Bruising, bleeding
  - Changed to Occasional from Rare: Infection, especially when white blood cell count is low
  - Changed to Common from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain
  - Changed to Occasional from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Loss of appetite; Fever; Headache; Muscle weakness; Numbness, tingling or pain of the arms and legs; Rash

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to talazoparib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Talazoparib CAEPR – Version 2.1, December 29, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Talazoparib (BMN 673, NSC 771561)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 232 patients.* Below is the CAEPR for Talazoparib (BMN 673).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, December 29, 2016[1]

Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 4.0 Term) [n= 232]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
Nausea			***Nausea (Gr 2)***
		Typhlitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection [2] (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypokalemia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***

Action Letter

Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 4.0 Term) [n= 232]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral)[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOURS SYSTEM DISORDERS.

Adverse events reported on talazoparib (BMN 673) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talazoparib (BMN 673) caused the adverse event:

CARDIAC DISORDERS - Atrial flutter
GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Weight loss
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Dysgeusia
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin

Note: Talazoparib (BMN 673) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for Talazoparib

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for Talazoparib in your ICD.

Risk Profile for Talazoparib (CAEPR Version 2.1, December 29, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The talazoparib (BMN 673) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for Talazoparib (BMN 673) in your ICD.

COMMON, SOME MAY BE SERIOUS
In 100 people receiving talazoparib (BMN 673), more than 20 and up to 100 may have:

Action Letter

- Anemia which may require blood transfusion
- Pain
- Diarrhea, nausea
- Tiredness
- Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving talazoparib (BMN 673), from 4 to 20 may have:

- Infection, especially when white blood cell count is low
- Constipation, heartburn, vomiting
- Fever
- Loss of appetite
- Dizziness, headache
- Muscle weakness
- Numbness, tingling or pain of the arms and legs
- Nose bleed
- Hair loss, rash

RARE, AND SERIOUS

In 100 people receiving talazoparib (BMN 673), 3 or fewer may have:

- Swelling of the bowels which may require surgery

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

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swog.org

April 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutic	Mar. 03, 2017 AE-2093875

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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swog.org

April 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung **S1609** Early Therapeutics	Mar. 03, 2017 AE-2093875

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March 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

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This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutic	Feb. 23, 2017 AE-2728211

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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March 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1609** Early Therapeutics	Jan. 09, 2017 Mfr Rpt #BMS2016070192 Jan. 31, 2017 Mfr Rpt #BMS2017007497 Feb. 06, 2017 Mfr Rpt #BMS2016107222 FU Feb. 07, 2017 Mfr Rpt #BMS2016076340 FU Feb. 17, 2017 Mfr Rpt #BMS2015079040 Feb. 21, 2017 Mfr Rpt #BMS2016109072 Feb. 23, 2017 AE-2728211 Feb. 27, 2017 AE-2525865 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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March 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 25, 2017 Mfr Rpt #BMS2017004099
S1404 Melanoma	Feb. 06, 2017 AE2568911
S1609 Early Therapeutic	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reporst to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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March 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 25, 2017 Mfr Rpt #BMS2017004099
S1609 Early Therapeutics	Feb. 06, 2017 AE2568911

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

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February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification require- see details below
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of the *potential* requirement to close local accrual to the below-referenced sub-study in response to the CTEP Action Letter distributed on February 9, 2017.

S1400I, "A Phase III Randomized Study of Nivolumab plus Ipilimumab versus Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarker (Lung-Map Sub-Study)"

CTEP has updated the standard language included in their Action Letters to require immediate suspension of accrual to active studies until the revision incorporating the changes outlined in the Request for Rapid Amendment and Action Letter have been

incorporated into the protocol/consent and approved by both CTEP and the IRB of record. CTEP and CIRB have approved this revision (Revision #7) for this study.

Sites whose IRBs of record have already reviewed and approved Revision #7 (including sites utilizing CIRB as the IRB of record) DO NOT need to suspend local accrual.

Any site not utilizing CIRB and whose IRB of record has not approved Revision #7 MUST suspend local accrual to sub-study, S1400I only until the IRB of record has approved Revision #7.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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swog.org

February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Dec. 21, 2016	Mfr Rpt #BMS2016102751 FU
S1404 Melanoma	Jan. 11, 2017	Mfr Rpt #BMS2016111478
S1609 Early Therapeutic	Jan. 13, 2017	Mfr Rpt #BMS2016109074 FU
	Jan. 18, 2017	Mfr Rpt #BMS2016031599 FU
	Jan. 19, 2017	AE-2077443

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reporst to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local

policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1609** Early Therapeutics	Dec. 21, 2016 Mfr Rpt #BMS2016102751 FU Jan. 11, 2017 Mfr Rpt #BMS2016111478 Jan. 13, 2017 Mfr Rpt #BMS2016109074 FU Jan. 18, 2017 Mfr Rpt #BMS2016031599 FU Jan. 18, 2017 Mfr Rpt #BMS2016110187 FU Jan. 19, 2017 AE-2077443 Jan. 23, 2017 AE-2066418

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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Distribution Date: February 15, 2017
Email Date: February 7, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

STATUS CHANGE

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
(√) Full board review required
( ) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
(√) Initial Sub-study Activation – **S1400G**
( ) Temporary Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

S1400G ACTIVATION

Effective 2:00 p.m. Pacific Time on February 7, 2017, the following sub-study will be open for patient accrual.

S1400G: A Phase II Study of Talazoparib (BMN 673) in Patients with Homologous Recombination Repair Deficiency Positive Stage IV Squamous Cell Lung Cancer (Lung-Map Sub-Study)

Protocol Specific Requirements – Protocol Training

A member of each institution (CRA or investigator, etc.) must complete the Protocol Specific Requirements (PSR) prior to patient registration. The PSR will need to be renewed prior to

patient registration each time a new sub-study has been added. The PSR can be satisfied by completing the training online and submitting the verification at: https://swog.org/members/Training/S1400Training.asp. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Updated Forms

Please discard old versions of these forms and replace with the updated versions listed as follows.

S1400
S1400 Request for Sub-Study Reassignment (500072v1.3)
S1400 Status Update (New form 500228v1.1)
S1400 Request for New Sub-study Assignment (New form 500229v1.1)
S1400 Onstudy Form (500014v1.5)

S1400B
S1400B Onstudy Form (500029v1.6)

S1400I
S1400I Onstudy Form (500153v1.1)

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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Louise Highleyman
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Genentech, Inc.
Pfizer, Inc.
Bristol Myers Squib
Medivation, Inc. / Pfizer
Foundation Medicine Inc.
TRIAD
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Distribution Date: February 15, 2017
Email Date: February 2, 2017
CTEP Submission Date: August 29, 2016 and January 19, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

REVISION #6 and #7

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
(√) Full board review required
( ) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
(√) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required (for a sub-set of the changes made in Revision #7 only - see details below)
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
(√) Data Submission / Forms changes
(√) Editorial / Administrative changes
(√) Other: New Sub-Study **S1400G** has been added

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice. If local approval is not granted within 30 days, accrual must be suspended until approval is obtained.

Sites not using the NCI CIRB*:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes in this revision are effective upon approval by the local IRB; however, any changes to eligibility become effective 6 weeks after distribution of this notice. If local approval is not granted within 6 weeks, accrual must be suspended until approval is obtained.

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REVISION #6 and #7

Revision #6 and Revision #7 are combined here to ease the burden on participating institutions. SWOG received NCI approval of Revision #7 (version date 1/19/17) at the same time as receiving NCI approval of Revision #6 (version date 8/29/16). Therefore, the protocol with version date 8/29/16 was never the active version of the protocol and does not need to be processed separately.

Revision #7 (version date 1/19/17) is posted on the SWOG and CTSU websites. Although it should not be necessary, Revision #6 (version date 8/29/16) is accessible on the S1400 abstract page under "Previous Updates".

The Revision Memo has been organized by revision number with the protocol edits for **S1400** and each of the sub-studies, followed by the model consent form edits.

Revision #6

Revision #6 includes the following changes:

1) Administrative updates and clarifications throughout the protocol and consents;
2) New Sub-study: **S1400G**: A biomarker-driven study including a PARP inhibitor. This study will follow the Phase II design from Design #2: Seamless Phase II followed by Phase III (see Section 11.2 of **S1400**) among patients defined to be HRRD MDVN-positive.

The revision has been organized by protocol edits for **S1400** and each of the sub-studies, followed by the model consent form edits.

General throughout Protocol

1. The Version Date of the protocol and the model consent forms has been updated.

2. Table of Contents: The page numbers have been updated for the following sections: **S1400**, **S1400A**, **S1400B**, **S1400C**, **S1400D**, **S1400E, S1400I**.

3. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

S1400

1. **Page 1, Title Page:** The title page has been updated to include Talazoparib in the list of study agents.

2. **Page 4, Table of Contents:** A new section, 18.2 g, **S1400G**: HRRD-Talazoparib has been added.
3. **Page 6, Schema**: The schema has been updated to reflect the addition of a new sub-study, **S1400G** and the removal of the closed sub-study, **S1400C**. ß footnote has been removed.

4. **Page 15, Section 5.1b, Screening/Pre-Screening Registration:** "or recurrent" has been added after "Stage IV" in two locations.

5. **Page 16, Section 5.1c, Screening/Pre-Screening Registration:** This eligibility criterion regarding adequate tissue has been reformatted for easier readability.

6. **Page 49, Section 16.0, Trial Master File:** A new section has been added to provide information on FDA inspections.

7. **Page 51, Section 18, Appendix: S1400G:** A new appendix has been added, HRRD-Talazoparib.

8. **Page 52, Section 18.1a.1, Biomarker Exclusion Rules and Section 18.1a.2 Sub-study biomarker eligibility definitions:** These sections have been removed as they contain duplicate information already contained in Section 5 of the sub-studies.

9. **Page 54, Section 18.1a, Hybrid Selection & Sequencing:** The Illumina HiSeq system has been updated to the Illumina HiSeq 4,000 system.

10. **Page 65, Section 18.1d, Dose and Administration Schedules Overview: S1400G** has been added to Table 1.1 ("Sub-studies Open to Accrual"). **S1400C** has been relocated to Table 1.2 ("Sub-studies Closed to Accrual").

S1400B

1. **Page 146, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The row regarding detailed information on the regulatory and monitoring procedures for CTSU has been removed.

2. **Page 163, Section 7.0, Treatment Plan:** The Sub-Study Chairs have been updated.

3. **Page 176, Section 8.5, Dose Modification Contacts:** The Sub-Study Chairs have been updated.

4. **Pages 177, 178, & 181, Sections 9.1 Arm 1 GDC-0032 (Taselisib) and 9.3 Arm 3 Re-Registration GDC-0032 (Taselisib):**

    - The SWOG's Best Practices note has been relocated as a note above the footnotes and removed from ß footnote.
    - **Ω** has been added in the Disease Assessment row and CT or MRI row for Cycle 3 at week 7, Subsequent Cycles at week 13, Off Tx Follow-up prior to prog.
    - A new column "At Off Tx" has been added and the Off Tx prior to prog and Off Tx after prog columns have been updated with the addition.

5. **Page 195, Section 16.1h.2, Adverse Events Reporting Requirements:** The first sentence has been revised to indicate the location to submit AE supporting documentation.

S1400C

1. **Pages 198-255:** A water mark has been added for the closure of the sub-study.

2. **Page 200, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The row regarding detailed information on the regulatory and monitoring procedures for CTSU has been removed.

3. **Pages 236, 237, 240, & 241, Section 9.1 Arm 1 (Palbociclib) & 9.3 Arm 3 Re-Registration (Palbociclib) Study Calendar:**

    - The SWOG's Best Practices note has been relocated as a note above the footnotes and removed from ß footnote
    - **Ω** Has been added to Disease Assessment row and CT or MRI row for Cycle 2 at week 7, Cycle 4 at week 13, Subsequent cycles, Off Tx FU Prior to Prog.
    - A new column "At Off Tx" has been added and the Off Tx prior to prog and Off Tx after prog columns have been updated with the addition.

4. **Page 253, Section 16.1h.2, Adverse Events Reporting Requirements:** The first sentence has been revised to indicate the location to submit AE supporting documentation.

S1400D

1. **Page 258, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The row regarding detailed information on the regulatory and monitoring procedures for CTSU has been removed.

2. **Page 270, Section 5.2b, Sub-study Specific Clinical Laboratory Criteria:** The eligibility criterion related to CYP3A4 medications has been revised from "substrates" to "inhibitors and/or inducers."

3. **Pages 287-289, & 292-294, Section 9.1 Arm 1 (AZD4547) & 9.3 Arm 3 Re-Registration (AZD4547) Study Calendar:**

   - The SWOG's Best Practices note has been relocated as a note above the footnotes and removed from ß footnote
   - **Ω** has been added to Disease Assessment row and CT or MRI row at Cycle 3, week 7, Subsequent Cycles, Off Tx Follow-Up Prior to Prog.
   - A new column, "At off Tx" has been added and the Off Tx prior to prog and Off Tx after prog columns have been updated with the addition.
   - **X** Ophthalmologic Assessment at Subsequent Cycles has been deleted.

4. **Page 305, Section 16.1h.2,** Adverse Event Reporting Requirements: The first sentence has been revised to indicate the location to submit AE supporting documentation.

S1400I

1. **Page 363, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The row regarding detailed information on the regulatory and monitoring procedures for CTSU has been removed.

2. **Page 364, Schema**: A footnote has been inserted to state that upon progression, patients may be eligible for another sub-study.

3. **Page 390, Section 5.2h, Sub-Study Specific Clinical/Laboratory Criteria:** "Revision #5" has been replaced with "9/1/16" on the criteria regarding Patient Reported Outcomes

4. **Page 395, Section 7.3a, Criteria for Removal from Protocol Treatment:** A footnote * has been added providing information on new sub-study assignment.

5. **Page 396, Section 7.5, Follow-Up Period:** A note has been added for patients that enroll on a new sub-study following progression.

6. **Page 402, Section 8.5g, Treatment Discontinuation Criteria Nivolumab:** The third paragraph has been removed as it is duplicated information.

7. **Page 412-413, Section 9.0 Study Calendar:**

   - The SWOG's Best Practices note has been relocated as a note above the footnotes and removed from ß footnote
   - **Ω** Has been added to Disease Assessment row and CT or MRI row at Cycle 4, week 7, Subsequent Cycles, Off Tx FU Prior to Prog.

- A new column "At Off Tx" has been added and the Off Tx prior to prog and Off Tx after prog columns have been updated with the addition.
- The cover sheet information has been removed from calendar and the ☺ footnote has been corrected to specify the timepoints the Cover Sheet for the PROs should be completed.
- "Cycle 7" has been added to the ɯ footnote

8. **Page 418, Section 14.4c, Data Submission Overview:** Section 14.4d has been incorporated into Section 14.c and the data submission for PROs has been updated.

   Subsequent sections have been re-numbered accordingly.

9. **Page 419, Section 14.4g, Data Submission Overview:** A note has been added for patients that enroll on a new sub-study following progression.

10. **Page 419, Section 14.4j, Data Submission Overview:** A new section has been added for the request for new sub-study assignment.

11. **Page 428, Section 16.1h.2,** Adverse Event Reporting Requirements: The first sentence has been revised to indicate the location to submit AE supporting documentation.

12. **Page 440, Section 18.2, Patient Questionnaires: Instructions for Administration:** In the Method, "Revision #5" has been replaced with "9/1/16" in the last sentence.

S1400G

1. **Pages 451-502, Section 18.2g, S1400G:** A new sub-study, **S1400G**, has been inserted. **S1400G** is a new biomarker driven study. This study will employ Design # 2, the seamless Phase II followed by Phase III design. The objective of **S1400G** is to evaluate talazoparib (BMN 673) a poly (ADP) ribose polymerase (PARP) inhibitor, in Homologous Recombination Repair Deficiency (HRRD) Positive patients.

Model Consent Forms Changes

The following refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. Throughout the consent form, typographical errors were corrected.

3. **Pages 5 [S1400] & 19 [S1400PS]:** The screening and pre-screening schemas have been updated to a more simplified format. The idea is to provide a very simple and generic schema to patients. The details of each sub-study will be contained in the specific sub-study.

4. **Pages 10 [S1400], 24 [S1400PS], 53 [S1400B], 82 [S1400D], 111 [S1400I]** "What is involved?": The amount of blood collected in the optional studies has been corrected to 1 tablespoon.

5. **Pages 6 [S1400] & 19 [S1400PS], "What extra tests,":** The following sentence has been added to the end of the first paragraph. "This will be a standard surgical consent form from the institution where the biopsy procedure takes place."

6. **Pages 114-126 S1400G, New Sub-study Model Consent Form:** A new Sub-study Model Consent Form, **S1400G**, has been inserted.

Revision #7

Revision #7 has been prepared in response to the Request for Rapid Amendment (RRA) received on January 4, 2017 from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov). The associate Action Letter is attached.

The above-referenced study has been updated as follows:

1. The Version Date of the protocol and Model Consent Forms has been updated.

2. Table of Contents: The page numbers have been updated.

S1400I

1. **Section 3.1c.1, Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC # 748726) (IND-119672):** The nivolumab adverse effects section has been replaced with Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.2, November 15, 2016. The section has been updated as follows:

   Added New Risk:
   - Less Likely: Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)
   - Rare but Serious: Immune system disorders - Other (GVHD in the setting of allotransplant); Myositis; Nervous system disorders - Other (encephalitis)
   - Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Immune system disorders - Other (autoimmune thrombotic microangiopathy)

   Increase in Risk Attribution:
   - Changed to Less Likely from Rare But Serious: Infusion related reaction
   - Changed to Rare but Serious from Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Pericarditis

   Deleted Risk:
   - Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Alkaline phosphatase increased; Arthritis; CPK increased; Encephalitis infection; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Enterocolitis; Hepatobiliary disorders - Other (autoimmune hepatitis); Investigations - Other (CRP increased); Investigations - Other (eosinophil count increased); Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine free decreased); Nervous system disorders - Other (autoimmune neuropathy); Renal and urinary disorders - Other (nephritis); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Stroke; Wheezing; White blood cell decreased

   Provided Further Clarification:
   - The following footnote #7 was added: “Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite

intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT."

2. **Section 3.2c.1, Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442) (IND-119672):** The ipilimumab adverse effects section has been replaced with Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.8, December 21, 2016. The section has been updated as follows:

   Added New Risk:
   - Rare but Serious: Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)

   Increase in Risk Attribution:
   - Changed to Rare but Serious from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution: Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)

   Decrease in Risk Attribution:
   - Changed to Rare but Serious from Less Likely: Infections and infestations - Other (aseptic meningitis)

   Provided Further Clarification:
   - The following footnote #4 was added: "Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT."
   - Footnotes have been renumbered.

3. **Section 5.2h, Sub-Study Specific Clinical/Laboratory Criteria:** The eligibility criterion regarding cardiac disease has been removed from Section 5.3l and relocated to Section 5.2h. Additional suggestions regarding cardiac disease have been added.

   The subsequent sections have been re-numbered accordingly.

4. **Section 5.3l, Common Eligibility Criteria for all Sub-Studies:** The eligibility criterion regarding cardiac disease has been removed from Section 5.3l and relocated to Section 5.2h. A place holder remains to keep consistency across all sub-studies.

5. **Section 8.2d, General Considerations:** A new section has been added to include a comment on cardiotoxic drugs.

6. **Sections 8.3, 8.4, 8.5, 8.6, and 8.7:** A sentence referencing the location for dose modification and management for cardiomyopathy myocarditis has been added to the beginning of each section.

7. **Section 8.8, Dose Modification and Management for Cardiomyopathy Myocarditis:** A new section on the dose modification and management for cardiomyopathy myocarditis has been added in response to the RRA.

   The subsequent sections have been re-numbered accordingly.

8. **Section 9.0, Study Calendar**: Laboratory tests (Creatine phosphokinase (CPK) and Troponin) and the scans (EKG and ECHO) have been added to the pre-study, C4W7, and subsequent cycles. The associated Ж footnote has been added noting

the above tests are to be performed prestudy if clinically indicated (see Section 5.2) and are to be repeated every 6 weeks as clinically indicated while on treatment.

Model Consent Forms Changes

The following section refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. **Pages 106-107 [S1400l], "What possible risks…":** Patients currently receiving nivolumab **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, patients must be notified at their next visit and this conversation must be documented in the patient chart. The following changes have been made to the nivolumab side effects information:

   Added New Risk:
   - **Occasional: Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly; Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [both terms are clinical manifestations of lab values not previously listed on the risk list]**
   - **Rare but Serious: Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased; Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck**

   Increase in Risk Attribution:
   - **Changed to Occasional from Rare: Reaction during or following a drug infusion which may cause fever, chills, rash**

   Provided Further Clarification:
   - Swelling and redness of the eye which may cause blurred vision with a chance of blindness is now reported as Swelling and redness of the eye
   - Pain is now reported as Pain in belly and Pain or swelling of the joints
   - Fluid in the body is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); and 2) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
   - Swelling of the body which may cause shortness of breath or headache, tiredness, and nerve pain is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2)

Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare); and 3) Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck (under Rare).

- Itching, rash, skin changes is now reported as Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- A tear or hole in the stomach that may require surgery (under Rare) is now described as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).
- Damage to organs which may cause weakness or shortness of breath and/or cough (under Rare) is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare); and 3) Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement (under Rare).
- Visual disturbances and Swelling and pain around the eyes which may lead to vision changes and difficulty closing eyes are now reported as Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- Muscle pain and/or weakness with dark red urine and Muscle weakness are now reported as Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Confusion, Abnormal movement of the facial muscles, Weakness and paralysis, and Numbness, tingling or pain of the arms and legs are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- The following statement was added (under Occasional and Rare): “BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body.”

3. **Pages 108-110 [S1400I], “What possible risks…”:** Patients currently receiving ipilimumab **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, patients must be notified at their next visit and this conversation must be documented in the patient chart. The following changes have been made to the ipilimumab side effects information:

Added New Risk:

- **Occasional: Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness**

or fainting [the term above is a clinical manifestation of lab values not previously listed on the risk list]

Increase in Risk Attribution:

- **Changed to Rare from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution (i.e. added to risk profile): A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**

Provided Further Clarification:

- Rash (under Common); Itching, Hives, Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional); and Severe skin rash with blisters and peeling which can involve mouth and other parts of the body (under Rare) are now reported as Skin: itching; rash, blisters including inside the mouth (can be severe); hives (under Common).
- Pain is now reported as Pain in belly and Pain or swelling of the joints.
- Constipation (under Occasional) is now reported as Blockage of the bowels which may cause constipation (under Rare).
- Swelling of the body which may cause shortness of breath is now reported as part of 1) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional); 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly (under Occasional); 4) Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion (under Rare); and 5) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
- Chills and Reaction during or following infusion of the drug are now reported as Reaction during or following a drug infusion which may cause fever, chills, rash.
- Damage to organs leading to prolonged hospitalization is now reported as part of 1) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath; and 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Difficulty eating, Abnormal movement of the facial muscles, and Weakness and paralysis are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- A tear or hole in the stomach that may require surgery (under Rare) is now reported as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).

- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin is now reported as Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Headache is now reported as part of Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- The following statement was added (under Common, Occasional, and Rare): "Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body."

[Note: Sites should seek an updated investigator brochure as required by site's IRB of record. The Investigator's brochure is available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms or by clicking on the study link. Complete and return to ctsucontact@westat.com].

An entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of **S1400**.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Nationwide

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **February 1, 2017**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Ipilimumab (MDX-010, NSCs 732442 and 720801)

TO: Investigators for CTEP-supported Studies Involving Ipilimumab (MDX-010, NSCs 732442 and 720801)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with ipilimumab, and to request all trials with ipilimumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes ipilimumab. See the accompanying list of CTEP trials with ipilimumab.

In response to the new/modified risk information CTEP is requiring that all trials with ipilimumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on February 15, 2017** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since ipilimumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

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CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

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SPECIFIC INSTRUCTION

Background

On August 30, 2016, the FDA requested that CTEP 1) revise the ICD for all clinical trials that are investigating the use of ipilimumab and BMS-936558 (nivolumab) and ipilimumab to include the event of myocarditis, and 2) revise all protocols investigating ipilimumab and nivolumab and ipilimumab to include additional monitoring and management for myocarditis.

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with ipilimumab.

Risk Mitigation Plan

- Protocols will be revised to provide more specific guidelines for cardiac toxicities.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Specific Protocol Revisions to Address Risk Mitigation Plan: (insert section and page # as appropriate)

- Provide more specific guidelines for cardiac toxicities, including the stipulations listed below:
  - Add on study evaluation of cardiac function including EKG and ECHO cardiogram for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated.
  - For patients with evidence of CHF, MI, cardiomyopathy, or myositis cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram.
  - Drug modification table for cardiomyopathy myocarditis should be included in the appropriate section
    - Drug will be held for grade 2 cardiac dysfunction pending evaluation
    - Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
    - Treatment with steroids as clinically indicated
    - Add the table as follows in the treatment modification and AE management section

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.

Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

3) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.8, December 21, 2016): ___
Page Number(s): ____

- Added New Risk:
  - Rare but Serious: Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)

- Increase in Risk Attribution:
  - Changed to Rare but Serious from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution: Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Infections and infestations - Other (aseptic meningitis)

- Provided Further Clarification:
  - The following footnote #4 was added: "Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT."
  - Footnotes have been renumbered.

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.8, and associated risk information for the ICD, to the most recent CAEPR Version 2.7. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.7), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

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4) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Occasional: Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [the term above is a clinical manifestation of lab values not previously listed on the risk list]

- Increase in Risk Attribution:
  - Changed to Rare from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution (i.e. added to risk profile): A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma

- Provided Further Clarification:
  - Rash (under Common); Itching, Hives, Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional); and Severe skin rash with blisters and peeling which can involve mouth and other parts of the body (under Rare) are now reported as Skin: itching; rash, blisters including inside the mouth (can be severe); hives (under Common).
  - Pain is now reported as Pain in belly and Pain or swelling of the joints.
  - Constipation (under Occasional) is now reported as Blockage of the bowels which may cause constipation (under Rare).
  - Swelling of the body which may cause shortness of breath is now reported as part of 1) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional); 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly (under Occasional); 4) Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion (under Rare); and 5) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
  - Chills and Reaction during or following infusion of the drug are now reported as Reaction during or following a drug infusion which may cause fever, chills, rash.
  - Damage to organs leading to prolonged hospitalization is now reported as part of 1) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath; and 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.

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- Difficulty eating, Abnormal movement of the facial muscles, and Weakness and paralysis are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- A tear or hole in the stomach that may require surgery (under Rare) is now reported as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin is now reported as Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Headache is now reported as part of Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- The following statement was added (under Common, Occasional, and Rare): “Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body.”

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to ipilimumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

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Attachment 1: Revised Ipilimumab CAEPR – Version 2.8, December 21, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, December 21, 2016[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypopituitarism/hypophysitis)[2]		
	Endocrine disorders - Other (testosterone deficiency)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		

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Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction		
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
	Facial nerve disorder		
	Headache		
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]		
	Nervous system disorders - Other (myasthenia gravis)[2]		
	Trigeminal nerve disorder		

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Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage,

Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[6]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia, Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Attachment 2: Revised ICD Section(s) for Ipilimumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for ipilimumab in your ICD.

Risk Profile for Ipilimumab (CAEPR Version 2.8, December 21, 2016)

Special precautions Side effects of ipilimumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving ipilimumab, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Skin: itching; rash, blisters including inside the mouth (can be severe); hives

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OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving ipilimumab, from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain in belly
- Difficulty swallowing, vomiting, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

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RARE, AND SERIOUS

In 100 people receiving ipilimumab , 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.

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Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

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B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **February 1, 2017**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

TO: Investigators for CTEP-supported Studies Involving BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with BMS-936558, and to request all trials with BMS-936558 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes BMS-936558. See the accompanying list of CTEP trials with BMS-936558.

In response to the new/modified risk information CTEP is requiring that all trials with BMS-936558 be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on February 15, 2017** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since BMS-936558 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

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CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

On August 30, 2016, the FDA requested that CTEP 1) revise the ICD for all clinical trials that are investigating the use of ipilimumab and BMS-936558 (nivolumab) and ipilimumab to include the event of myocarditis, and 2) revise all protocols investigating ipilimumab and BMS-936558 and ipilimumab to include additional monitoring and management for myocarditis.

In addition, as part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with BMS-936558.

Risk Mitigation Plan

- Protocols will be revised to provide more specific guidelines for cardiac toxicities.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Specific Protocol Revisions to Address Risk Mitigation Plan: (insert section and page # as appropriate)

- Provide more specific guidelines for cardiac toxicities, including the stipulations listed below:
  - Add on study evaluation of cardiac function including EKG and ECHO cardiogram for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated.
  - For patients with evidence of CHF, MI, cardiomyopathy, or myositis cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram.
  - Drug modification table for cardiomyopathy myocarditis should be included in the appropriate section
    - Drug will be held for grade 2 cardiac dysfunction pending evaluation
    - Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
    - Treatment with steroids as clinically indicated
    - Add the table as follows in the treatment modification and AE management section

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation

Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

3) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, November 15, 2016): ___
Page Number(s): ____

- Added New Risk:
  - Less Likely: Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)
  - Rare but Serious: Immune system disorders - Other (GVHD in the setting of allotransplant); Myositis; Nervous system disorders - Other (encephalitis)
  - Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Immune system disorders - Other (autoimmune thrombotic microangiopathy)

- Increase in Risk Attribution:
  - Changed to Less Likely from Rare But Serious: Infusion related reaction
  - Changed to Rare but Serious from Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Pericarditis

- Deleted Risk:
  - Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Alkaline phosphatase increased; Arthritis; CPK increased; Encephalitis infection; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Enterocolitis; Hepatobiliary disorders - Other (autoimmune hepatitis); Investigations - Other (CRP increased); Investigations - Other (eosinophil count increased); Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine free decreased); Nervous system disorders - Other (autoimmune neuropathy); Renal and urinary disorders - Other (nephritis); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Stroke; Wheezing; White blood cell decreased

- Provided Further Clarification:
  - The following footnote #7 was added: "Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after

receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT."

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the ICD, to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

4) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Occasional: Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly; Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [both terms are clinical manifestations of lab values not previously listed on the risk list]
  - Rare but Serious: Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased; Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck

- Increase in Risk Attribution:
  - Changed to Occasional from Rare: Reaction during or following a drug infusion which may cause fever, chills, rash

- Provided Further Clarification:
  - Swelling and redness of the eye which may cause blurred vision with a chance of blindness is now reported as Swelling and redness of the eye
  - Pain is now reported as Pain in belly and Pain or swelling of the joints
  - Fluid in the body is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); and 2) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
  - Swelling of the body which may cause shortness of breath or headache, tiredness, and nerve pain is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms

may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare); and 3) Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck (under Rare).

- Itching, rash, skin changes is now reported as Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- A tear or hole in the stomach that may require surgery (under Rare) is now described as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).
- Damage to organs which may cause weakness or shortness of breath and/or cough (under Rare) is now reported as part of 1) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare); and 3) Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement (under Rare).
- Visual disturbances and Swelling and pain around the eyes which may lead to vision changes and difficulty closing eyes are now reported as Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- Muscle pain and/or weakness with dark red urine and Muscle weakness are now reported as Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Confusion, Abnormal movement of the facial muscles, Weakness and paralysis, and Numbness, tingling or pain of the arms and legs are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- The following statement was added (under Occasional and Rare): “BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body.”

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to BMS-936558 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

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Attachment 1: Revised BMS-936558 CAEPR – Version 2.2, November 15, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, November 15, 2016[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency		
	Endocrine disorders - Other (hypophysitis)		
	Hyperthyroidism		
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders - Other (diplopia)	
		Eye disorders - Other (Graves ophthalmopathy)	
		Eye disorders - Other (optic neuritis retrobulbar)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		
		Colonic perforation	
	Diarrhea		***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***

Action Letter

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Gastritis	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[3]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction[4]		
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Autoimmune disorder[5]	
		Cytokine release syndrome[6]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[7]	
		Immune system disorders - Other (sarcoid granuloma)[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
		Myositis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy	
		Facial nerve disorder[5]	

Action Letter

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)	
		Nervous system disorders - Other (Guillain-Barre syndrome)[5]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)	
		Nervous system disorders - Other (myasthenia gravis)[5]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion		
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[4]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

[5]BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune

checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[6]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[7]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (protein total decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for BMS-936558

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for BMS-936558 in your ICD.

Risk Profile for BMS-936558 (CAEPR Version 2.2, November 15, 2016)

Special precautions Side effects of BMS-936558 (nivolumab) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving BMS-936558, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving BMS-936558, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Swelling and redness of the eye
- Pain in belly
- Diarrhea, nausea, loss of appetite
- Dry mouth
- Fever
- Swelling and redness at the site of the medication injection
- Bruising, bleeding
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash

BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

Action Letter

RARE, AND SERIOUS

In 100 people receiving BMS-936558, 3 or fewer may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

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February 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of the following error within sub-study **S1400I**.

The **S1400I** Patient Reported Outcomes (PRO) and EQ-5D Questionnaires are to be synchronized with the clinical follow-up visits. Below are the correct timepoints the questionnaires should be completed. This error will be corrected in a subsequent revision.

The **S1400I** Patient Reported Outcomes (PRO) Questionnaire is administered at Pre-study (within 14 days prior to **S1400I** registration) and at Weeks 3, 5, 7, 9, 11, 13, **25** and **37**. The **S1400I** EQ-5D Questionnaire is administered at Prestudy, Weeks 5, 7, 9, 13, **25**, **37**, and Years 1, 2, and 3.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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February 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Dec. 20, 2016 Mfr Rpt #BMS2016102236
S1609 Early Therapeutic	Dec, 23, 2016 Mfr Rpt #BMS2016022351 FU
	Dec. 23, 2016 Mfr Rpt #BMS2016105281
	Jan. 05, 2017 AE-2820490

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies

and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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swog.org

February 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Nov. 29, 2016 Mfr Rpt #BMS2016031762
S1609 Early Therapeutics	Dec. 19, 2016 Mfr RPt #BMS2016075427 FU
	Dec. 20, 2016 Mfr Rpt #BMS2016102236
	Dec. 20, 2016 Mfr Rpt #BMS2016105930
	Dec. 20, 2016 Mfr Rpt #BMS2016106698
	Dec. 23, 2016 Mfr Rpt #BMS2016022351 FU
	Dec. 23, 2016 Mfr Rpt #BMS2016073775
	Dec. 23, 2016 Mfr Rpt #BMS2016105281
	Dec. 29, 2016 Mfr Rpt #BMS2016107222 FU
	Dec. 29, 2016 Mfr Rpt #BMS2016109496

Jan. 03, 2017	AE-2216731 FU
Jan. 03, 2017	Mfr Rpt #BMS2016107228 FU
Jan. 05, 2017	AE-2820490
Jan. 05, 2017	Mfr Rpt #BMS2016112163
Jan. 06, 2017	Mfr Rpt #BMS2016112319

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
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swog.org

January 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
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  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
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( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Nov. 21, 2016 Mfr Rpt #BMS2016084841 Nov. 22, 2016 Mfr Rpt #BMS2016091101 Nov. 22, 2016 Mfr Rpt #BMS2016092973 FU Dec. 01, 2016 Mfr Rpt #BMS2016085259 FU Dec. 08, 2016 Mfr Rpt #BMS20797825 FU Dec. 08, 2016 Mfr Rpt #BMS2016080089 FU Dec. 08, 2016 Mfr Rpt #BMS2016102275 Dec. 08, 2016 Mfr Rpt #BMS2016102361 Dec. 12, 2016 Mfr Rpt #BMS2016103615 Dec. 22, 2016 AE-2957042

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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January 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
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( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Nov. 21, 2016 Mfr Rpt #BMS2016084841 Nov. 22, 2016 Mfr Rpt #BMS2016091101 Nov. 22, 2016 Mfr Rpt #BMS2016092973 FU Dec. 01, 2016 Mfr Rpt #BMS2016085259 FU Dec. 08, 2016 Mfr Rpt #BMS20797825 FU Dec. 08, 2016 Mfr Rpt #BMS2016080089 FU Dec. 08, 2016 Mfr Rpt #BMS2016102275 Dec. 08, 2016 Mfr Rpt #BMS2016102361 Dec. 12, 2016 Mfr Rpt #BMS2016103615

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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January 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Dec. 05, 2016 AE-2216731

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
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Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Nov. 10, 2016 AE-2470812 Nov. 16, 2016 Mfr Rpt #BMS2016086653

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your

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December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
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These safety reports pertain to the following study:	Reports:
S1400I Lung	Nov. 04, 2016 AE-2785084 Nov. 10, 2016 AE-2470812 Nov. 11, 2016 AE-2786738 Nov. 15, 2016 Mfr Rpt # BMS2016094814 Nov. 15, 2016 Mfr Rpt # BMS2016093850 Nov. 16, 2016 Mfr Rpt # BMS2016086653 Nov. 17, 2016 AE-2340974 FU Nov. 22, 2016 Mfr Rpt # BMS2016097201

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Oct. 07, 2016 Mfr Rpt #BMS2016079104 Oct. 18, 2016 Mfr Rpt #BMS2016085054 Oct. 21, 2016 Mfr Rpt #BMS2016084607

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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These safety reports pertain to the following study:	Reports:
S1400I Lung	Oct. 07, 2016 Mfr Rpt #BMS2016079104
	Oct. 14, 2016 Mfr Rpt #2016IN002758 FU
	Oct. 18, 2016 Mfr Rpt #BMS2016085054
	Oct. 18, 2016 Mfr Rpt #BMS2016086465
	Oct. 21, 2016 Mfr Rpt #BMS2016084607

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
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MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Sep. 27, 2016 Mfr Rpt #BMS2016010123 FU Oct. 04, 2016 AE-2929582

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your

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November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Sep. 27, 2016 Mfr Rpt #BMS2016010123 FU

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October 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Sep. 09, 2016 Mfr Rpt #BMS2016067654 Sep. 19, 2016 Mfr Rpt #BMS2016073689 Sep. 22, 2016 Mfr Rpt #BMS2016075033 Sep. 29, 2016 AE-2667227

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swog.org

October 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
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Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Sep. 09, 2016 Mfr Rpt #BMS2016067654 Sep. 19, 2016 Mfr Rpt #BMS2016073689 Sep. 22, 2016 Mfr Rpt #BMS2016075033

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October 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
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This safety report pertain to the following study:	Reports:
S1400I Lung	Aug. 31, 2016 AE-2745409 Sep. 01, 2016 Mfr Rpt #BMS2016070761 Sep. 02, 2016 AE-2078817 Sep. 15, 2016 AE-2011772

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jul. 22, 2016 Mfr Rpt #BMS2016059790 Aug. 23, 2016 Mfr Rpt #BMS2016067147 Aug. 29, 2016 Mfr Rpt #BMS2016IN004847 FU Sep. 01, 2016 Mfr Rpt #BMS2016064730 Sep. 01, 2016 Mfr Rpt #BMS2016070761 Sep. 02, 2016 AE-2078817 Sep. 14, 2016 Mfr Rpt #BMS2016073278

Sep. 20, 2016	Mfr Rpt #BMS2016035850 FU
Sep. 22, 2016	AE-2510609

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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September 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Aug. 10, 2016 Mfr Rpt #BMS2016063547 Aug. 16, 2016 Mfr Rpt #BMS2016064385 Aug. 18, 2016 Mfr Rpt #BMS2016058028 Aug. 22, 2016 AE2525865 Aug. 25, 2016 AE2301322 Aug. 25, 2016 AE2318852

Aug. 31, 2016 AE2340974

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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September 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung	Aug. 18, 2016 Mfr Rpt #BMS2016058028 Aug. 25, 2016 AE2301322 Aug. 25, 2016 AE2318852

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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September 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
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( ) Closure
( ) Reactivation

Protocol changes
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( ) Specimen Submission changes
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( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of the following items:

1. A revised **S1400** Funding Memo is available on the **S1400** Abstract Page Links on the SWOG (http://swog.org) and CTSU (https://www.ctsu.org) websites. An additional site payment is being offered to sites for a limited duration.

2. New Investigator's Brochures are now available for the following investigational agents.

Sub-Study: **S1400B** Agent: GDC-0032
May2016_Ver6 Addendum 1

Sub-Study: **S1400I** Agent: Nivolumab
24Jun2016_Ver 15 and 5Jul2016_Ver 15_Err01

SWOG's standard procedures will be followed in updating the drug information sections based on the most recent Investigator's brochure versions. Sites should seek updated Investigator's brochures as required by site's IRB of record.

The Investigator's brochures are available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms. Complete and return to ctsucontact@westat.com.

3. The final aspects of Revision #5 are in effect as of September 1, 2016.

   a. Patient Reported Outcomes (PRO) have been added to the sub-study **S1400I**.

   b. Patients who progress on a sub-study now have the option to be assigned to a new sub-study.

   c. Status Update Form submission requirement has been added. The following forms for the above-noted study have been updated.

      Note: Please discard old versions of these forms and replace with the new versions.

      S1400
      S1400 Rave Form Display Form
      S1400 Notice of Progression (500043v1.2)

      S1400 Status Update (New form 500228v1.0)
      S1400 Request for New Sub-study Assignment (New form 500229v1.0)

      S1400A
      S1400A Rave Form Display Form
      S1400A Adverse Events (500039v1.2)

      S1400B
      S1400B Rave Form Display
      S1400B Adverse Event Form (500096v1.1)

      S1400B Pre-Treatment Laboratory Values Form (New form 500230v1.0)

      S1400C
      S1400C Rave Form Display
      S1400C Adverse Event Form (500040v1.1)

      S1400C Pre-Treatment Laboratory Values Form (New form 500231v1.0)

      S1400D
      S1400D Rave Form Display
      S1400D Adverse Event Form (500041v1.1)

      S1400D Pre-Treatment Laboratory Values Form (New form 500232v1.0)

S1400I
S1400I Rave Form Display
S1400I Registration Worksheet (500151v1.1)
S1400I Adverse Event Form (500160v1.1)

S1400I Pre-Treatment Laboratory Values Form (New form 500233v1.0)
S1400I Cover Sheet for PRO Questionnaires (New form 500234v1.0)
S1400I EQ-5D Questionnaire (New form 500235v1.0)
S1400I PRO Questionnaire(New form 500236v1.0)

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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September 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung	Jul. 29, 2016 Mfr Rpt #BMS2016001137 Aug. 01, 2016 Mfr Rpt #BMS2016057203 FU Aug. 01, 2016 Mfr Rpt #BMS2016060237 Aug. 05, 2016 Mfr Rpt #BMS2016061701

Aug. 16, 2016	AE1636062
Aug. 16, 2016	AE2054219
Aug. 16, 2016	AE2507112

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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September 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

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Aug. 16, 2016	AE1636062
Aug. 16, 2016	AE2054219
Aug. 16, 2016	AE2507112

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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August 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

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This safety report pertain to the following study:	Reports:
S1400I Lung	Aug. 02, 2016 AE2507112

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your

institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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August 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jun. 30, 2016	Mfr Rpt #2016IN003459
	Jul. 11, 2016	Mfr Rpt #BMS2016041014
	Jul. 27, 2016	Mfr Rpt #2016IN004076

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Distribution Date: August 15, 2016
E-mailed Date: August 10, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "Phase II/III Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
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Protocol changes
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( ) Other:

MEMORANDUM

The purpose of this memorandum is to correct an error in the Revision #5 cover memo that was distributed on August 4, 2016. That memo indicated that patients need not be notified of the changes. It has come to our attention that, despite the CIRB's assessment that patients need not be notified of the changes in this revision, CTEP's Action Letter **does** require patient notification.

Therefore, patients currently receiving MEDI4736, GDC-0032, palbociclib, or AZD4745 and patients who sign a sub-study consent form prior to the revised consent being implemented must be informed of the new and modified risk information outlined in Revision #5.

The manner by which the notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart. A **S1400D** [AZD4547] consent addendum was provided as a tool for notifying patients.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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Distribution Date: August 15, 2016
E-mailed Date: August 4, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
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( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(√) Other: Instructions for Revision #5

MEMORANDUM

Although Revision #5 will be e-mailed to sites on August 4, 2016, some aspects of the revision do not go into effect until September 1, 2016. Listed below are the changes and their effective dates:

1) Administrative updates and clarifications throughout the protocol and consents. **Effective August 4, 2016.**

2) Changes to protocol and Model Consent Form in response to a Request for Amendment (RA) for MEDI4736 (**S1400A**), GDC-0032 (taselisib) (**S1400B**), palbociclib (**S1400C**), and AZD4647 (**S1400D**). **Effective August 4, 2016.**

3) Patient Reported Outcomes (PRO) have been added to the sub-study **S1400I. Effective September 1, 2016.**

4) Patients who progress on a sub-study now have the option to be assigned to a new sub-study. **Effective September 1, 2016.**

5) Status Update Form submission requirement has been added. **Effective September 1, 2016.**

Also, please note that **S1400C** remains temporarily closed to accrual while an interim analysis of the study is being performed.

For questions, please e-mail S1400question@crab.org.

cc: PROTOCOL & INFORMATION OFFICE
Hossein Borghaei, D.O.
James L. Wade III, M.D.
Corey J. Langer, M.D.
Martin J. Edelman, M.D.
Charu Aggarwal, M.D., M.P.
Mark A. Socinski, M.D.
Scott Gettinger, M.D.
Lyudmila A. Bazhenova, M.D.
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S.
Jieling Miao, M.S.
Katherine Griffin, M.S.
Monica Yee, B.A.
Louise Highleyman
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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

REVISION #5

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
(√) Required local accrual suspension of **S1400C** and **S1400D** only
Accrual of new patients to sub-studies **S1400C** and **S1400D** must be suspended until the revised Model Consent Forms are approved by the site's IRB of record and **implemented**.
( ) Closure
( ) Reactivation

Protocol changes
(√) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
( ) Patient notification not required
(√) Patient notification required for patients being treated on **S1400D** only. The changes in this amendment are significant enough to impact a patient's willingness to continue. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart. A consent addendum is provided as a tool for notifying patients.
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
(√) Data Submission / Forms changes
(√) Editorial / Administrative changes
(√) Other: Addition of Patient Reported Outcomes for new patients on **S1400I**

REVISION #5

The above-referenced protocol has been revised.

This revision includes the following changes:

1) Administrative updates and clarifications throughout the protocol and consents
2) Changes in response to a modified Request for Amendment (RA) for MEDI4736 (**S1400A**), GDC-0032 (taselisib) (**S1400B**), palbociclib (**S1400C**), and AZD4647 (**S1400D**), received on June 30, 2016 from Dr. Meg Mooney mooneym@ctep.nci.nih.gov.
3) Patient Reported Outcomes (PRO) for the sub-study **S1400I**
4) Patients who progress on a sub-study now have the option to be assigned to a new sub-study.

The revision has been organized by protocol edits for **S1400** and each of the sub-studies, followed by the model consent form edits.

General throughout Protocol

1. The Version Date of the protocol and the model consent forms have been updated.

2. Table of Contents: The page numbers have been updated for the following sections: **S1400**, **S1400A**, **S1400B**, **S1400C**, **S1400D**, **S1400E**, **S1400I**.

3. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

S1400

1. **Page 1, Title Page:** The email address has been updated for Dr. David Gandara and Dr. Schwartz. Katharine Griffin has been added under the Biostatisticians.

2. **Page 2, Participants Page:** The participants page has been updated as follows:
   - Dr. Glenwood Goss has been added as the CCTG Study Chair
   - Dr. Karen Kelly has been added as the SWOG Study Chair.
   - "NCIC CTG Study Chair" has been revised to "CCTG Study Chair"
   - "NCIC CTG/NCI Canada Clinical Trials Group" has been revised to "CCTG/Canadian Cancer Trials Group"

3. **Page 5, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The email address for treatment or toxicity related questions has been updated.

4. **Page 6, Schema**: The sub-study **S1400A** has been removed. A footnote has been inserted to state that upon progression, patients may be eligible for another sub-study. "Phase II" has been added to **S1400I**. "Phase II" has been relocated next to sub-studies **S1400B**, **S1400C**, and **S1400D**.

5. **Page 16, Section 5.1c, Screening/Pre-Screening Registration:** The second sentence has been edited for clarification in the eligibility criterion related to adequate tissue.

6. **Page 16, Section 5.1d, Screening/Pre-Screening Registration:** The following sentence has been added to the eligibility criterion related to mutations: "EGFR/ALK testing is not required prior to registration and is included in the FMI testing for screening/prescreening."

7. **Pages 16-17, Section 5.2, Sub-Study Registration:** A paragraph has been added to provide information on receiving a new sub-study assignment after progression on a sub-study. A sentence has been added to the end of the third paragraph providing contact information for eligibility questions.

8. **Page 17, Section 5.2b, Sub-Study Registration:** The eligibility criterion related to progression has been revised from "pre RECIST 1.1 (see Section 10.1)" to "(in the opinion of the treating investigator)".

9. **Page 17, Section 5.2c, Sub-Study Registration:** The eligibility criterion related to prior therapy has been revised as follows:

    - The third sentence has been replaced with: “Patients must not have received any radiation therapy within 14 days prior to sub-study registration.”
    - The last sentence has been removed
    - A reference to CNS metastases criteria has been added

10. **Page 18, Section 5.2e, Sub-Study Registration:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

11. **Pages 21-22, Section 10.1c, Notes on measurability:** This section has been revised to elaborate upon CT, PET/CT, and MRI to allow for use of scanners from different manufacturers.

12. **Page 35, Section 11.4c, Accrual Information:** “screened” has been added to the first sentence.

13. **Pages 37-38**, Section 13.2, Requirements for Site Registration: New information for downloading site registration documents, submitting regulatory documents, and checking your site’s registration status have been added.

14. **Page 42, Section 14.4d, Data Submission Overview:** This section has been added to notify sites to submit a screening/pre-screening status update after receiving sub-study assignment. The subsequent sections have been re-numbered accordingly.

15. **Page 42, Section 14.4e, Data Submission Overview:** Follow-up on screening/prescreening registrations has been updated to occur more frequently.

16. **Page 43, Section 14.6, Data Submission Overview**: This section has been added to notify sites of the forms required to submit for patients who have progressed on a sub-study wishing to register to a new sub-study.

17. **Page 44, Section 15.2b, BioMarker Profiling:** The contact information for Foundation Medicine, Inc. has been updated.

18. **Page 45, Section 15.3b.1, Specimen Collection:** “at the time of progression on current treatment” has been added for clarity.

19. **Page 46, Section 15.4, Radiology Review:** The timepoints for CT, PET/CT, and/or MRI images have been clarified. Imaging is only required once a patient is registered to an **S1400** sub-study.

20. **Page 67, Section 18.1d, List of Sub-studies, Table 1.1**: “q” has been added to the S1400I, Ipilimumab’s cycle column for clarification.

S1400A

1. **Pages 82-84, Section 3.1c.1, MEDI4736 NSC 778709:** The MEDI4736 adverse effects section has been replaced with a CTEP Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.0, February 2, 2016. The section has been updated as follows:

   Added New Risks:
   - Less Likely: Dental caries; Anorexia

   Increased in Risk Attribution:
   - Changed from Rare but Serious to Less Likely: Hypothyroidism

   Decreased in Risk Attribution:
   - Changed from Likely to Less Likely: Nausea; Fatigue

   Skin and Subcutaneous Tissue Disorders – Rash is now reported as Rash maculo-papular

   Removal of Risks:
   - Less Likely: Anemia, Constipation; Abdominal pain; Pyrexia; Chills; Peripheral edema; Urinary tract infection; Increase gamma-glutamyltransferase; Elevated alanine aminotransferase; Elevated aspartate aminotransferase; Decreased appetite; Dehydration; Dizziness; Headache; Dyspnea; Cough; Chest pain; Arthralgia; Back pain; Myalgia
   - Rare but Serious: Sepsis sinusitis; Hypercalcemia; Peripheral neuropathy; Pleural effusion; Pneumonitis; Angiopathy

   Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements column has been removed.

   Also Reported but With Insufficient Evidence for Attribution: Anemia; Disseminated intravascular coagulation; Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade; Hearing impaired; Adrenal insufficiency; Hyperthyroidism; Eye disorders - Other (choroidal effusion with shut down of ciliary body); Abdominal pain; Colitis; Esophageal perforation; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage; Edema limbs; Fever; Infusion related reaction; Non-cardiac chest pain; Hepatic hemorrhage; Hepatobiliary disorders - Other (hepatitis); Immune system disorders - Other (drug-induced liver injury); Infections and infestations - Other (liver abscess); Lung infection; Rash pustular; Urinary tract infection; Alanine aminotransferase increased; Aspartate aminotransferase increased; GGT increased; Investigations - Other (electrocardiogram T wave inversion); Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased; Dehydration; Hypercalcemia; Hyperglycemia; Hypomagnesemia; Hyponatremia; Arthralgia; Arthritis; Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myalgia; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Treatment related secondary malignancy; Tumor pain; Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (axonal neuropathy); Paresthesia; Seizure; Acute kidney injury; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis); Bronchopulmonary hemorrhage; Cough; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis; Respiratory failure; Dry skin; Skin and subcutaneous tissue disorders - Other (blister); Skin and subcutaneous tissue disorders - Other (dermatitis); Skin hypopigmentation

   A note regarding the effects of MEDI4736 in combination with other agents has been added to the end of the section.

2. **Page 93, Section 5.4, Registration Step #2 – MEDI4736 Re-Treatment:** A sentence has been added providing contact information for eligibility questions.

3. **Page 94, Section 5.4c, Registration Step #2 – MEDI4736 Re-Treatment:** The eligibility criterion related to CT/MRI scans has been revised as follows:
   - "and prior to Re-TREATMENT registration" has been added to the second sentence
   - "1 day" has been revised to "24 hours"

4. **Page 97, Section 7.2a, Treatment Arm 1: MEDI4736:** "for the first year, then every 3 months" has been added to the second sentence in the note.

5. **Page 98, Section 7.2c, Treatment Arm 3: MEDI4736 Re-treatment:** “for the first year, then every 3 months” has been added to the second sentence in the note.

6. **Pages 101-112, Section 8.3, Dose Modifications for MEDI4736:** This section has been updated as follows:
    - “Immune Mediated Reaction” has been revised to “Immune Related Adverse Events” throughout the section
    - “CTC” has been updated to “CTCAE”
    - Immune-Related Adverse Events: Toxicity Management has been revised to include additional guidelines, specifically to potent immunosuppressive and endocrinopathies
    - Grade 2 for the following toxicities have had the dose modifications updated to include a timeframe for steroid taper: Immune-Related Adverse Events, Pneumonitis/ILD, Diarrhea/Enterocolitis, Hepatitis, Rash, Endocrinopathy, Immune Medicated Neurotoxicity,
    - “4 weeks” has been updated to “28 days”
    - “Study Physician” has been updated to “Study Chair”
    - Rash: Toxicity Management for Grade 3 and 4 has been revised to include additional guidelines, specifically to endocrinopathies
    - “IVIgG” has been revised to “IVIG”

7. **Pages 116-117, 120-121, Sections 9.1 and 9.3, Calendar for MEDI4736:** The following footnotes have been updated:
    - In the Ω footnote, “for the first year, then every 3 months” has been added.
    - In the ß footnote, “unless otherwise noted.” and “for the first year, then every 3 months.” have been added.

8. **Page 130, Section 15.4a, Radiology Review:** “for the first year, then every 3 months” has been added to the second bullet and to the second paragraph, second sentence.

S1400B

1. **Page 146, Title Page:** The Sub-Study Chairs have been revised; Dr. Corey Lander is now listed as the Chair and Dr. Wade is listed as the Co-Chair.

2. **Page 148, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The email address for treatment or toxicity related questions has been updated.

3. **Page 149, Schema**: A footnote has been inserted to state that upon progression, patients may be eligible for another sub-study.

4. **Page 154, Section 3.1c.1, Taselisib (GDC-0032) NSC 778795:** The Taselisib (GDC-0032) adverse effects section has been replaced with a CTEP Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.1, January 24, 2016. The section has been updated as follows:

   Added New Risks:
   - Less Likely: Dry mouth, Dyspepsia, Mucositis oral, Aspartate aminotransferase increased, Neutrophil count decrease, Dysgeusia, Dry skin, Skin and subcutaneous tissue disorders (rash)
   - Likely: Anorexia

   Increased in Risk Attribution:
   - Changed to Less Likely from Rare but Serious: Abdominal pain, Colitis, Alanine aminotransferase increased, Pruritis

   Decreased in Risk Attribution:
   - Changed to Less Likely from Likely: Vomiting

   Removal of Risks:
   - Rare but Serious: Anemia, Neutropenia, Lymphopenia, Congestive cardiac failure, Oral pain, Urinary tract infection, Clostridium difficile infection, Increased lipase, Hypokalemia, Hyponatremia, Hypophosphatemia, Peripheral neuropathy, Acute renal failure, Dyspnea, Pneumonia, Hypoxia, Respiratory failure
   - Less Likely: Stomatitis, Mucosal inflammation, Pyrexia, Dizziness, Cough, Rash
   - Likely: Decreased appetite
   - The adverse events also reported on GDC-0032 for which there is insufficient evident to suggest that there was a reasonable possibility that GDC-0032 caused the adverse event have been added: Anemia, Constipation; Oral pain; Sepsis; Cholesterol high; Lymphocyte count decreased; White blood cell decreased; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Dizziness; Peripheral sensory neuropathy; Respiratory failure

5. **Page 155, Section 3.1c.3, Taselisib (GDC-0032), Drug Interactions:** The following statement has been added to the first paragraph: “GDC-0032 displays weak time-dependent inhibition of CYP3A4 and has the potential to induce CYP3A4/5.”.

6. **Page 158, Section 5.0, Eligibility Criteria:** A sentence has been added at the end of the instructions providing contact information for eligibility questions.

7. **Page 159, Section 5.2g, Clinical laboratory Criteria:** The following criterion has been added:

   “Patients must have a Lipase and Amylase performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.“

   The subsequent sections have been re-numbered accordingly.

8. **Page 159, Section 5.3b, Common Eligibility Criteria:** The eligibility criterion related to progression has been revised from “pre RECIST 1.1 (see Section 10.1)” to “(in the opinion of the treating investigator)”.

9. **Page 159, Section 5.3c, Common Eligibility Criteria:** The eligibility criterion related to prior therapy has been revised as follows:

    - The third sentence has been replaced with: “Patients must not have received any radiation therapy within 14 days prior to sub-study registration.”
    - The last sentence has been removed.
    - A reference to CNS metastases criteria has been added.

10. **Page 160, Section 5.3e, Common Eligibility Criteria:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

11. **Page 163, Section 5.4d, Step 2 GDC-0032 Re-Registration:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

12. **Page 163, Section 5.4j, Step 2 GDC-0032 Re-Registration:** The following criterion has been added:

    “Patients must have a Lipase and Amylase performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.“

    The subsequent sections have been re-numbered accordingly.

13. **Page 165, Section 6.0, Stratification Factors:** A sentence has been added regarding the continued stratification by PIK3CA to the first paragraph.

14. **Page 167, Section 7.5a, Criteria for Removal from Protocol Treatment:** A footnote * has been added providing information on new sub-study assignment.

15. **Page 167, Section 7.7, Follow-Up Period:** A note has been added for patients that enroll on a new sub-study following progression.

16. **Pages 179-180, 183-184, Section 9.1, Arm 1 GDC-0032 (Taselisib) and Section 9.3, Arm 3 GDC-0032 (Taselisib) Calendars:** The following items have been updated:

    - Smoking Status Assessment has been added to Off Tx FU After Progression
    - The € footnote has been removed from the Pre-study Laboratory tests
    - Laboratory tests have been added to C1W1 with the € footnote noting if the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated
    - Laboratory tests have been added to Off Tx Follow-up After Progression with the ɗ footnote noting assessments should continue until resolution of all acute adverse events
    - The footnote ɗ has been added to the laboratory tests performed at Off Tx follow-up Prior to Progression
    - In the Ω footnote, “while on treatment” has been removed
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted. The Best Practices website has been updated
    - The footnote √, a note has been added for patients that enroll on a new sub-study following progression.
    - The footnote € has been revised for clarification
    - The footnote ð has been added to the blood for banking noting the off treatment after progression must be collected at first progression after study treatment

17. **Page 188, Section 14.4d, Data Submission Overview:** A pre-treatment laboratory form has been added for cycle 1 only.

18. **Pages 188-189, Section 14.4g, Data Submission Overview:** A note has been added for patients that enroll on a new sub-study following progression.

19. **Page 189, Section 14.4j, Data Submission Overview:** A new section has been added for the request for new sub-study assignment.

20. **Page 190, Section 15.2a.1, Peripheral Blood:** “at the time of progression on current treatment or” has been added to the note of the first bullet.

S1400C

1. **Page 200, Title Page:** Dr. Edelman's NCTN Group has been revised to Alliance.

2. **Page 202, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The email address for treatment or toxicity related questions has been updated.

3. **Page 203, Schema**: A footnote has been inserted to state that upon progression, patients may be eligible for another sub-study.

4. **Pages 208-211, Section 3.1c.1, Palbociclib NSC 772256:** The palbociclib adverse effects section has been replaced with a CTEP Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.2, April 1, 2016. The section has been updated as follows:

   Added New Risk:
   - Reported but With Insufficient Evidence for Attribution: Ascites; Bone marrow hypocellular; Cataract; Eye disorders - Other (retinal hemorrhage); Gastrointestinal disorders - Other (large intestine perforation); Hepatic failure; Hypoxia; Intra-abdominal hemorrhage; Intracranial hemorrhage; Investigations - Other (pancytopenia); Localized edema; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Pericarditis; Pneumonitis; Pulmonary edema; Pulmonary hypertension; Small intestinal perforation; Syncope

   Increase in Risk Attribution:
   - Changed to Likely from Less Likely: Infection
   - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Dry skin; Headache
   - Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: Thromboembolic event

   Decrease in Risk Attribution:
   - Changed to Less Likely from Likely: Lymphocyte count decreased
   - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Arthralgia; Blurred vision; Dyspnea; Edema limbs; Flatulence; Hyperglycemia; Nervous system disorders - Other (peripheral neuropathy)

   Provided Further Clarification:
   - Footnote #3, "Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fuvestrant," has been added.
   - Footnote number #4 has been altered to read, "Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, dermatitis, and palmar-plantar erythrodysesthesia syndrome."

   Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: Column has been removed.

   Deleted Risk:
   - Reported but With Insufficient Evidence for Attribution: Respiratory, thoracic and mediastinal disorders - Other (alveolitis allergic)

5. **Page 217, Section 5.0, Eligibility Criteria:** A sentence has been added at the end of the instructions providing contact information for eligibility questions.

6. **Page 218, Section 5.2e, Clinical laboratory Criteria:** The following criterion has been added:

   "Patients must have a Na, K, Cl, Ca, Mg, and HbA1c performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar."

The subsequent sections have been re-numbered accordingly.

7. **Page 218, Section 5.3b, Common Eligibility Criteria:** The eligibility criterion related to progression has been revised from “pre RECIST 1.1 (see Section 10.1)” to “(in the opinion of the treating investigator)”.

8. **Page 219, Section 5.3c, Common Eligibility Criteria:** The eligibility criterion related to prior therapy has been revised as follows:

    - The third sentence has been replaced with: “Patients must not have received any radiation therapy within 14 days prior to sub-study registration.”
    - The last sentence has been removed
    - A reference to CNS metastases criteria has been added

9. **Page 219, Section 5.3e, Common Eligibility Criteria:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

10. **Page 222, Section 5.4d, Step 2 Palbociclib Re-Registration:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

11. **Page 223, Section 5.4j, Step 2 Palbociclib Re-Registration:** The following criterion has been added:

    “Patients must have a Na, K, Cl, Ca, Mg, and HbA1c performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.“

    The subsequent sections have been re-numbered accordingly.

12. **Page 231, Section 7.4a, Criteria for Removal from Protocol Treatment:** A footnote * has been added providing information on new sub-study assignment.

13. **Page 231, Section 7.6, Follow-Up Period:** A note has been added for patients that enroll on a new sub-study following progression.

14. **Pages 238-239, 242-243, Section 9.1, Arm 1 Palbociclib and Section 9.3, Arm 3 Palbociclib Calendars:** The following items have been updated:

    - Smoking Status Assessment has been added to Off Tx FU After Progression
    - The € footnote has been removed from the Pre-study Laboratory tests
    - Laboratory tests have been added to C1W1 with the € footnote noting if the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated
    - Laboratory tests have been added to Off Tx Follow-up After Progression with the ɗ footnote noting assessments should continue until resolution of all acute adverse events
    - The footnote ɗ has been added to the laboratory tests performed at Off Tx follow-up Prior to Progression
    - In the Ω footnote, “while on treatment” has been removed
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted. The Best Practices website has been updated
    - In the footnote √, a note has been added for patients that enroll on a new sub-study following progression.
    - The footnote € has been revised for clarification
    - The footnote ð has been added to the blood for banking noting the off treatment after progression sample must be collected at first progression after study treatment

15. **Page 247, Section 14.4d, Data Submission Overview:** A pre-treatment laboratory form has been added for cycle 1 only.

16. **Page 247, Section 14.4g, Data Submission Overview:** A note has been added for patients that enroll on a new sub-study following progression.

17. **Page 248, Section 14.4j, Data Submission Overview:** A new section has been added for the request for new sub-study assignment.

18. **Page 248-249, Section 15.2a.1, Peripheral Blood, Arm1 and Arm 3:** “at the time of progression on current treatment or” has been added to the note of the first bullet.

S1400D

1. **Page 258, Title Page:** The email address has been updated for Dr. Primo Lara.

2. **Page 260, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The email address for treatment or toxicity related questions has been updated.

3. **Page 261, Schema**: A footnote has been inserted to state that upon progression, patients may be eligible for another sub-study.

4. **Pages 267-269, Section 3.1c.1, AZD4547 NSC 765338:** The AZD4547 adverse effects section has been replaced with a CTEP Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.2, May 24, 2016. The section has been updated as follows:

   Added New Risks:
   - Likely: Eye disorders – other (retinal pigment epithelium detachment), Constipation; Vomiting; Fatigue; Anorexia
   - Less Likely: Anemia; Retinopathy; Abdominal pain; Nausea; Alkaline phosphatase increased; Blood bilirubin increased; Ejection fraction decreased; Neutrophil count decreased; Alopecia; Palmar-plantar erythrodysesthesia syndrome
   - Rare but Serious: Electrocardiogram QT corrected interval prolonged

   Increase in Risk Attribution:
   - Changed from Less Likely to Likely: Diarrhea; Dry mouth; Mucositis oral; Alanine aminotransferase increased; Aspartate aminotransferase increased; Metabolism and nutrition disorders – Other (hyperphosphatemia)

   Removal of Risks: Eye disorders - Other (chorioretinopathy)
   The adverse events also reported on AZD4547 for which there is insufficient evident to suggest that there was a reasonable possibility that AZD4547 caused the adverse event have been replaced: Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Retinal detachment; Dyspepsia; Dysphagia; Hemorrhoids; Oral pain; Edema limbs; Fever; Malaise; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice); Paronychia; Sepsis; Upper respiratory infection; Urinary tract infection; Cardiac troponin T increased; GGT increased; Investigations - Other (increase in LVEF); Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Back pain; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity; Lethargy; Peripheral sensory neuropathy; Insomnia; Acute kidney injury; Dyspnea; Epistaxis; Nasal congestion; Pleural effusion; Pleuritic pain; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal); Rash maculo-papular; Hypotension

5. **Page 272, Section 5.0, Eligibility Criteria:** A sentence has been added at the end of the instructions providing contact information for eligibility questions.

6. **Page 273, Section 5.2k, Clinical laboratory Criteria:** The following criterion has been added:

   "Patients must have albumin, urinalysis, and Troponin I obtained within 7 days prior to sub-study registration."

   The subsequent sections have been re-numbered accordingly.

7. **Page 273, Section 5.2l, Clinical laboratory Criteria:** A corrected calcium equation has been added.

8. **Page 274, Section 5.3b, Common Eligibility Criteria:** The eligibility criterion related to progression has been revised from "pre RECIST 1.1 (see Section 10.1)" to "(in the opinion of the treating investigator)".

9. **Page 274, Section 5.3c, Common Eligibility Criteria:** The eligibility criterion related to prior therapy has been revised as follows:

    - The third sentence has been replaced with: “Patients must not have received any radiation therapy within 14 days prior to sub-study registration.”
    - The last sentence has been removed
    - A reference to CNS metastases criteria has been added

10. **Page 275, Section 5.3e, Common Eligibility Criteria:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

11. **Page 278, Section 5.4d, Step 2 AZD4547 Re-Registration:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

12. **Page 278, Section 5.4f, Step 2 AZD4547 Re-Registration:** The following criterion has been added:

    “Patients must have albumin, urinalysis, and Troponin I obtained within 7 days prior to sub-study registration.”

    The subsequent sections have been re-numbered accordingly.

13. **Page 278, Section 5.4g, Step 2 AZD4547 Re-Registration:** A corrected calcium equation has been added.

14. **Page 282, Section 7.4a, Criteria for Removal from Protocol Treatment:** A footnote * has been added providing information on new sub-study assignment.

15. **Page 283, Section 7.6, Follow-Up Period:** A note has been added for patients that enroll on a new sub-study following progression.

16. **Page 283, Section 8.2b, General Considerations:** This section has been added to provide information on radiation therapy needed while on study treatment.

17. **Pages 289-291, 294-296, Section 9.1, Arm 1 AZD4547 and Section 9.3, Arm 3 AZD4547 Calendars:** The following items have been updated:

    - Smoking Status Assessment has been added to Off Tx FU After Progression
    - The € footnote has been removed from the Pre-study Laboratory tests
    - Laboratory tests have been added to C1W1 with the € footnote noting if the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated
    - Albumin testing has been added to C1W1, W2, W3, C2W4,C3W7, C4W10, and subsequent cycles because this is needed to calculate the corrected calcium. The footnote ¥ has been removed
    - Laboratory tests have been added to Off Tx Follow-up After Progression with the ɗ footnote noting assessments should continue until resolution of all acute adverse events
    - The footnote ɗ has been added to the laboratory tests performed at Off Tx follow-up Prior to Progression
    - In the β footnote, the Best Practices website has been updated
    - The footnote √, a note has been added for patients that enroll on a new sub-study following progression.
    - The footnote ¥ has been revised to reflect a single test
    - The footnote € has been revised for clarification.
    - The footnote ð has been added to the blood for banking noting the off treatment after progression must be collected at first progression after study treatment

19. **Page 299, Section 14.4d, Data Submission Overview:** A pre-treatment laboratory form has been added for cycle 1 only.

20. **Page 299, Section 14.4g, Data Submission Overview:** A note has been added for patients that enroll on a new sub-study following progression.

21. **Page 301, Section 14.4j, Data Submission Overview:** A new section has been added for the request for new sub-study assignment.

22. **Page 301, Section 15.2a.1, Peripheral Blood:** “at the time of progression on current treatment or” has been added to the note of the first bullet.

S1400I

1. **Page 363, Title Page:** The Bristol Myers Squibb Protocol number has been added. Dr. Joseph Unger and Dr. Susan S. Tavernier has have been added to the title page.

2. **Page 365, Cancer Trials Support Unit (CTSU) Address and Contact Information:** The email address for treatment or toxicity related questions has been updated.

3. **Page 367, Section 1.3b, Translational Medicine Objectives:** An objective has been added for the patient reported outcomes (PROs).

4. **Pages 380 and 389, Section 3.1i.1 and 3.2g.1, Drug ordering:** Two sentences have been added informing sites that drug supplies will be provided once a patient has been randomized and starter supplies will not be provided.

5. **Page 391, Section 5.0, Eligibility Criteria:** A sentence has been added at the end of the instructions providing contact information for eligibility questions.

6. **Page 392, Section 5.2g, Clinical Laboratory Criteria:** An eligibility criterion related to laboratory tests that are required prior to sub-study registration has been added.

7. **Page 392, Section 5.2h, Clinical Laboratory Criteria:** An eligibility criterion related to the patient reported outcomes has been added.

8. **Page 392, Section 5.3b, Common Eligibility Criteria:** The eligibility criterion related to progression has been revised from “pre RECIST 1.1 (see Section 10.1)” to “(in the opinion of the treating investigator)”.

9. **Page 393, Section 5.3c, Common Eligibility Criteria:** The eligibility criterion related to prior therapy has been revised as follows:

    - The third sentence has been replaced with: “Patients must not have received any radiation therapy within 14 days prior to sub-study registration.”
    - The last sentence has been removed
    - A reference to CNS metastases criteria has been added

10. **Page 393, Section 5.3e, Common Eligibility Criteria:** The eligibility criterion related to CT/MRI scans has been revised as follows:
    - “and prior to registration” has been added to the second sentence
    - “1 day” has been revised to “24 hours”

11. **Page 396, Section 7.1, Pre-Medication and Supportive Care:** A statement has been added regarding premedication for the use of prophylaxis for infusion reactions at the end of the first paragraph. The second paragraph has been moved below the third paragraph for a better flow.

12. **Page 397, Section 7.2a, Arm1: Nivolumab plus Ipilimumab:** “q” has been added to the cycle schedule of ipilimumab for clarification. Statements have been added to clarify the order of administration and the delay between dosing. A paragraph has been added to provide information on dose recalculations based on weight.

13. **Page 397, Section 7.2b, Arm 2:** Nivolumab: A paragraph has been added to provide information on dose recalculations based on weight.

14. **Page 397, Section 7.3a, Criteria for Removal from Protocol Treatment:** The last sentence has been replaced with “Patients should still be removed from protocol treatment for criteria below.”

15. **Pages 398-402, Sections 8.3 and 8.4, Dose Modifications:** The order of the sections has been switched. Nivolumab/Ipilimumab Arm has been corrected to Arm 1 and Nivolumab Arm has been corrected to Arm 2 to be consistent with Section 7 and Section 9.

16. **Pages 414-415, Section 9.0, Study Calendars:** The following items have been updated:

- Smoking Status Assessment has been added to Off Tx FU After Progression
- The **S1400I** PRO Questionnaires have been added at Pre-study, Wk3, Wk5, Wk7, Wk9, Wk11, Subsequent cycles, Off Tx FU Prior to Prog and Off Tx FU After Prog. The footnote ☺ has been added noting the details of PROs and EQ-5D questionnaires.
- The EQ-5Dhas been added at Pre-study, Wk5, Wk7, Wk9, Subsequent cycles, Off Tx FU Prior to Prog and Off Tx FU After Prog. The footnote ☺ has been added noting the details of PROs and EQ-5D questionnaires.
- The € footnote has been removed from the Pre-study Laboratory tests
- Laboratory tests have been added to C1W1 with the € footnote
- The LDH testing has been removed from Wk3, Wk5, Wk7, Wk9, Wk11, and Subsequent cycles
- Laboratory tests have been added to Off Tx Follow-up After Progression with the ɗ footnote noting assessments should continue until resolution of all acute adverse events
- The footnote ɗ has been added to the laboratory tests performed at Off Tx follow-up Prior to Progression
- In the footnote π, "until disease progression" has been replaced with "while on treatment"
- The footnote € has been revised for clarification.
- The footnote ɯ has been added to Ipilimumab noting the treatment administration of subsequent cycles
- The footnote ð has been added to the blood for banking noting the off treatment after progression sample must be collected at first progression after study treatment

17. **Page 416, Section 10.0, Criteria for Evaluation and Endpoint Analysis:** A statement has been added for the evaluation and endpoint analysis of PROs.

18. **Page 418, Section 11.5, Translational Medicine:** This section has been added to reference the location of the statistical considerations for PROs.

19. **Page 420, Section 14.4c, Data Submission Overview:** This section has been inserted to provide information on forms to be submitted for patients participating in the PROs. The subsequent sections have been re-numbered accordingly.

20. **Page 420, Section 14.4d, Data Submission Overview:** This section has been inserted to provide information on forms to be submitted for patients participating in the PROs – EQ-5D Questionnaire.

21. **Page 420, Section 14.4e, Data Submission Overview:** A pre-treatment laboratory form has been added for cycle 1 only.

22. **Page 422, Section 15.2a.1, Peripheral Blood:** "at the time of progression on current treatment or" has been added to the note of the first bullet.

23. **Page 424, Section 15.5, S1400I PRO Questionnaire Administration Instructions:** This section has been added.

24. **Pages 433 and 435, Section 18.1, Translational Medicine – PD-L1 IHC Testing:** "Lab# 167" has been added to the contact information for Dr. Hirsch's lab.

25. **Pages 437-450, Section 18.2, Translational Medicine – S1400I Patient Reported Outcomes (PRO):** This section has been added.

Model Consent Forms Changes

The following section refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. **Pages 12 [S1400], 27 [S1400PS], 42 [S1400A], 56 [S1400B], 70 [S1400C], 84 [S1400D], 114 [S1400I], "What are the possible risks?":** The duplicated sentence, "There are laws against misuse of genetic information, but they may not give full protection." has been removed.

3. **Page 16 [S1400PS], Title Page:** "first-line" has been replaced with "current" in the title.

4. **Page 36 [S1400A], "What extra tests and procedures…":** "for the first year, then every 3 months" has been added to the first sentence of the first paragraph.

5. **Pages 37-40 [S1400A], "What possible risks…":** The following changes have been made to the MEDI4736 side effects information:
   Decreased in attribution from Common, some may be Serious (Likely) to Occasional, some may be Serious (Less-Likely):
   - Nausea
   - Tiredness

   Removed from Occasional, some may be Serious (Less-Likely):
   - Anemia which may require blood transfusions
   - Constipation, belly pain
   - Pain or burning during urination, frequent urination
   - Severe loss of body water
   - Dizziness
   - Headaches
   - Shortness of breath, wheezing
   - Cough
   - Chest pain, joint pain, back pain, muscle pain
   - Fever
   - Chills
   - Swelling of arms, legs, or face

   Added to Occasional, some may be Serious (Less-Likely):
   - Cavities, tooth decay

   Removed from Rare, and Serious (Rare, but Serious):
   - Severe blood infection
   - Numbness and tingling in arms and legs
   - Infection of the lungs, may cause cough, fever, shortness of breath

6. **Page 49 [S1400B], 63 [S1400C], 77 [S1400D], "How long will I be in this study?":** A paragraph has been added to inform patients of the option to screen for another sub-study after progression on the current sub-study.

7. **Page 51 [S1400B], "What possible risks…":** The following changes have been made to the GDC-0032 side effects information:
   Added to Occasional, some may be Serious (Less-Likely):
   - Heartburn
   - Changes in taste
   - Dry mouth, skin
   - Pain
   - Itching rash

   Added to Rare and Serious (Rare, but Serious):
   - Swelling of the lungs which may cause shortness of breath

   Decreased in Risk Attribution:
   - Vomiting

   Removed from Common, some may be Serious (Likely):

- High blood sugar

Removed from Occasional, some may be Serious (Less-Likely):

- Fever
- Dizziness
- Cough

Removed from Rare, and Serious (Rare, but Serious):

- Anemia which may require blood transfusions
- Congestive heart failure
- Watery diarrhea
- Dizziness, shortness of breath, mental confusion due to lack of oxygen in body
- Infection, especially when white blood cell count is low
- Oral pain
- Pain or burning during urination, frequent urination
- Belly pain
- Numbness and tingling in arms and legs
- Kidney damage, kidney failure
- Infection of the lungs, may cause cough, fever, shortness of breath
- Itching skin rash

8. **Page 65 [S1400C], "What possible risks…":** The following changes have been made to the palbociclib side effects information:

Increase in Risk Attribution:

- **Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Headache; Dry skin**
- **Changed to Rare and Serious from Reported but With Insufficient Evidence for Attribution: Blood clot which may cause swelling, pain, shortness of breath**

Decrease in Risk Attribution:

- Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Pain in joints; Blurred vision; Swelling of arms, legs; Passing gas; Numbness, tingling or pain of the arms and legs; Muscle weakness

Provided Further Clarification:

- **Shortness of breath (previously under Occasional) is now listed as a symptom of Blood clot which may cause swelling, pain, shortness of breath (under Rare and Serious).**

9. **Page 69 [S1400C], "What is involved?":** "If you are on the palbociclib arm," has been removed from the second bullet. "Rarely, patients may experience partial lung collapse that may require a chest tube or even a breathing machine. The samples will be kept until they are used up." has been added to the end of the fourth bullet.

10. **Page 78 [S1400D], "What extra tests and procedures…":** "blood tests to check" has been added to the fifth bullet.

11. **Pages 79-80 [S1400D], "What possible risks…":** Patients currently receiving AZD4547 and patients who sign a consent form prior to local implementation of the consent form changes must be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart. The following changes have been made to the AZD4547 side effects information:

Increased in attribution from Occasional, some may be serious (Less-Likely) to Common, some may be serious (Likely):

- Dry mouth
- Visual changes (updated from "Visual loss")
- Diarrhea

- Sores in mouth which may cause difficulty swallowing

Added to Common, some may be serious (Likely):

- Constipation, vomiting
- Tiredness
- Loss of appetite

Added to Occasional, some may be serious (Less-Likely):

- Anemia which may require blood transfusion
- Belly pain
- Nausea
- **Change in heart function**
- Hair loss
- Redness, pain or peeling of palms and soles

Added to Rare, and serious

- **Change in the heart rhythm**

Removed from Occasional some may be Serious (Less-Likely):

- Swelling on the inside of the eye

12. **Page 105 [S1400I], "What extra tests and procedures…":** The "before you begin the study" has been updated as follows:
    - EKG procedure has been removed
    - Questionnaires have been added

13. **Page 106 [S1400I], "What extra tests and procedures…":** The "during the study" has been updated as follows:
    - Questionnaires have been added
    - "on Day 1 of each cycle" has been updated to "every 6 weeks" in the first sentence of the first paragraph
    - A paragraph has been added to inform patients of the details of the questionnaires

Due to the extensive repagination, an entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of S1400. This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Genentech, Inc.
Pfizer, Inc.
AstraZeneca
Bristol Myers Squib
Foundation Medicine Inc.
TRIAD
Nationwide

Informed Consent Addendum Model for S1400D

S1400, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer"

S1400D, "A Phase II Study of AZD4547 for Previously Treated FGFR-Positive Patients with Stage IV Squamous Cell Lung Cancer (Lung-MAP Sub-Study)"

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

The purpose of a consent addendum is to:

- *Inform patients of any significant new findings developed during the course of participation that may have a bearing on their willingness to continue in the study.*
- *Inform patients of specific changes (rather than having them sign a modified consent). The addendum will facilitate discussion since the changes/new findings are the focus of the document.*

This consent addendum has been prepared for patients currently registered to S1400D and/or receiving the study drug, AZD4547

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The tables provided below show the most common and the most serious side effects that researchers know about related to AZD4547. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS **In 100 people receiving AZD4547, more than 20 and up to 100 may have:**
• **Visual changes** • **Constipation, diarrhea, vomiting** • **Dry mouth** • **Sores in the mouth which may cause difficulty swallowing** • **Tiredness** • **Loss of appetite**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving AZD4547, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Dry eye, skin** • **Swelling and redness of the eye** • **Belly pain** • **Nausea** • **Change in heart function** • **Changes in taste** • **Hair loss** • **Redness, pain or peeling of palms and soles** • **Change in or loss of some or all of the finger or toenails**

RARE, AND SERIOUS In 100 people receiving AZD4547, 3 or fewer may have:
• **Change in the heart rhythm**

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant's signature_____

Date of signature_____

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter for Study S1400

DATE: **August 2, 2016**

FROM: Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for S1400 Study (A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer – LUNG-MAP) Involving the Following Sub-Studies and Associated Agents:

- ***Sub-Study 1400A:*** *A Phase II Study of MEDI4736 for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarkers* (Agent: MEDI4736; NSC 778709)

- ***Sub-Study 1400B:*** *A Phase II Study of GDC-0032 (taselisib) for Previously Treated PI3K Positive Patients with Stage IV Squamous Cell Lung Cancer* (Agent: GDC-0032; NSC 778795)

- ***Sub-Study 1400C:*** *A Phase II Study of Palbociclib for Previously Treated Cell Cycle Gene Alteration Positive Patients with Stage IV Squamous Cell Lung Cancer* (Agent: PD-0332991, NSC 772256)

- ***Sub-Study 1400D:*** *A Phase II Study of AZD4547 for Previously Treated FGFR-Positive Patients with Stage IV Squamous Cell Lung Cancer* (Agent: AZD4547; NSC 765338)

TO: Principal Investigators and Protocol Coordinators of the CTEP-supported S1400 and Associated Sub-Studies Involving Associated Agents MEDI4736 (NSC 778709), GDC-0032 (NSC 778795), PD-0332991 (NSC 772256), and AZD4547 (NSC 765338)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with MEDI4736, GDC-0032, PD-0332991, and AZD4547.

The SWOG clinical trials Operations Office is receiving this letter because it is conducting the S1400 trial (which includes associated sub-studies) which involves all these agents. After review of all the available data, CTEP believes that the new and/or modified risk information for all these agents does not significantly alter the risk-benefit profile for patients in the S1400 study and its associated sub-studies since these agents are already known to cause serious adverse events and the new/modified risk information does not change the overall weight given to risks versus benefits for patients in S1400 and the associated sub-studies. CTEP considers all the proposed protocol and informed consent changes for S1400 and the associated sub-studies affected by this Action Letter to be minor.

Action Letter for Study S1400

SWOG has prepared an amendment for S1400 and the associated sub-studies to include this new/modified risk information for these agents and other general and administrative information that has been approved by CTEP and the NCI Central Institutional Review Board (NCI CIRB). The CTEP and NCI CIRB-approved amendment is being distributed by SWOG for the S1400 study along with this Action Letter. For S1400 participating sites that use a local Institutional Review Board (IRB) as the IRB of record for the S1400 study, the local IRB will decide whether it can review the CTEP-approved amendment through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 since the amendment includes the new/modified risk information for the agents **as well as** other general and administrative information.

The following sections, *Specific Amendment Instructions*, include background information on the risk(s) and any risk mitigation strategies included in the CTEP-approved amendment for each sub-study (i.e., S1400A, S1400B, S1400C, and S1400D). The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also included for each sub-study.

Action Letter GENERAL INSTRUCTIONS for distribution of the S1400 Action Letter with the CTEP-approved amendment are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3** on the last two pages of this Action Letter.

Action Letter for Study S1400

SPECIFIC AMENDMENT INSTRUCTIONS FOR NEW/MODIFIED RISK INFORMATION – Sub-Study 1400A (MEDI4736; NSC 778709)

Background

As part of Good Clinical Practice, CTEP reviews and generates a CAEPR list for agents on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has generated risk information associated with MEDI4736.

Attachment 1 - S1400 Sub-Study 1400A: MEDI4736 CAEPR – Version 2.0, February 2, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MEDI4736 (NSC 778709)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1432 patients.* Below is the CAEPR for MEDI4736.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.0, February 2, 2016[1]

Adverse Events with Possible Relationship to MEDI4736 (CTCAE 4.0 Term) [n= 1432]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
ENDOCRINE DISORDERS			
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Dental caries		
	Diarrhea		
	Nausea		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on MEDI4736 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MEDI4736 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade
EAR AND LABYRINTH DISORDERS - Hearing impaired
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Esophageal perforation; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Infusion related reaction; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic hemorrhage; Hepatobiliary disorders - Other (hepatitis)
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury)
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (liver abscess); Lung infection; Rash pustular; Urinary tract infection
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; GGT increased; Investigations - Other (electrocardiogram T wave inversion); Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS- Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (axonal neuropathy); Paresthesia; Seizure
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Cough; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Skin and subcutaneous tissue disorders - Other (blister); Skin and subcutaneous tissue disorders - Other (dermatitis); Skin hypopigmentation

Note: MEDI4736 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter for Study S1400

Attachment 2 - S1400 Sub-Study 1400A: ICD Section(s) for MEDI4736

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for MEDI4736 in your ICD.

Risk Profile for MEDI4736 (CAEPR Version 2.0, February 2, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- **You may be asked sensitive or private questions which you normally do not discuss**

The MEDI4736 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Action Letter for Study S1400

Please insert this condensed risk profile as the Table of Possible Side Effects for MEDI4736 in your ICD.

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MEDI4736, from 4 to 20 may have:
• Cavities, tooth decay • Diarrhea, nausea, vomiting • Tiredness • Loss of appetite • Itching, rash

Action Letter for Study S1400

SPECIFIC AMENDMENT INSTRUCTIONS FOR NEW/MODIFIED RISK INFORMATION – Sub-Study 1400B (GDC-0032; NSC 778795)

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with GDC-0032.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.1, August 18, 2015): ___
   Page Number(s): ____

- Added New Risk:
  - Less Likely: Abdominal pain; Alanine aminotransferase increased
  - Also Reported on GDC-0032 Trials But With Insufficient Evidence for Attribution: Constipation; Dizziness; Lymphocyte count decreased; Myalgia; Respiratory failure; Sepsis

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Aspartate aminotransferase increased; Dry mouth; Neutrophil count decreased; Pruritus

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Skin and subcutaneous tissue disorders (rash)

- Provided Further Clarification:
  - Footnote #2 has been altered to read: "Rash may include rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, and rash vesicular."

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Anorexia; Fatigue; Nausea; Vomiting

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.1, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.0. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.0), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

Action Letter for Study S1400

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Increase in Risk Attribution:
  - Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Dry mouth

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Itching; Rash

- Provided Further Clarification:
  - Belly pain (under Occasional) is now reported as Pain (under Occasional)

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to GDC-0032 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter for Study S1400

Attachment 1 - S1400 Sub-Study 1400B: Revised GDC 0032 CAEPR – Version 2.1, January 24, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for GDC-0032 (Taselisib, NSC 778795)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 425 patients.* Below is the CAEPR for GDC-0032 (taselisib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, January 24, 2016[1]

Adverse Events with Possible Relationship to GDC-0032 (taselisib) (CTCAE 4.0 Term) [n= 425]			Specific Protocol Exceptions to Expedited Reporting
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis		***Colitis (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		
	Dyspepsia		
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		

Action Letter for Study S1400

Adverse Events with Possible Relationship to GDC-0032 (taselisib) (CTCAE 4.0 Term) [n= 425]			Specific Protocol Exceptions to Expedited Reporting
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders (rash)[2]		***Skin and subcutaneous tissue disorders (rash)[2] (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Rash may include rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, and rash vesicular.

Adverse events reported on GDC-0032 (taselisib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility GDC-0032 (taselisib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
GASTROINTESTINAL DISORDERS - Constipation; Oral pain
INFECTIONS AND INFESTATIONS - Sepsis
INVESTIGATIONS - Cholesterol high; Lymphocyte count decreased; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia
NERVOUS SYSTEM DISORDERS - Dizziness; Peripheral sensory neuropathy
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Respiratory failure

Note: GDC-0032 (taselisib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter for Study S1400

Attachment 2 - S1400 Sub-Study 1400B: Revised ICD section(s) for GDC-0032

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for GDC 0032 in your ICD.

Risk Profile for GDC-0032 (CAEPR Version 2.1, January 24, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- **You may be asked sensitive or private questions which you normally do not discuss**

The GDC-0032 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Action Letter for Study S1400

Please insert this condensed risk profile as the Table of Possible Side Effects for GDC-0032 in your ICD.

COMMON, SOME MAY BE SERIOUS In 100 people receiving GDC-0032, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving GDC-0032, from 4 to 20 may have:
• Pain • Dry mouth, skin • Heartburn, vomiting • Sores in mouth which may cause difficulty swallowing • Changes in taste • Itching, rash

RARE, AND SERIOUS In 100 people receiving GDC-0032, 3 or fewer may have:
• Swelling of the lungs which may cause shortness of breath

Action Letter for Study S1400

SPECIFIC AMENDMENT INSTRUCTIONS FOR NEW/MODIFIED RISK INFORMATION – Sub-Study S1400C (PD-0332991; NSC 772256)

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with palbociclib.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

4) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

Protocol Cover Page: Page Number(s): _____
Version Date: _____

5) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, April 1, 2016): ___
Page Number(s): ____

- Added New Risk:
  - Reported but With Insufficient Evidence for Attribution: Ascites; Bone marrow hypocellular; Cataract; Eye disorders - Other (retinal hemorrhage); Gastrointestinal disorders - Other (large intestine perforation); Hepatic failure; Hypoxia; Intra-abdominal hemorrhage; Intracranial hemorrhage; Investigations - Other (pancytopenia); Localized edema; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Pericarditis; Pneumonitis; Pulmonary edema; Pulmonary hypertension; Small intestinal perforation; Syncope

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Infection
  - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Dry skin; Headache
  - Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: Thromboembolic event

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Lymphocyte count decreased
  - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Arthralgia; Blurred vision; Dyspnea; Edema limbs; Flatulence; Hyperglycemia; Nervous system disorders - Other (peripheral neuropathy)

- Provided Further Clarification:
  - Footnote #3, "Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fuvestrant," has been added.
  - Footnote number #4 has been altered to read, "Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, dermatitis, and palmar-plantar erythrodysesthesia syndrome."

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Alopecia; Mucositis oral
- Deleted Risk:
  - Reported but With Insufficient Evidence for Attribution: Respiratory, thoracic and mediastinal disorders - Other (alveolitis allergic)

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

6) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Increase in Risk Attribution:
  - Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Headache; Dry skin
  - Changed to Rare and Serious from Reported but With Insufficient Evidence for Attribution: Blood clot which may cause swelling, pain, shortness of breath

- Decrease in Risk Attribution:
  - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Pain in joints; Blurred vision; Swelling of arms, legs; Passing gas; Numbness, tingling or pain of the arms and legs; Muscle weakness

- Provided Further Clarification:
  - Shortness of breath (previously under Occasional) is now listed as a symptom of Blood clot which may cause swelling, pain, shortness of breath (under Rare and Serious).

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to palbociclib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter for Study S1400

Attachment 1- S1400 Sub-Study 1400C: Revised Palbociclib CAEPR – Version 2.2, April 1, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Palbociclib (PD-0332991, NSC 772256)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 759 patients.* Below is the CAEPR for Palbociclib (PD-0332991).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, April 1, 2016[1]

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 4.0 Term) [n= 759]			**Specific Protocol Exceptions to Expedited**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
EYE DISORDERS			
	Dry eye		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Action Letter for Study S1400

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 4.0 Term) [n= 759]			Specific Protocol Exceptions to Expedited
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[4]		
VASCULAR DISORDERS			
		Thromboembolic event	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fuvestrant.

[4]Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, dermatitis, and palmar-plantar erythrodysesthesia syndrome.

[5]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on Palbociclib (PD-0332991) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Palbociclib (PD-0332991) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (retinal hemorrhage)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (large intestine perforation); Gastrointestinal disorders - Other (oropharyngeal pain); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Investigations - Other (pancytopenia); Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Musculoskeletal and connective tissue disorder - Other (osteonecrosis); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysphasia; Intracranial hemorrhage; Nervous system disorders - Other (peripheral neuropathy)[5]; Syncope
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Palbociclib (PD-0332991) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter for Study S1400

Attachment 2 - S1400 Sub-Study 1400C: Revised ICD Section(s) for Palbociclib

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in theICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for palbociclib in your ICD.

Risk Profile for Palbociclib (CAEPR Version 2.2, April 1, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- **You may be asked sensitive or private questions which you normally do not discuss**

The palbociclib used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Action Letter for Study S1400

Please insert this condensed risk profile as the Table of Possible Side Effects for palbociclib in your ICD.

COMMON, SOME MAY BE SERIOUS In 100 people receiving palbociclib, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Nausea • Tiredness • Infection, especially when white blood cell count is low • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving palbociclib, from 4 to 20 may have:
• Dry eye, skin • Watering eyes • Constipation, diarrhea, vomiting • Sores the in mouth which may cause difficulty swallowing • Fever • Loss of appetite • Changes in taste • Headache • Nose bleed • Hair loss, rash

RARE, AND SERIOUS In 100 people receiving palbociclib, 3 or fewer may have:
• Blood clot which may cause swelling, pain, shortness of breath

Action Letter for Study S1400

SPECIFIC AMENDMENT INSTRUCTIONS FOR NEW/MODIFIED RISK INFORMATION – Sub-Study S1400D (AZD4547; NSC 765338)

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with AZD4547.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.0, March 25, 2015): ___
   Page Number(s): ____

- Added New Risk(s):
  - Likely: Eye disorders - Other (retinal pigment epithelium detachment)[2] - with corresponding footnote 2 stating that "Retinal Pigment Epithelium Detachment (RPED) is characterized as RPED, detachment of macular retinal pigment epithelium, subretinal fluid, serous retinal detachment."
  - Less Likely: retinopathy; abdominal pain; alopecia; palmar-plantar erythrodysesthesia syndrome
  - Rare but Serious: Electrocardiogram QT corrected interval prolonged
  - **Reported but With Insufficient Evidence for Attribution: Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Dyspepsia; Dysphasia; Hemorrhoids; Oral pain; edema limbs; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice); Paronychia; Upper respiratory infection; Urinary tract infection; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypophosphatemia; Back pain; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity; Lethargy; Peripheral sensory neuropathy; Insomnia; Nasal congestion; Pleuritic pain; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal); Rash maculo-papular; Hypotension**

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: diarrhea; dry mouth; mucositis oral; alanine aminotransferase increased; aspartate aminotransferase increased; metabolishm and butrition distorders – Other hyperphosphatemia
  - Changed to Likely from Reported but With Insufficient Evidence for Attribution: constipation; vomiting; fatigue; anorexia
  - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: anemia; nausea; alkaline phosphatase increased; blood bilirubin increased; ejection fraction decreased; neutrophil count decreased;

- Reported but With Insufficient Evidence for Attribution:
  - **EYE DISORDERS - Retinal detachment**

- Deleted Risk(s):
  - Eye disorders – Other (chorioretinopathy) (which was been replaced by retinopathy under Less Likely)
  - Retinal detachment (which was been moved to "Reported but With Insufficient Evidence for Attribution" as noted above)

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirement(s):
  - Added: Anemia; Eye disorders – Other (retinal pigment epithelium detachment); Abdominal pain; Constipation; Dry Mouth; Mucositis oral; Vomiting; Fatigue; Aspartate aminotransferase increased; Creatinine increased; Anorexia; Metabolism and nutrition – Other (hyperphosphatemia); Dysgeusia; Alopecia; Dry skin; Skin and subcutaneous tissue disorders – Other (nail disorders)

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.0. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

- **Increase in Risk Attribution:**
  - **Changed to Common from Occasional: Dry mouth; Diarrhea; Sores in the mouth which may cause difficulty swallowing**
  - **Changed to Common from Reported but With Insufficient Evidence for Attribution: Constipation; Vomiting; Tiredness; Loss of Appetite**
  - **Added to Occasional as New Risk: Belly pain**
  - **Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Nausea; Change in heart function; Hair loss; Redness, pain or peeling of palms and soles**
  - **Changed to Rare and Serious as New Risk: Change in the heart rhythm**

- **Provided Further Clarification:**
  - **Since the risk of retinal pigment epithelium detachment (RPED) results in symptoms of visual changes (and the risk of retinal detachment has been moved to "Reported but With Insufficient Evidence for Attribution"), Visual loss has been changed to Visual changes under Common**
  - **Swelling on the inside of the eye deleted under Occasional as it is covered by Swelling and redness of the eye under Occasional**

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to AZD4547 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter for Study S1400

Attachment 1 - S1400 Sub-Study 1400D: Revised AZD4547 CAEPR – Version 2.2, May 24, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for AZD4547 (NSC 765338)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 168 patients.* Below is the CAEPR for AZD4547.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, May 24, 2016 [1]

Adverse Events with Possible Relationship to AZD4547 (CTCAE 4.0 Term) [n= 168]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
EYE DISORDERS			
	Dry eye		
	Keratitis		
Eye disorders - Other (retinal pigment epithelium detachment)[2]			***Eye disorders - Other (retinal pigment epithelium detachment)[2]***
	Retinopathy		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
Dry mouth			***Dry mouth (Gr 2)***
Mucositis oral			***Mucositis oral (Gr 2)***
	Nausea		
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	Ejection fraction decreased		
		Electrocardiogram QT corrected interval prolonged	

Action Letter for Study S1400

Adverse Events with Possible Relationship to AZD4547 (CTCAE 4.0 Term) [n= 168]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Metabolism and nutrition disorders - Other (hyperphosphatemia)			***Metabolism and nutrition disorders - Other (hyperphosphatemia) (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Skin and subcutaneous tissue disorders - Other (nail disorders)[3]		***Skin and subcutaneous tissue disorders - Other (nail disorders)[3] (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Retinal Pigment Epithelium Detachment (RPED) is characterized as RPED, detachment of macular retinal pigment epithelium, subretinal fluid, serous retinal detachment.

[3]Nail disorders include nail discoloration, and/or dystrophy.

Adverse events reported on AZD4547 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD4547 caused the adverse event:
CARDIAC DISORDERS - Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EYE DISORDERS - Retinal detachment
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Hemorrhoids; Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Malaise
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice)
INFECTIONS AND INFESTATIONS - Paronychia; Sepsis; Upper respiratory infection; Urinary tract infection
INVESTIGATIONS - Cardiac troponin T increased; GGT increased; Investigations - Other (increase in LVEF)
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Lethargy; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Epistaxis; Nasal congestion; Pleural effusion; Pleuritic pain; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypotension

Action Letter for Study S1400

Note: AZD4547 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Attachment 2 - S1400 Sub-Study 1400D: **Revised ICD Section(s) for AZD4547**

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for AZD4547 in your ICD.

Risk Profile for AZD4547 (CAEPR Version 2.2, May 24, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- **You may be asked sensitive or private questions which you normally do not discuss**

The AZD4547 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Action Letter for Study S1400

Please insert this condensed risk profile as the Table of Possible Side Effects for AZD4547 in your ICD.

COMMON, SOME MAY BE SERIOUS In 100 people receiving AZD4547, more than 20 and up to 100 may have:
• Visual changes • Constipation, diarrhea, vomiting • Dry mouth • Sores in the mouth which may cause difficulty swallowing • Tiredness • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving AZD4547, from 4 to 20 may have:
• Anemia which may require blood transfusion • Dry eye, skin • Swelling and redness of the eye • Belly pain • Nausea • Change in heart function • Changes in taste • Hair loss • Redness, pain or peeling of palms and soles • Change in or loss of some or all of the finger or toenails

RARE, AND SERIOUS In 100 people receiving AZD4547, 3 or fewer may have:
• Change in the heart rhythm

Action Letter for Study S1400

Attachment 3: Action Letter GENERAL INSTRUCTIONS for distribution of the S1400 Action Letter with the CTEP-approved Amendment

1. **Distribute this Action Letter (and the accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** Since S1400 is a National Clinical Trials Network (NCTN) study, please follow instructions from the SWOG Operations office. For sites participating using the NCI Central-IRB (CIRB) as the IRB of record for the S1400 study, CTEP has provided a copy of this Action Letter to the NCI CIRB. The SWOG clinical trial Operations Office may use its own Change Memo to detail the changes made in the CTEP-approved office when it distributes the amendment to sites participating in the S1400 study.

2. **For Institutions/Sites Participating in S1400 Using NCI CIRB as the IRB of Record for S1400**:
   - This CTEP-approved amendment has also been approved by the NCI CIRB. Sites using the NCI CIRB should implement the amendment per the usual procedures for a CTEP Action Letter amendment.

3. **For Institutions/Sites Participating in S1400 Using a Local IRB as the IRB of Record for S1400:**
   - The site's local IRB which reviews the CTEP-approved amendment will decide whether it can review the amendment through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110 since the CTEP approved amendment includes the new/modified risk information for the agents listed on the first page of the Action Letter **as well as** other general and administrative information.

   - **Patients are considered to be "on study" for S1400 with respect to the changes required by the CTEP-approved amendment if they are/were registered to S1400 as of the date SWOG distributes the amendment & Action Letter to S1400 participating sites.** If patients are already enrolled on (or are eventually assigned/registered to) one of the biomarker driven sub-studies affected by this Action Letter (i.e., S1400A, S1400B, S1400C, or S1400D) **prior** to local implementation of the consent forms, the patients should be informed of the new and/or modified risk information for the sub-study. This information should be communicated to these patients already enrolled "on study" without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and, per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to patients already "on study." Documentation of their informed consent should be carried out according to local IRB requirements.

   - **Patients who are not registered to S1400 as of the date SWOG distributes the CTEP-approved amendment & Action Letter to S1400 participating sites are not considered to be "on study" with respect to the changes required by the amendment.** Depending on the extent of the new/modified risk information included in the amendment for a particular sub-study, patients may not be able to be registered to the sub-study until the site's local IRB of record has approved the amendment and sub-study consent form and both have been implemented, as outlined below:

     - **S1400A – Suspension of new patient accrual is not applicable to this sub-study** since it is already permanently closed to new accrual.

Action Letter for Study S1400

- **S1400B – Suspension of new patient accrual is <u>not applicable</u> to this sub-study** with GDC-0032 since the added risks are similar to the risks that were already included in the sub-study protocol and would have already been communicated to patients in the informed consent document: (1) an increase in the frequency of abdominal pain, colitis, pruritus, and alanine aminotransferase resulted in these risks, which were already in the sub-study CAEPR/ICD, being moved from rare to less likely; (2) decreased neutrophil count is very similar to neutropenia which was previously included in the sub-study CAEPR/ICD; (3) increased aspartate aminotransferase is similar to increases in other liver function tests like increased alanine aminotransferase which was already in the sub-study CAEPR/ICD; (4) anorexia is similar to decreased appetite and its consequences which was already in the sub-study CAEPR/ICD; and (5) dry mouth, mucositis oral, and dysgeusia can be associated with other adverse events affecting the oral area such as oral pain, stomatitis, and mucosal inflammation which were previously identified side effects in the CAEPR/ICD.

- **S1400C – Suspension of new patient accrual is <u>required</u> to this sub-study** until the revised Model Consent Form, in association with this CTEP-approved amendment, is approved by the local IRB of record and is implemented.

- **S1400D – Suspension of new patient accrual is <u>required</u> to this sub-study** until the revised Model Consent Form, in association with this CTEP-approved amendment, is approved by the local IRB of record and is implemented.

4. **Save a copy of the Action Letter (and any CTEP approval letter for the accompanying amendment) for your records.**

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August 1, 2016

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swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access this safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jun. 28, 2016 Mfr Rpt #BMS2016049140 Jul. 05, 2016 Mfr Rpt #BMS2016043389 FU Jul. 11, 2016 Mfr Rpt # BMS2016054075

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

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August 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jun. 28, 2016	Mfr Rpt #BMS2016049140
	Jul. 05, 2016	Mfr Rpt #BMS2016043389 FU
	Jul. 11, 2016	Mfr Rpt #BMS2016054075

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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cc: PROTOCOL & INFORMATION OFFICE
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July 15, 2016

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung	Jun. 13, 2016 Mfr Rpt #BMS2016043759

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

July 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
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( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jun. 13, 2016 Mfr Rpt #BMS2016043759
	Jun. 14, 2016 Mfr Rpt #BMS2016043722
	Jun. 17, 2016 Mfr Rpt #BMS2016046657

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	May 10, 2016 Mfr Rpt #BMS2016022351 FU May 19, 2016 Mfr Rpt #BMS2016014349 Jun. 08, 2016 Mfr Rpt #BMS2016003371

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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July 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	May 10, 2016 Mfr Rpt #BMS2016022351 FU May 16, 2016 Mfr Rpt #2016IN002471 May 19, 2016 Mfr Rpt #BMS2016014349 May 25, 2016 Mfr Rpt #2016IN002778

Jun. 08, 2016 Mfr Rpt #BMS2016003371
Jun. 10, 2016 Mfr Rpt #BMS2016042534

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb
May Venturanza – Merck

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June 15, 2016

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1400I Lung	May 24, 2016 Mfr Rpt #AE2478723

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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cc: PROTOCOL & INFORMATION OFFICE
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June 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
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( ) Informed Consent changes
  ( ) Patient notification not required
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MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug nivolumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1400I Lung	Jun. 03, 2016 Mfr Rpt # AE-2069632

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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cc: PROTOCOL & INFORMATION OFFICE
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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
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( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma	Apr. 27, 2016 Mfr Rpt #BMS2016011751 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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June 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Apr. 27, 2016 Mfr Rpt #BMS2016011751 FU
S1404 Melanoma	May 02, 2016 Mfr Rpt #BMS2016031021
	May 03, 2016 Mfr Rpt #BMS2016031561

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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May 15, 2016

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Apr. 13, 2016 AWARE #BMS2016022351

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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May 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 11, 2016	AE-2079770
	Apr. 13, 2016	AWARE #BMS2016022351
	Apr. 14, 2016	AE2364708

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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April 15, 2016

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
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( ) Reactivation

Protocol changes
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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Mar. 16, 2016 AE-2433848 Mar. 18, 2016 Mfr Rpt #BMS2015060871

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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April 15, 2016

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
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( ) Closure
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Protocol changes
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S1400I Lung	Mar. 18, 2016 Mfr Rpt #BMS2015060871 Mar. 30, 2016 AWARE #21409321

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to clarify patient notification and IRB requirements related to **S1400** Revision #4, which was distributed April 1, 2016.

Patient notification requirements for all sites:

Patients currently receiving nivolumab and/or ipilimumab on **S1400I**, and patients who signed an **S1400I** consent form prior to local implementation of the Revision #4 consent form changes, must be informed of the new risk information. This information should be communicated to patients without waiting for IRB review/approval since this represents a significant new finding(s) that developed during the course of the research that may affect a patient's willingness to continue participation and per the Office for Human Research Protections, regulations do not require IRB review before such information is provided to already-enrolled patients. Documentation of a patient's informed consent should be carried out according to local IRB requirements. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

Additional requirements for sites *not* using the CIRB:

Accrual of new patients to S1400I must be suspended until the IRB of record has approved Revision #4 and the revised Model Consent Form has been implemented. The Revision may undergo expedited review if the local IRB agrees that the changes are minor. Suspension of the screening/pre-screening portion of **S1400** is not required.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (LUNG-MAP)". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to notify sites that a new Investigator's Brochure is now available for the following investigational agent.

Sub-Study: **S1400I** Agent: Ipilimmab Version 19 Erratum 01 18Mar2016

SWOG's standard procedures will be followed in updating the drug information sections based on the most recent Investigator's brochure versions. Sites should seek updated Investigator's brochures as required by site's IRB of record.

The Investigator's brochures are available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms. Complete and return to ctsucontact@westat.com.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

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April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that the following forms for the above-noted study have been updated.

S1400 Local Pathology Review Form (500091v1.3)
Note: Please discard old versions of this form and replace with the new version.

S1400
S1400 Onstudy Form (#500014v1.4)

S1400B
S1400B Onstudy Form (#500029v1.5)
S1400B Re-registration Eligibility Verification Form (500149v1.0)

S1400C
S1400C Onstudy Form (#500031v1.6)
S1400C Re-registration Eligibility Verification Form (500152v1.0)

S1400D
S1400D Onstudy Form (#500035v1.6)
S1400D Re-registration Eligibility Verification Form (500155v1.0)

S1400I
S1400I Onstudy Form (#500153v1.0)

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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swog.org

April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 27, 2016 AE-2351578 Jan. 29, 2016 Mfr Rpt #BMS2016000410 Feb. 26, 2016 Mfr Rpt #BMS2016003978 Feb. 26, 2016 Mfr Rpt #BMS2016005818 Mar. 14, 2016 Mfr Rpt # BMS2016006635 Mar. 14, 2016 Mfr Rpt #BMS2016010639 Mar. 14, 2016 Mfr Rpt #BMS2016011704 Mar. 14, 2016 Mfr Rpt #BMS2016003606

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Jieling Miao, M.S.
Louise Highleyman
Kara Amber

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April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 27, 2016 AE-2351578 Jan. 29, 2016 Mfr Rpt #BMS2016000410 Feb. 26, 2016 Mfr Rpt #BMS2016003978 Feb. 26, 2016 Mfr Rpt #BMS2016005818 Mar. 14, 2016 Mfr Rpt # BMS2016006635 Mar. 14, 2016 Mfr Rpt #BMS2016010639 Mar. 14, 2016 Mfr Rpt #BMS2016011704 Mar. 14, 2016 Mfr Rpt #BMS2016003606

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Mary Redman, Ph.D.
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swog.org

Distribution Date: April 1, 2016
E-mail Date: March 18, 2016
CTEP Submission Date: March 3, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

REVISION #4

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial sub-study activation
- ( ) Increased risk to patient
- ( ) Complete sub-study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #4

This revision has been prepared in response to the Request for Rapid Amendments (RRA) for ipilimumab and for BMS-936558 (nivolumab) received on February 18, 2016 from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov). The associated Action Letter is attached.

The above-referenced study has been updated as follows:

1. The Version Date of the protocol and Model Consent Forms have been updated.

2. **Table of Contents**: The page numbers have been updated for the following sections: **S1400** and **S1400I.**

3. **Pages 368-374, Section 3.1d.1, Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC # 748726) (IND-119672):** The nivolumab adverse effects section has been replace with a CTEP modified risk information Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.1, December 11, 2015. The section has been updated as follows:

Added New Risk:

- Less Likely: Hyperthyroidism; Injection site reaction; Lymphocyte count decreased; Platelet count decreased; Skin hypopigmentation
- Rare but Serious: Cardiac disorders - Other (cardiomyopathy); Cytokine release syndrome; Encephalopathy; Eye disorders - Other (Graves ophthalmopathy); Facial nerve disorder; Gastritis; Immune system disorders - Other (sarcoid granuloma); Musculoskeletal and connective tissue disorder - Other (polymyositis); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myocarditis; Nervous system disorders - Other (demyelination myasthenic syndrome); Nervous system disorders - Other (myasthenia gravis); Peripheral sensory neuropathy; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)

- Also Reported but With Insufficient Evidence for Attribution: Alopecia; Anaphylaxis; Atrial fibrillation; Atrioventricular block complete; Bile duct stenosis; Bronchial infection; Bronchospasm; CPK increased; Chills; Duodenal ulcer; Encephalitis infection; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Enterocolitis; Eye disorders - Other (iridocyclitis); Flatulence; Flushing; Gastrointestinal disorders - Other (mouth sores); Heart failure; Hyperhidrosis; Hypertension; Hypocalcemia; Hyponatremia; Hypophosphatemia; Immune system disorders - Other (limbic encephalitis); Malaise; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis); Nervous system disorders - Other (autoimmune neuropathy); Optic nerve disorder; Pain of skin; Pericarditis; Periorbital edema; Photosensitivity; Rash acneiform; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis); Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Skin and subcutaneous tissue disorders - Other (rosacea); Stroke; Toxic epidermal necrolysis; Upper respiratory infection; Vasculitis; Vestibular disorder; Wheezing; White blood cell decreased

Increase in Risk Attribution:

- Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Blood bilirubin increased; Creatinine increased; Lipase increased; Neutrophil count decreased; Serum amylase increased
- Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: Peripheral motor neuropathy

Decrease in Risk Attribution:

- Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Constipation; Cough; Dyspnea; Vomiting

Provided Further Clarification (e.g., changed from ‘arrhythmia’ to ‘ventricular fibrillation’):

- Immune system disorders - Other (Guillain-Barre syndrome) is now reported as Nervous system disorders - Other (Guillain-Barre syndrome)
- Footnote #5 has been modified to read “BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic

failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome."
- The following footnote #6 was added: "Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia"

Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
- Added: Abdominal pain; Alanine aminotransferase increased; Anemia; Aspartate aminotransferase increased; Blood bilirubin increased; Dry mouth; Fever; Hyperglycemia; Injection site reaction; Lymphocyte count decreased; Nausea

4. **Pages 378-379, Section 3.1c.1, Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442) (IND-119672):** The Ipilimumab adverse effects section has been replace with a CTEP modified risk information Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.7, June 28, 2015. The section has been updated as follows:

- Added New Risk:
  - Rare But Serious: Immune system disorders - Other (GVHD in the setting of allotransplant)
  - Also Reported on ipilimumab Trials But With Insufficient Evidence for Attribution: Alopecia

Model Consent Forms Changes

The following section refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. **Pages 106 [S1400I], "What possible risks…":** Patients currently receiving nivolumab **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. The following changes have been made to the nivolumab side effects information:

   - Added New Risk:
     - Occasional: Bruising, bleeding; Skin changes; Swelling and redness at the site of the medication injection
     - Rare, and Serious: Abnormal movement of the facial muscles; Confusion; Muscle pain and/or weakness with dark red urine; Numbness, tingling or pain of the arms and legs; Reaction during or following a drug infusion which may cause fever, chills, rash; Swelling and pain around the eyes which may lead to vision changes and difficulty closing eyes
   - Decrease in Risk Attribution:
     - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Cough; Shortness of breath; Constipation; Vomiting

   - Provided Further Clarification:
     - Damage to the body by own immune system (under Rare) is now reported as Damage to organs which may cause weakness or shortness of breath and/or cough (under Rare)

3. **Pages 107 [S1400I], "What possible risks…":** Patients currently receiving ipilimumab **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. The following changes have been made to the ipilimumab side effects information:

   - Added New Risk:

- Rare: Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin

- Provided Further Clarification:
  - Rash which may cause fever and swollen, red, painful bumps in the skin (previously under Common) is now reported as Rash (under Common) and Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional).

[Note: Sites should seek an updated investigator brochure as required by site's IRB of record. The Investigator's brochure is available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms or by clicking on the study link. Complete and return to ctsucontact@westat.com].

An entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of S1400.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
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Mary Redman, Ph.D.
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Louise Highleyman
Kara Amber
Bristol Myers Squibb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **March 17, 2016**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Ipilimumab (MDX-010, NSCs 732442 and 720801)

TO: Investigators for CTEP-supported Studies Involving Ipilimumab (MDX-010, NSCs 732442 and 720801)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with ipilimumab, and to request all trials with ipilimumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes ipilimumab. See the accompanying list of CTEP trials with ipilimumab.

The RRA dated February 18, 2016 contained "instructional text" which is highlighted below that was for the Investigator/Treating Physician and which was **not** intended to be inserted into the informed consent document since the risks are already part of the condensed risks list. This updated RRA letter now makes this distinction clear. We regret that the instructions were not clear in this regard on the RRA of February 18, 2016 as well as on any previous RRAs for ipilimumab.

CTEP is requesting that this language be removed from the informed consent document. If you have submitted your amendment by close of business (COB) on March 1, 2016, CTEP's Protocol and Information Office (PIO) will remove this language from your amendment for you and return it to you (or your NCTN Group Operations Office) after review by the NCI Central Institutional Review Board. If you have not submitted your amendment by COB on March 1, 2016, CTEP requests that you remove the highlighted language prior to submission. The Action letter will now be sent out on March 17, 2016 instead of on March 10, 2016. If you have any questions about this information, please do not hesitate to contact PIO.

INSTRUCTIONAL TEXT IN PREVIOUS RRA (Dated 2/18/16) THAT SHOULD BE REMOVED:

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS:

Ipilimumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving ipilimumab. In clinical trials, most immune-mediated side effects were reversible and managed by stopping ipilimumab temporarily, administration of corticosteroids and supportive care.

Action Letter

In response to the new/modified risk information CTEP is requiring that all trials with ipilimumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on March 31, 2016** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since ipilimumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice CTEP reviews each Comprehensive Adverse Events and Potential Risks (CAEPR) list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with ipilimumab.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:
   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.7, June 28, 2015): ___
   Page Number(s): ____

   - Added New Risk:
     - Rare But Serious: Immune system disorders - Other (GVHD in the setting of allotransplant)
     - Also Reported on ipilimumab Trials But With Insufficient Evidence for Attribution: Alopecia

   PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.7, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.6. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.6), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as specified below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Rare: Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin

- Provided Further Clarification:
  - Rash which may cause fever and swollen, red, painful bumps in the skin (previously under Common) is now reported as Rash (under Common) and Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional).

Action Letter

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to ipilimumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Ipilimumab CAEPR – Version 2.7, June 28, 2015

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, June 28, 2015[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypopituitarism/hypophysitis)[2]		
	Endocrine disorders - Other (testosterone deficiency)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction		
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (aseptic meningitis)[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
	Facial nerve disorder		
	Headache		
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]		
	Nervous system disorders - Other (myasthenia gravis)[2]		
	Trigeminal nerve disorder		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[5]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC

[6]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia

CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[4]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[5]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[6]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia, Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for Ipilimumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab in your ICD.

Risk Profile for Ipilimumab (CAEPR Version 2.7, June 28, 2015)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The Ipilimumab used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab in your ICD.

HIGHLIGHTED LANGUAGE IS INSTRUCTIONAL TEXT FOR PRINCIPAL INVESTIGATOR—NOT TO BE INCLUDED IN THE INFORMED CONSENT DOCUMENT

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS:

Action Letter

Ipilimumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving ipilimumab. In clinical trials, most immune-mediated side effects were reversible and managed by stopping ipilimumab temporarily, administration of corticosteroids and supportive care.

COMMON, SOME MAY BE SERIOUS In 100 people receiving ipilimumab, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ipilimumab, from 4 to 20 may have:
• Abnormal heartbeat • Hearing loss • Swelling and redness of the eye • Pain • Constipation, vomiting • Swelling of the body which may cause shortness of breath • Difficulty swallowing, eating • Chills, fever • Reaction during or following infusion of the drug • Damage to organs leading to prolonged hospitalization • Loss of appetite, dehydration • Abnormal movement of the facial muscles • Headache • Weakness and paralysis • Kidney damage which may require dialysis • Itching, hives • Rash which may cause fever and swollen, red, painful bumps in the skin • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving ipilimumab, 3 or fewer may have:
• Bleeding • A tear or hole in the stomach that may require surgery • Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin* • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

*This is applicable for patients who have undergone a stem cell transplant.

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **March 17, 2016**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

TO: Investigators for CTEP-supported Studies Involving BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with BMS-936558 (Nivolumab), and to request all trials with BMS-936558 (Nivolumab) be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes BMS-936558 (Nivolumab). See the accompanying list of CTEP trials with BMS-936558 (Nivolumab).

The RRA dated February 18, 2016 contained "instructional text" which is highlighted below that was for the Investigator/Treating Physician and which was **not** intended to be inserted into the informed consent document since the risks are already part of the condensed risks list. This updated RRA letter now makes this distinction clear. We regret that the instructions were not clear in this regard on the RRA of February 18, 2016 as well as on any previous RRAs for BMS-936558 (Nivolumab).

CTEP is requesting that this language be removed from the informed consent document. If you have submitted your amendment by close of business (COB) on March 1, 2016, CTEP's Protocol and Information Office (PIO) will remove this language from your amendment for you and return it to you (or your NCTN Group Operations Office) after review by the NCI Central Institutional Review Board. If you have not submitted your amendment by COB on March 1, 2016, CTEP requests that you remove the highlighted language prior to submission. The Action letter will now be sent out on March 17, 2016 instead of on March 10, 2016. Also please note that you may use either "BMS-936558" or "Nivolumab" in the informed consent document (ICD) and ICD risk tables to refer to the agent depending on how you previously worded your consent. If you have any questions about this information, please do not hesitate to contact PIO.

INSTRUCTIONAL TEXT IN PREVIOUS RRA (Dated 2/18/16) THAT SHOULD BE REMOVED:

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS

BMS-936558 is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving BMS-936558. In clinical trials, most immune-mediated side effects were reversible and managed by stopping BMS-936558 temporarily, administration of corticosteroids and supportive care.

Action Letter

In response to the new/modified risk information CTEP is requiring that all trials with BMS-936558 (Nivolumab) be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on March 31, 2016** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since BMS-936558 (Nivolumab) is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice CTEP reviews each Comprehensive Adverse Events and Potential Risks (CAEPR) list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with BMS-936558.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:
   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.1, December 11, 2015): ___
   Page Number(s): ____

- Added New Risk:
  - Less Likely: Hyperthyroidism; Injection site reaction; Lymphocyte count decreased; Platelet count decreased; Skin hypopigmentation
  - Rare but Serious: Cardiac disorders - Other (cardiomyopathy); Cytokine release syndrome; Encephalopathy; Eye disorders - Other (Graves ophthalmopathy); Facial nerve disorder; Gastritis; Immune system disorders - Other (sarcoid granuloma); Musculoskeletal and connective tissue disorder - Other (polymyositis); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myocarditis; Nervous system disorders - Other (demyelination myasthenic syndrome); Nervous system disorders - Other (myasthenia gravis); Peripheral sensory neuropathy; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)
  - Also Reported but With Insufficient Evidence for Attribution: Alopecia; Anaphylaxis; Atrial fibrillation; Atrioventricular block complete; Bile duct stenosis; Bronchial infection; Bronchospasm; CPK increased; Chills; Duodenal ulcer; Encephalitis infection; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Enterocolitis; Eye disorders - Other (iridocyclitis); Flatulence; Flushing; Gastrointestinal disorders - Other (mouth sores); Heart failure; Hyperhidrosis; Hypertension; Hypocalcemia; Hyponatremia; Hypophosphatemia; Immune system disorders - Other (limbic encephalitis); Malaise; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis); Nervous system disorders - Other (autoimmune neuropathy); Optic nerve disorder; Pain of skin; Pericarditis; Periorbital edema; Photosensitivity; Rash acneiform; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis); Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Skin and subcutaneous tissue disorders - Other (rosacea); Stroke; Toxic epidermal necrolysis; Upper respiratory infection; Vasculitis; Vestibular disorder; Wheezing; White blood cell decreased

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Blood bilirubin increased; Creatinine increased; Lipase increased; Neutrophil count decreased; Serum amylase increased
  - Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: Peripheral motor neuropathy

- Decrease in Risk Attribution:
  - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Constipation; Cough; Dyspnea; Vomiting

- Provided Further Clarification (e.g., changed from 'arrhythmia' to 'ventricular fibrillation'):
  - Immune system disorders - Other (Guillain-Barre syndrome) is now reported as Nervous system disorders - Other (Guillain-Barre syndrome)
  - Footnote #5 has been modified to read "BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome."
  - The following footnote #6 was added: "Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia"

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Abdominal pain; Alanine aminotransferase increased; Anemia; Aspartate aminotransferase increased; Blood bilirubin increased; Dry mouth; Fever; Hyperglycemia; Injection site reaction; Lymphocyte count decreased; Nausea

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.1, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.0. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.0), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as specified below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

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- Added New Risk:
  - Occasional: Bruising, bleeding; Skin changes; Swelling and redness at the site of the medication injection
  - Rare, and Serious: Abnormal movement of the facial muscles; Confusion; Muscle pain and/or weakness with dark red urine; Numbness, tingling or pain of the arms and legs; Reaction during or following a drug infusion which may cause fever, chills, rash; Swelling and pain around the eyes which may lead to vision changes and difficulty closing eyes

- Decrease in Risk Attribution:
  - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Cough; Shortness of breath; Constipation; Vomiting

- Provided Further Clarification:
  - Damage to the body by own immune system (under Rare) is now reported as Damage to organs which may cause weakness or shortness of breath and/or cough (under Rare)

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to BMS-936558 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised BMS-936558 CAEPR – Version 2.1, December 11, 2015

Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, December 11, 2015[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency		
	Endocrine disorders - Other (hypophysitis)		
	Hyperthyroidism		
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders - Other (diplopia)	
		Eye disorders - Other (Graves ophthalmopathy)	
		Eye disorders - Other (optic neuritis retrobulbar)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		
		Colonic perforation	
	Diarrhea		***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***

Action Letter

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Gastritis	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[3]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Infusion related reaction[4]	
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Autoimmune disorder[5]	
		Cytokine release syndrome[6]	
		Immune system disorders - Other (sarcoid granuloma)[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy	
		Facial nerve disorder[5]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (Guillain-Barre syndrome)[5]	

Action Letter

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)	
		Nervous system disorders - Other (myasthenia gravis)[5]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion		
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[4]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

[5]BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[6]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and

pancytopenia.

Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Pericarditis; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism)
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Enterocolitis; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis; Hepatobiliary disorders - Other (autoimmune hepatitis)
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Encephalitis infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Alkaline phosphatase increased; CPK increased; GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (CRP increased); Investigations - Other (eosinophil count increased); Investigations - Other (protein total decreased); Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine free decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage; Nervous system disorders - Other (autoimmune neuropathy); Stroke
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for BMS-936558

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for BMS-936558 in your ICD.

Risk Profile for BMS-936558 (CAEPR Version 2.1, December 11, 2015)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The BMS-936558 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for BMS-936558 in your ICD.

HIGHLIGHTED LANGUAGE IS INSTRUCTIONAL TEXT FOR PRINCIPAL INVESTIGATOR—NOT TO BE INCLUDED IN THE INFORMED CONSENT DOCUMENT

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS:

Action Letter

BMS-936558 is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving BMS-936558. In clinical trials, most immune-mediated side effects were reversible and managed by stopping BMS-936558 temporarily, administration of corticosteroids and supportive care.

COMMON, SOME MAY BE SERIOUS In 100 people receiving BMS-936558, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BMS-936558, from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye which may cause blurred vision with a chance of blindness • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Loss of appetite • Fluid in the body • Swelling of the body which may cause shortness of breath or headache, tiredness, and nerve pain • Itching, rash, skin changes

RARE, AND SERIOUS In 100 people receiving BMS-936558, 3 or fewer may have:
• Damage to organs which may cause weakness or shortness of breath and/or cough • Visual disturbances • Swelling and pain around the eyes which may lead to vision changes and difficulty closing eyes • A tear or hole in the stomach that may require surgery • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma • Muscle pain and/or weakness with dark red urine • Confusion • Abnormal movement of the facial muscles • Weakness and paralysis • Muscle weakness • Numbness, tingling or pain of the arms and legs • Kidney damage which may require dialysis

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

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swog.org

March 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (LUNG-MAP)". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to notify sites that a new Investigator's Brochure is now available for the following investigational agent.

Sub-Study: **S1400I** Agent: Ipilimumab Version 19 02Mar2016

SWOG's standard procedures will be followed in updating the drug information sections based on the most recent Investigator's brochure versions. Sites should seek updated Investigator's brochures as required by site's IRB of record.

The Investigator's brochures are available through the CTSU website. Complete the CTSU Request for Clinical Brochure form located under LPO Documents – Pharmacy Forms. Complete and return to ctsucontact@westat.com.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Monica Yee, B.A.
Louise Highleyman
Kara Amber
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S.
Jieling Miao, M.S.
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

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February 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 21, 2016 Mfr Rpt #BMS2015000505 Jan. 21, 2016 Mfr Rpt #BMS2015092636 Jan. 21, 2016 Mfr Rpt #BMS2015092954

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S
Scott Gettinger, M.D.
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February 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 21, 2016 Mfr Rpt #BMS2015000505 Jan. 21, 2016 Mfr Rpt #BMS2015092636 Jan. 21, 2016 Mfr Rpt #BMS2015092954

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S.
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February 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 15, 2016 Mfr Rpt #BMS2015036876 Jan. 15, 2016 Mfr Rpt # BMS2015088798

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

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February 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jan. 12, 2016	Mfr Rpt #BMS2015080781
	Jan. 12, 2016	Mfr Rpt #BMS2015087836
	Jan. 15, 2016	Mfr Rpt #BMS2015036876
	Jan. 15, 2016	Mfr Rpt #BMS2015088798

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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January 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

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( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Dec. 18, 2015 Mfr Rpt #BMS2015064996 Dec. 18, 2015 Mfr Rpt #BMS2015078346 Dec 18, 2015 Mfr Rpt #BMS2015054840 Dec 18, 2015 Mfr Rpt #BMS2015082700 Dec. 22, 2015 Mfr Rpt #2009520 Dec. 31, 2015 Mfr Rpt #2054219

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Mary Redman, Ph.D.
James Moon, M.S.
Shannon McDonough, M.S
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Jieling Miao, M.S.
Louise Highleyman
Kara Amber

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swog.org

January 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Dec. 18, 2015 Mfr Rpt #BMS2015064996 Dec. 18, 2015 Mfr Rpt #BMS2015078346 Dec 18, 2015 Mfr Rpt #BMS2015054840 Dec 18, 2015 Mfr Rpt #BMS2015082700 Dec. 31, 2015 Mfr Rpt #2054219

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

Distribution Date: January 1, 2016
E-mailed Date: December 18, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

MEMORANDUM

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial sub-study activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

S1400I ACTIVATION

Effective 2:00 p.m. Pacific Time on December 18, 2015, the following sub-study will be open for patient accrual.

S1400I: A Phase III Randomized Study of Nivolumab plus Ipilimumab versus Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarker (LUNG-MAP SUB-STUDY)

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

Hossein Borghaei, D.O.	Mary Redman, Ph.D.	Genentech, Inc.
Jeffrey A. Engelman, M.D., Ph.D.	James Moon, M.S.	Pfizer, Inc.
	Shannon McDonough, M.S.	AstraZeneca
Corey J. Langer, M.D.	Monica Yee, B.A.	Bristol Myers Squib
Martin J. Edelman, M.D.	Louise Highleyman	Foundation Medicine Inc.
Charu Aggarwal, M.D., M.P.H.	Kara Amber	Clarient, Inc.
Mark A. Socinski, M.D.	MedImmune, LLC.	

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Distribution Date: January 1, 2015
E-mail Date: December 18, 2015
CTEP Submission Date: November 18, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Crystal Miwa, Protocol Coordinator (E-mail: cmiwa@swog.org)

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

REVISION #3

Study Chair: Vassiliki A. Papadimitrakopoulou, M.D.
Phone number: 713/792-6363
E-mail: vpapadim@mdanderson.org

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial sub-study activation
- ( ) Increased risk to patient
- (√) Complete sub-study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

PARTIAL PERMANENT CLOSURE (S1400B, S1400C, and S1400D, Arm 2-Docetaxel)

SHOW STOPPER REVISION #3

CLOSURE (S1400A)

ACTIVATION (S1400I)

Partial Permanent Closure (S1400B, S1400C, S1400D, Arm 2-Docetaxel):
Partial Permanent Closure (**S1400B, S1400C, S1400D**, Arm 2-Docetaxel): **S1400B, S1400C, S1400D**, Arm 2 - Docetaxel will be permanently closed to accrual from distribution of this notice.

SWOG considers the Protocol and Model Consent Forms changes to represent a major modification to **S1400**. Therefore, accrual of new patients will be suspended to **S1400 and the sub-studies** at the time of this notice until the revised Model Consent Forms, in association with this revision, as approved by the site's IRB of record, **are implemented**, and proof of that IRB approval is received by CTSU. For sites using the CIRB as their IRB of record, the date of CIRB approval was received on 11/22/2015.

All Sites Must Complete the NEW Protocol Specific Training (PSR) - A member must have reviewed the Updated S1400 Lung-MAP Training Slides presentation prior to registering patients under this revision. The updated slides review the new study design and contain an overview on the new sub-study, **S1400I**. The PSR can be satisfied by completing the training online and submitting the verification at: https://swog.org/members/Training/S1400Training.asp. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org

SHOW STOPPER REVISION #3:

- **Design Modification to a "hybrid" master protocol**
  The hybrid protocol allows for different designs across sub-studies depending on biomarker prevalence. 1) The current Phase II/III design and 2) a two stage approach, with stage 1 being a single arm study, followed by a randomized Phase III study as appropriate.
- **Sub-studies - S1400B, S1400C, S1400D** have been modified to the second approach above.
  Single arm Phase II studies (the docetaxel comparator arms are dropped) followed by randomized Phase III studies (of the investigational drug *vs*. SoC) where feasible. Modifications to the original design were deemed necessary. There is no information that suggests that treatment with docetaxel is less effective than the investigational targeted therapy. The decision to change these sub-studies to single arm studies was based on a practical concern regarding the need to quickly evaluate the investigational agent's utility in this setting. If the sub-study meets the threshold outlined in the protocol's statistical section, then it may proceed to a randomized Phase III design. The choice of the standard of care comparator arm will be made at the time the decision is made to move forward. Patients who were randomized to the docetaxel arms will continue to receive treatment with docetaxel as a medical intervention if deriving clinical benefit, if the patient agrees to continue treatment, and if the treating physician feels that it is in the patient's best interest to continue the treatment at this time. Patients will continue to be followed 'per protocol'. Patients who were randomized to the docetaxel arms on each of the sub-studies will have the opportunity to receive the investigational drug upon progression.
  Investigators must notify their local Institutional Review Board (IRB) and must inform their patients of the information in the manner recommended by their local IRB (see attached Dear Investigator Letter). For patients currently registered to **S1400B**, **S1400C**, and **S1400D** and randomized to receive docetaxel, a "Patient Information Letter" is enclosed as a model for your use.
  While the patient letter need not be provided verbatim, the information in the letter must be provided in a manner recommended by the local IRB. Documentation that this information was provided must be retained in the patient's research record on site and will be subject to verification at the time of a Quality Assurance audit. (See attached Dear Investigator Letter and Patient Letter for patients randomized to docetaxel on **S1400B**, **S1400C**, and **S1400D**)
  For patients currently registered to **S1400B**, **S1400C**, and **S1400D** and randomized to receive the targeted therapy, institutions **must** update their local consent forms to include the changes to the Model Consent Form within 60 days of distribution of this notice. Patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.
- **Performance status (PS):** In addition, following Revision #3, patients with Performance status (PS) of 2 will no longer be eligible to register to **S1400** or any of the sub-studies. PS 2 patients who wish to register, must do so before Revision #3 is activated.
- **New Sub-study – S1400I**: Immunotherapy Non-match Study

S1400A (MEDI4736, non-match sub-study, now a single-arm Phase II study) will be permanently closed to accrual effective 12/18/2015. A new immunotherapy non-match study, **S1400I**, has been added to Revision #3. This is the combination of nivolumab (anti-PD1) + ipilimumab *vs.* nivolumab for nivolumab-naïve patients. This study will follow the first approach described above.
S1400A [MEDI4736] and **S1400I** [Nivolumab vs. Nivolumab/Ipilimumab] have overlapping eligibility and cannot be opened at the same time. Therefore, **S1400A** will close to accrual and **S1400I** will be activated upon distribution of the revision to sites. Patents assigned to **S1400A**, but not registered will automatically be reassigned to **S1400I**. Sites will receive a notification from the SWOG Stats Center stating the patient has been reassigned.

- **Updated Risk Information for S1400C and S1400D CAEPRs**
  As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with agent name. Patients currently receiving Palbociclib *or* AZD4547 **must** be informed of the changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.
  S1400C [Palbociclib]
  S1400D [AZD4547]

  [Note: Sites should seek an updated investigator brochure as required by site's IRB of record.].

The revision has been organized by protocol edits for **S1400** and each of the sub-studies, followed by the model consent form edits.

General Throughout Protocol

1. The Version Date of the protocol and the model consent forms have been updated.

2. Table of Contents: The page numbers have been updated for the following sections: **S1400**, **S1400A**, **S1400B**, **S1400C**, **S1400D**, **S1400E**.

3. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

S1400

1. **Page 1, Title Page:** The title page has been updated as follows:
   - The **S1400** title has been revised from "PHASE II/III" to "A"
   - In the list of agents, an asterisk has been inserted after docetaxel. The accompanying footnote has been inserted to state that docetaxel is no longer a current study agent.
   - Nivolumab and Ipilimumab have been added to the Pharmaceutical Collaborators
   - Jieling Miao has been added to the list of biostatisticians.

2. **Page 2, Participants:** The Participants page has been update to include the NCIC CTG Participation.

3. **Page 6, Schema**: The Schema has been updated to reflect the new study design described at the beginning of this memo and the addition of the new sub-study, **S1400I**. The accompanying footnotes have been inserted to state that docetaxel is no longer a current agent and the new sub-study, **S1400I** will open to accrual and **S1400A** will close.

4. **Pages 7-9, Section 1.0, Objective:** This section has been replaced a modified "hybrid" design to be used for different sub-studies depending on the prevalence of the biomarker and other factors for a given sub-study. This section has two design options:
   - The protocol has retained a modified Phase II/III design as Design #1.
   - The new design option, Design #2 is a two-stage design: the 1st stage is a Single Arm Phase II design and the 2nd stage, is a randomized Phase III design. For studies employing Design #2, the sub-study will proceed to Phase III (2nd stage) if Phase II meets pre-specified clinical endpoints and it is feasible to accrue to a randomized Phase III study.

5. **Pages 9, Section 2.0, General Background:** This section has been updated as follows:

   - Choice of Disease Setting: Information on nivolumab approval has been added to the last paragraph.
   - Study Design: The first sentence has been updated to reflect the new study design.
   - Figure 1: The figure has been removed.
   - Inclusion of Women and Minorities: This section has been updated based on new accrual projections.

6. **Page 13, Section 3.0, Drug Information:** The drug information for both docetaxel and erlotinib has been removed. Specific drug information is included in Section 3 of each sub-study.

7. **Page 15, Section 5.1b, Screening/Pre-Screening Registration**: This eligibility criterion related to screening at progression or pre-screening prior to progression has been revised as follows:
   - "first-line" has been revised to "current" in the first sentence.
   - Screening at progression: The fourth sentence previously stated, "For patients who received platinum-based chemotherapy for Stage I-III disease progression must have occurred within one year from receiving that therapy." The sentence has been replaced with "For patients whose prior systemic therapy was for Stage I-III disease only (i.e. patient has not received any treatment for Stage IV disease), disease progression on platinum-based chemotherapy must have occurred within one year from the last date that patient received that therapy."
   - Pre-screening prior to progression: This section previously stated:

"Pre-Screening prior to progression on first-line treatment:

To be eligible for pre-screening, patients must have received at least one dose of Cycle 1 of a first-line platinum-based chemotherapy regimen for Stage IV disease. Patients are eligible upon receiving Cycle 1, Day 1 infusion. **Note: Patients will not receive their sub-study assignment until they progress and the S1400 Notice of Progression on First-Line Therapy is submitted.**"

This section has been revised to state:

"Pre-Screening prior to progression on current treatment:

To be eligible for pre-screening, current treatment must be for Stage IV disease and patient must have received at least one dose of the current regimen. Patients must have previously received or currently be receiving a platinum-based chemotherapy regimen. Patients on first-line platinum-based treatment are eligible upon receiving Cycle 1, Day 1 infusion. **Note: Patients will not receive their sub-study assignment until they progress and the S1400 Notice of Progression is submitted.**"

8. **Page 15, Section 5.1, Screening/Pre-Screening Registration**: The eligibility criterion related to prior docetaxel treatment (formerly Section 5.1c) has been removed. The subsequent sections have been re-numbered accordingly.

9. **Page 16, Section 5.1e, Screening/Pre-Screening Registration:** The Zubrod performance eligibility criterion has been revised from "≤ 2" to "0-1".

10. **Page 16, Section 5.1j, Screening/Pre-Screening Registration**: The following eligibility criteria has been added:

"Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines."

11. **Page 16, Section 5.2, Sub-Study Registration**: The instructions have been updated based upon the revised eligibility criteria and the following sentences have been added to the third paragraph:

"The common eligibility criteria are included here. For ease of reference, these common eligibility criteria have also been incorporated into Section 5.0 of each of the sub-studies."

12. **Page 17, Section 5.2b, Sub-Study Registration**: The eligibility criteria related to radiation therapy has been revised as follows:

"Patients must have progressed per RECIST 1.1 (see Section 10.1) following the most recent line of therapy."

This criterion previously read as follows: "Patients must not have received radiation therapy within 28 days prior to sub-study registration."

13. **Page 17, Section 5.2c, Sub-Study Registration**: The first sentence has been revised to include the statement, "therapy (systemic chemotherapy, immunotherapy)". The last sentence in the eligibility criterion related to systemic chemotherapy has been revised as follows:

"Localized palliative radiation therapy is allowed for symptom management, provided treatment is completed ≥ 14 days prior to sub-study registration. All other types of radiation must be completed ≥ 28 days prior to sub-study registration.

This sentence previously read as follows: "Localized palliative radiation therapy must be completed ≥ 14 days prior to sub-study registration."

14. **Page 18, Section 5.2f, Sub-Study Registration**: "at least 14 days" has been added to the eligibility criteria related recovery from surgery.

15. **Page 18, Section 5.2j, Sub-Study Registration:** The following footnotes have been added to the Creatinine Clearance criteria:

    "†The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
    *Actual lab serum creatinine value with a minimum of 0.8 mg/dl."

16. **Page 18, Section 5.2k, Sub-Study Registration**: The Zubrod performance eligibility criterion has been revised from "≤ 2" to "0-1".

17. **Page 19, Section 5.2t, Sub-Study Registration**: The following eligibility criteria has been added:

    "Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines."

18. **Page 20, Section 6.0, Stratification Factors**: "For sub-studies employing Design #1," has been added to the first sentence.

19. **Page 20, Section 7.4, Follow Up Period:** "pre-screening/" and "registered/" have been added to the first sentence.

20. **Page 25, Section 10.6, Investigator-Assessed Progression-Free Survival:** "contact" has been replaced with "disease assessment" in the second sentence.

21. **Page 25, Section 10.7, Progression-Free Survival by Central Review:** "contact" has been replaced with "disease assessment" in the second sentence.

22. **Page 25, Section 10.8, Duration of Response (DoR):** This section has been added.

23. **Pages 25-35, Section 11.0, Statistical Considerations:** This section has been replaced to include the "hybrid" master protocol design options, sample size, and analysis plan as described at the beginning of this memo.

24. **Page 36, Section 13.2, Investigator/Site Registration**: The second paragraph has been updated to include new protocol specific requirements.

25. **Page 37, Section 13.4, Registration Procedures:** A sentence has been added to the end pf the paragraph to include information on patients re-registering.

26. **Page 40, Section 14.4, Data Submission Schedule:** Data submission for after submission of tissue but prior to registration on any sub-study and after receiving sub-study assignment but prior to registration on any sub-study have been added. The subsequent sections have been re-numbered accordingly.

27. **Page 40, Section 14.5b*:*** "/PRE-SCREENING" has been inserted in the follow up for patients not registered to any of the sub-studies

28. **Page 43, Section 15.3b**, **Specimen Collection**: The first paragraph has been revised to the following: "Specimens must be collected at Pre-screening or Screening. See Section 15 of each of the sub-studies for additional timepoints." In the first full paragraph, in the third sentence, the statement "and the serum tube should be kept at room temperature until processing can be performed" has been removed to clarify which tube should be collected. The timing of shipping in batches has been revised from 6 months to 3 months.

29. **Page 44, Section 15.4a, Radiology Review:** The last paragraph of this section has been revised to state that the central review of scans will not be triggered if the study will not be submitted for FDA approval. This paragraph previously stated that the review would be triggered should the study be stopped for efficacy based on objective response rate or investigator-assessed progression-free survival.

30. **Page 48, Section 17.0, Bibliography:** The following reference has been added as reference #8. The subsequent references have been re-numbered accordingly.

    Brahmer J, Reckamp KL, Baas P, et al. N Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. PMID [PMID: 26028407], 2015.

31. **Page 49, Section 18.0, Appendix**: The statement "versus Docetaxel" has been removed in Section 18.2b-d. A new Section 18.2f – S1400I has been added.

32. **Page 50, Section 18.1a.2, Sub-study biomarker eligibility definitions: S1400A** has been removed and replaced with **S1400I** as the non-match study.

33. **Page 52, Section 18.1a.3, Biomarker Reporting:** The biomarker reporting for patients pre-screened during current treatment has been updated to remove the reference to first line therapy and replace it with current therapy. Additional information has been added to the second paragraph for patients not intending to register will be provided biomarker results within one day of receiving the form.

34. **Page 60**, **Section 18.1c, On Site Auditing**: The statement “any significant” has been revised to ‘all” in the second sentence in the third paragraph.

35. **Page 65, Section 18.1d, Dose and Administration Schedule Overview**: **S1400I** has been added to "Table 1.1 Sub-studies Open to Accrual". The footnote "[a]" has been added to Table 1.1 and reads as follows: "Arm 2-Docetaxel has been closed to accrual with Revision #3". **S1400A** has been moved to “Table 1.2 Sub-studies Closed to Accrual”.

36. **Page 66, Section 18.1d, Protocol Instructions for Addition and Release …:** “and Figure 1” has been removed throughout the section.

S1400A

1. **Pages 68-142**: A water mark has been added for the closure of the sub-study.

2. **Page 68, Title Page:** The title page has been updated as follows:
   - The **S1400** title has been revised as described above in the **S1400** section of this memo.
   - The S1400A title has been revised by removing "AND DOCETAXEL" and "*(Revised 4/22/15)"*.
   - Jieling Miao has been added to the list of biostatisticians.

3. **Page 71, Schema**: The Schema has been updated to reflect the addition of Re-treatment on MEDI4736.

4. **Page 73, Section 1.5, MEDI4736 Re-Treatment Objectives:** The MEDI4736 Re-Treatment Objectives have been added.

5. **Page 79, Section 2.0 Background:** Background on the Re-Treatment Rationale has been added.

6. **Page 82, Section 3.1e.2, How Supplied:** A sentence has been added to the end of the paragraph to inform the packaging configuration will change in the future.

7. **Page 86, Section 5.0, Eligibility Criteria:** The first paragraph of this section has been revised to reflect the addition of Section 5.3 ("Common Eligibility Criteria for all Sub-Studies") and Section 5.4 ("Step 2 Re-Treatment").

8. **Page 86, Section 5.1, Disease Related Criteria:** "Registration Step #1" has been added to the section title.

9. **Pages 86-87, Section 5.2, Clinical/Laboratory Criteria:** This section has been updated as follows:
   - Registration Step #1" has been added to the section title.
   - "[*This criterion replaces common eligibility criteria in Section 5.3m and 5.3n*]" has been added to Section 5.2g for clarification purposes.
   - The following criterion has been added to Section 5.2h. The subsequent section has been re-numbered accordingly.

     "Patients must have a complete blood count (CBC), TSH, Free T3/T4, LDH, and Albumin performed within 28 days prior to sub-study registration to obtain baseline data for future toxicity assessments. If these tests are obtained within 14 days prior to sub-study registration as part of standard of care, tests need not be repeated. Additional timepoints are noted in Section 9.0, Study Calendar."

10. **Pages 87-90, Section 5.3, Registration Step #1 – Common Eligibility Criteria for all Sub-Studies:** This section, which is already included in Section 5.0 of the main study **S1400**, is now repeated here for convenience.

11. **Pages 90-93, Section 5.4, Registration Step #2 – MEDI4736 RE-TREATMENT:** This section has been inserted for registered patients who progress on MEDI4736 to re-start treatment.

12. **Page 95, Section 7.2c, Arm 3: MEDI4736 – Retreatment:** This section has been inserted to provide the treatment plan for patients who progress on MEDI4736 and register to Arm 3.

13. **Pages 95-96, Section 7.3, Criteria for Removal from Protocol Treatment**: This section has been updated as follows:
Section 7.3a: "to stay on" has been removed from the second sentence.
Section 7.3b: This section has been updated to include the criteria of Arm 3, MEDI4736 re-treatment.
Section 7.3f: "the sub-"has been replaced with "this".

14. **Page 96, Section 7.5, Follow-up Period:** "initial" has been added prior to "sub-study…"

15. **Pages 96-109, Section 8.3, Dose Modifications for MEDI4736:** This section has been updated as follows:
    - Immune-Related Adverse Events: A note for toxicities not noted below has been added. Grade 3 has been updated to include instructions for asymptomatic amylase or lipase levels. The toxicity management guidelines have been revised to suggest more aggressive management.
    - Pneumonitis: Grade 2 has been updated to state if toxicity worsens to treat as Grade 3 or 4. Grade 2 and 3 toxicity management guidelines have been revised to suggest more aggressive management.
    - Diarrhea/Enterocolitis: All toxicity management guidelines have been revised to include additional guidelines.
    - Hepatitis (Elevated LFTs): Grade 2 and Grade 3 Hepatitis toxicity management guidelines have been revised to suggest more aggressive management.
    - Nephritis or Renal Dysfunction: This section has been added.
    - Rash (excluding Bullous skin formations): The following statement has been added to the any grade toxicity management:
      "IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED**.**"
      All toxicity management guidelines have been revised to suggest more aggressive management.
    - Endocrinopathy: Grade 2 and Grade 3 dose modifications and toxicity management guidelines have been revised to suggest more aggressive management. Grade 4 has been removed.
    - Immune Mediated Neurotoxicity: Grade 2, and Grade 3/4 toxicity management guidelines have been revised to suggest more aggressive management.
    - Immune-Mediated Peripheral Neuromotor Syndromes: All Grades have been revised to suggest start IVIG for patients requiring steroid treatment.

16. **Page 109, Section 8.4, Dose Modifications for Docetaxel**: The following statement has been inserted "(NOTE: Arm 2 Closed to accrual per Revision #2, Version Date 4/22/15)".

17. **Pages 113-114, Section 9.1, Arm 1 MEDI4736:** The following footnotes have been updated:
    - The vital signs procedure has been added to Cycle 1, week 1 to clarify vitals should be performed at pre-study and pre-infusion, during, and post-infusion.
    - The € footnote has been added to the laboratory tests and notes these tests should be performed within 14 days prior to treatment.
    - In the Ω footnote, "while on treatment" has been removed.
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted.
    - In the □□and √ footnotes, at the end for the first sentence, the sentence "Patients who complete a year of MEDI4736 may be eligible for re-treatment following progression." has been added.

18. **Pages 115-116, Section 9.2, Arm 2 Docetaxel:** A watermark has been added to the section stating “DOCETAXEL ARM CLOSED”.

19. **Pages 117-118, Section 9.3, Arm 3 MED4736 – Retreatment:** This calendar has been inserted for patients who are re-treated after progression on MEDI4736.

20. **Page 122, Section 13.1, Registration Timing:** A timeframe for beginning treatment after registration Step 2 (Re-Treatment) has been inserted.

21. **Pages 123-125, Section 14.4, Data Submission Overview**: The section has been revised as follows:

    - Section 14.4a: The statement “SUB-STUDY” has been removed and “STEP 1” has been added.
    - Section 14.4b: inserted to provide information on forms to be submitted after registration Step 2 (Re- Registration Treatment). The subsequent section has been re-numbered accordingly.
    - Sections 14.4d and 14.4e: A reference to Arm 3 Re-treatment has been inserted.
    - Section 14.4f: The statement “OR RE-TREATMENT”, “**S1400A** Laboratory Values Form”, and “(not required during Re- Registration Treatment)” have been inserted.
    - Section 14.4g: The statement “FROM **S1400A** STEP 1 REGISTRATION” has been inserted.

22. **Pages 125-126, Section 15.2a.1, Peripheral Blood:** The first bullet regarding peripheral blood has been revised for clarification purposes. After the “Weeks 3, 7, 9”, a sentence has been inserted to say that patients are not required to continue submitting specimens after they go off protocol treatment. In the first full paragraph, in the third sentence, the statement "and the serum tube should be kept at room temperature until processing can be performed" has been removed to clarify which tube should be collected.

23. **Page 126, Section 15.2a.2, Whole Blood:** Arm 3, MEDI4736 – Re-treatment has been added to this section.

24. **Page 126, Section 15.2a.3, New Biopsy…:** This section has been reworded for clarification purposes.

25. **Page 127, Section 15.2b, Specimen Submission:** The timing of shipping in batches has been revised from 6 months to 3 months.

26. **Page 127, Section 15.4a, Radiology Review:** The last paragraph of this section has been revised to state that the central review of scans will not be triggered if the study will not be submitted for FDA approval. This paragraph previously stated that the review would be triggered should the study be stopped for efficacy based on objective response rate or investigator-assessed progression-free survival.

27. **Pages 137-138, Section 17.0, Bibliography:** Additional references (#36-#47) have been inserted to the end of this section.

28. **Page 139, Section 18.1, MEDI4736 Background on AESIs**: This section has been replaced with updated background information on AEs of special interest.

29. **Page 142, Section 18.2a, Specimen Flow Diagram**: “on an experimental arm” has been removed and “initially” has been inserted to footnote “b” for clarification purposes.

S1400B

1. **Page 143, Title Page:** The **S1400B** title page has been updated as follows:
   - Section 18.2b: "versus Docetaxel" has been removed
   - The **S1400** title has been revised as described above in the **S1400** section of this memo.
   - The **S1400B** title has been updated to reflect the new design modifications described at the beginning of this memo.
   - In the list of agents, GDC-0032 is now listed as GDC-0032, with taselisib in parentheses.
   - In the list of agents, an asterisk has been inserted after docetaxel. The accompanying footnote has been inserted to state that docetaxel is no longer a current study agent.
   - Jieling Miao has been added to the list of biostatisticians.

2. **Page 146, Schema:** A schema has been inserted to reflect the new study design described at the beginning of this memo. The "Old Schema" for patients registered prior to Revision #3 has been revised to show that after progression, patients on Arm 2 (docetaxel) may re-register to GDC-0032. An accompanying footnote has been inserted to provide a reference to the definition of progression.

3. **Page 147, Section 1.0, Objective:** This section has been replaced to include the "hybrid" master protocol design option #2 as follows:
   - Section 1.0: The first sentence of this section has been inserted to explain that S1400B will use Design #2 (sequential Phase II to Phase III) as described in **S1400**.

   - Section 1.2.a: The Phase II primary objective has changed from comparing investigator-assessed progression-free survival between GDC-0032and docetaxel to evaluating objective response rate for GDC-0032.

   - Section 1.2.b: The Phase III primary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.

   - Section 1.3: The following sentence has been deleted from the beginning of this section: "Secondary objectives will be evaluated in both the subset of patients defined to be PI3K GNE-positive and in the entire S1400B (PI3K FMI positive) study population."

   - Section 1.3.a: The Phase II secondary objectives have been revised. Instead of comparing response rates between GDC-0032and docetaxel, the study will evaluate investigator-assessed progression-free survival and overall survival. The objective pertaining to toxicities has been revised to remove the docetaxel comparison.

   - Section 1.3b: The Phase III secondary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.

   - Section 1.0: The section formerly numbered Section 1.4 ("Treatment Arm Randomization Acceptance Rate Objective") has been deleted since patients will no longer be randomized.

   - Section 1.4.a: This section has been revised to delete reference to prognostic biomarkers and to specify that the biomarkers of interest would pertain to GDC-0032.

4. **Page 149, Section 3.0, Drug Information**: The first sentence regarding docetaxel has been removed**.**

5. **Page 155, Section 5.0, Eligibility Criteria:** The first paragraph of this section has been revised to reflect the addition of Section 5.3 ("Common Eligibility Criteria for all Sub-Studies") and Section 5.4 ("Step 2 Re-Registration ").

6. **Page 155, Section 5.2.b:** This section has been revised for clarification purposes. Specifically, "Type 1 or 2 diabetes which" has been replaced by "Type I or II diabetes that".

8. **Pages 156-159, Section 5.3, Common Eligibility Criteria for all Sub-Studies:** This section, which is already included in Section 5.0 of the main study **S1400**, is now repeated here for convenience

9. **Pages 159-161, Section 5.4, Step 2 Re-Registration:** This section has been inserted to re-register patients who progressed on docetaxel to treatment with taselisib.

10. **Page 162, Section 6.0, Stratification Factors:** This section has been updated as follows:
    - Section 6.0: The first paragraph has been inserted to state that patients will no longer be randomized or stratified.

11. **Page 162, Section 7.2, Treatment:** The first paragraph has been inserted to state that patients will no longer randomized. Arm 3: Treatment with Taselisib has been added to define the treatment schedule.

12. **Page 163, Section 7.2c, Arm 3 Re-Registration:** This section has been inserted to provide the treatment plan for patients who progress on docetaxel and cross over to taselisib.

13. **Page 164, Section 7.7, Follow-Up Period**: This section has been updated to include the follow-up period for patients registered to Step 2 (Re-Registration).

14. **Page 165, Section 7.5b, Criteria for Removal from Protocol Treatment:** This section has been inserted to state that patients who progress on docetaxel and then re-register to taselisib and then progress must be removed from protocol treatment. The subsequent section has been re-numbered accordingly.

15. **Pages 169-170, Section 8.3d, Table 4 – Diarrhea or Colitis:** The dose modification and management guidelines for diarrhea and colitis have been revised to suggest more aggressive management, including infectious workups for Grade 1 and colonoscopies for Grade 2.

16. **Page 172, Section 8.4, Dose Modifications – Docetaxel:** The following statement has been inserted "(Closed to accrual per Revision #3)".

17. **Page 176-177, Section 9.1, Arm 1 GDC-0032:** The calendar has been revised as follows:
    - EKG line has been deleted as it is no longer required.
    - The € footnote has been added to the laboratory tests and notes these tests should be performed within 14 days prior to treatment.
    - In the Ω footnote, "while on treatment" has been removed.
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted.

18. **Pages 178-179, Section 9.2, Arm 2 Docetaxel:** A watermark has been added to the section stating “DOCETAXEL ARM CLOSED”.

19. **Pages 180-181, Section 9.3, Arm 3 Re-Registration – GDC-0032**: This calendar has been inserted for patients who cross over to taselisib after progressing on docetaxel.

20. **Page 182, Section 11.0, Statistical Considerations:** The first sentence has been inserted to state that this study will use Design #2 as described in the main study **S1400**.

21. **Page 182, Section 11.1, Primary Objective and Biomarker Prevalence**: In the last paragraph of this section, in the first sentence, the primary objective has been changed to remove the docetaxel comparison.

22. **Page 183, Section 11.2, Sample Size with Power Justification**: The first paragraph of this section has been inserted to state that this study will employ the Phase II design described in the main study **S1400**. As a result, the majority of the rest of Section 11.2 is no longer necessary and has been deleted.

23. **Page 183, Section 13.1, Registration Timing:** A timeframe for beginning treatment after registration Step 2 (Re-Registration) has been inserted.

24. **Pages 184-185, Section 14.4, Data Submission Overview**: The section has been revised as follows:

    - Section 14.4b, has been inserted to provide information on forms to be submitted after registration Step 2 (Re-Registration). The subsequent section has been re-numbered accordingly.
    - Section 14.4d and 14.4f, a reference to the re-registration arm has been inserted.
    - Section 14.4.f, the **S1400B** Laboratory Values From has been inserted.
    - Section 14.4g: has been revised to clarify that time is measured from the time of registration.

25. **Pages 186-187, Section 15.2a.1, Peripheral Blood:** This section has been revised as follows:
    - The first bullet regarding peripheral blood has been revised for clarification purposes.
    - After the “Weeks 4, 7, 10”, a sentence has been inserted to say that patients are not required to continue submitting specimens after they go off protocol treatment.
    - In the first full paragraph, in the third sentence, the statement "and the serum tube should be kept at room temperature until processing can be performed" has been removed to clarify which tube should be collected.

26. **Page 187, Section 15.2a.2, New Biopsy…:** This section has been reworded for clarification purposes.

27. **Page 187, Section 15.2b, Specimen Submission:** The timing of shipping in batches has been revised from 6 months to 3 months.

28. **Page 188, Section 15.3a, Radiology Review:** The last paragraph of this section has been revised to state that the central review of scans will not be triggered if the study will not be submitted for FDA approval. This paragraph previously stated that the review would be triggered should the study be stopped for efficacy based on objective response rate or investigator-assessed progression-free survival.

29. **Page 190, Section 16.1.e, Expedited reporting for investigational agents:** References to Arm 3 (Re-Registration) have been inserted since this arm includes GDC-0032.

30. **Page 192, Section 16.1.f.2, AESIs**: Grade 4 hyperglycemia has been revised to Grade $\geq$ 3 symptomatic hyperglycemia. Grade >= 2 diarrhea and Grade >= 3 stomatitis are now adverse events of special interest.

S1400C

1. **Page 197, Title Page**: The **S1400C** title page has been updated as follows:
   - Section 18.2c: "versus Docetaxel" has been removed
   - The **S1400** title has been revised as described above in the **S1400** section of this memo.
   - The **S1400C** title has been updated to reflect the new design modifications described at the beginning of this memo.
   - In the list of agents, an asterisk has been inserted after docetaxel. The accompanying footnote has been inserted to state that docetaxel is no longer a current study agent.
   - Jieling Miao has been added to the list of biostatisticians.

2. **Page 200, Schema:** A schema has been inserted to reflect the new study design described at the beginning of this memo. The "Old Schema" for patients registered prior to Revision #3 has been revised to show that after progression, patients on Arm 2 (docetaxel) may re-register to palbociclib. An accompanying footnote has been inserted to provide a reference to the definition of progression.

3. **Page 201, Section 1.0, Objective:** This section has been replaced to include the "hybrid" master protocol design option #2 as follows:
   - Page X, Section 1.0: The first sentence of this section has been inserted to explain that **S1400C** will use Design #2 (sequential Phase II to Phase III) as described in **S1400**.
   - Section 1.1.a: The Phase II primary objective has changed from comparing investigator-assessed progression-free survival between palbociclib and docetaxel to evaluating objective response rate for palbociclib.
   - Section 1.1.b: The Phase III primary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.
   - Section 1.2: The following sentence has been deleted from the beginning of this section: " The secondary objectives of the Phase II component of **S1400C** are:" The Phase II Secondary Objectives have been revised. Instead of comparing response rates between palbociclib and docetaxel, the study will evaluate investigator-assessed progression-free survival and overall survival. The objective pertaining to toxicities has been revised to remove the docetaxel comparison. In addition, an objective to estimate the duration of response among cell cycle gene alteration positive patients has been inserted.
   - Section 1.2: The Phase III secondary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.
   - Section 1.0: The section formerly numbered Section 1.3 ("Treatment Arm Randomization Acceptance Rate Objective") has been deleted since patients will no longer be randomized.
   - Section 1.4.a: This section has been revised to delete reference to prognostic biomarkers and to specify that the biomarkers of interest would pertain to palbociclib.

4. **Page 203, Section 3.0, Drug Information**: The first sentence regarding docetaxel has been removed**.**

5. **Pages 205-209, Section 3.1c.1, Palbociclib (PD-0332991) (NSC 772256) (IND-119672):** The palbociclib adverse effects section has been replace with a CTEP modified risk information Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.1, May 13, 2015. The section has been updated as follows:

- Added New Risk:
  - Less Likely: Dry eye; Mucositis oral; Watering eyes
  - Also Reported on PD-0332991 Trials But With the Relationship to PD-0332991 Still Undetermined: Acute kidney injury; Alanine aminotransferase increased; Alkaline phosphatase increased; Allergic reaction; Aspartate aminotransferase increased; Atrial fibrillation; Blood bilirubin increased; Cardiac arrest; Colitis; CPK increased; Creatinine increased; Dehydration; Dysphagia; Esophageal stenosis; Fall; Fracture; Gastric hemorrhage; GGT increased; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice); Hyperkalemia; Hypermagnesemia; Hypertension; Hypoalbuminemia; Hypocalcemia; INR increased; Lower gastrointestinal hemorrhage; Malaise; Musculoskeletal and connective tissue disorder - Other (osteonecrosis); Non-cardiac chest pain; Respiratory, thoracic and mediastinal disorders - Other (alveolitis allergic); Sinus bradycardia; Small intestinal obstruction; Supraventricular tachycardia; Thromboembolic event; Treatment related secondary malignancy

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Blurred vision; Dysgeusia; Hyperglycemia; Infection; Nervous system disorders – Other (peripheral neuropathy)
  - Changed to Rare but Serious from Reported But Undetermined: Febrile neutropenia

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Diarrhea
  - Changed to Reported But Undetermined from Less Likely: Abdominal pain; Chills; Cough; Dry mouth; Generalized muscle weakness; Headache; Musculoskeletal and connective tissue disorder - Other (muscle spasms)

- Provided Further Clarification:
  - All infections are now reported as Infection, and the following footnote #2 was added: Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
  - Peripheral motor neuropathy and peripheral sensory neuropathy are now reported as Nervous system disorders – Other (peripheral neuropathy, and the following footnote #3 was added: Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.
  - Rash maculo-papular is now reported as Skin and subcutaneous tissue disorders - Other (rash), and the following footnote #4 was added: Rash includes rash, rash maculo-papular, erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome.
  - General disorders and administration site conditions - Other (failure to thrive) is now reported as Metabolism and nutrition disorders - Other (failure to thrive).
  - Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain) is now reported as Gastrointestinal disorders - Other (oropharyngeal pain).

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) requirements:
  - Added: Anorexia

- Deleted Risk:
  - Also Reported on PD-0332991 Trials But With the Relationship to PD-0332991 Still Undetermined: Musculoskeletal and connective tissue disorder - Other (hip arthroplasty)

6. **Page 211, Section 3.1e.2, How Supplied**: The following sentence has been added to the end of this section: "In the future, supplies will transition to commercially labeled bottles that contain 21 capsules each."

7. **Page 214, Section 5.0, Eligibility Criteria:** The first paragraph of this section has been revised to reflect the addition of Section 5.3 ("Common Eligibility Criteria for all Sub-Studies") and Section 5.4 ("Step 2 Re-Registration ").

8. **Page 214, Section 5.2.b, Clinical/Laboratory Criteria:** This section has been revised for clarification purposes. Specifically, a URL has been provided to list the drugs known to prolong the QT interval.

9. **Page 215, Section 5.2d, Clinical/Laboratory Criteria:** This criterion has been removed and combined with Section 5.2e. The subsequent sections have been re-numbered accordingly.

10. **Pages 215-218, Section 5.3, Common Eligibility Criteria for all Sub-Studies:** This section, which is already included in Section 5.0 of the main study **S1400**, is now repeated here for convenience

11. **Pages 218-221, Section 5.4, Step 2 Re-Registration:** This section has been inserted for to register patients who progress on docetaxel to re-register to treatment with palbociclib.

12. **Page 222, Section 6.0, Stratification Factors:** This section has been updated as follows:
    - Section 6.0: The first paragraph has been inserted to state that patients will no longer be randomized or stratified.

13. **Page 222, Section 7.2, Treatment:** The first paragraph has been inserted to state that patients will no longer randomized. Arm 3: Re-Registration Treatment with palbociclib has been added to define the treatment schedule.

14. **Page 223, Section 7.2a, Arm 1 Palbociclib, Prohibited Medications**: A URL has been inserted at the end of the third paragraph to provide a list the drugs known to prolong the QT interval.

15. **Pages 225-227, Section 7.2c, Arm 3 Re-Registration:** This section has been inserted to provide the treatment plan for patients who progress on docetaxel and to palbociclib.

16. **Page 228, Section 7.4b, Criteria for Removal from Protocol Treatment:** This section has been inserted to state that patients who progress on docetaxel and then re-register to palbociclib and then progress must be removed from protocol treatment. The subsequent section has been re-numbered accordingly.

17. **Page 228, Section 7.6, Follow-Up Period**: This section has been updated to include the follow-up period for patients registered to Step 2 (Re-Registration).

18. **Page 231, Section 8.3, Dose Modifications – Palbociclib**: The dose modifications for Hepatic Dysfunction Grade 2 have been clarified.

19. **Page 231, Section 8.4, Dose Modifications – Docetaxel:** The following statement has been inserted "(Closed to accrual per Revision #3)".

20. **Page 236, Section 9.1, Arm 1 Palbociclib:** The calendar has been revised as follows:
    - In the Ω footnote, "while on treatment" has been removed.
    - The € footnote has been added to the laboratory tests and notes these tests should be performed within 14 days prior to treatment.
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted.

21. **Pages 237-238, Section 9.2, Arm 2 Docetaxel:** A watermark has been added to the section stating "DOCETAXEL ARM CLOSED".

22. **Pages 239-240, Section 9.3, Arm 3 Re-Registration – Palbociclib**: This calendar has been inserted for patients who cross over to palbociclib after progressing on docetaxel.

23. **Page 241, Section 11.0, Statistical Considerations:** The first sentence has been inserted to state that this study will use Design #2 as described in the main study **S1400**.

24. **Page 241, Section 11.1, Primary Objective and Biomarker Prevalence**: In the first paragraph of this section, in the first sentence, the primary objective has been changed to remove the docetaxel comparison.

25. **Page 241, Section 11.2, Sample Size with Power Justification**: The first paragraph of this section has been inserted to state that this study will employ the Phase II design described in the main study **S1400**. As a result, the majority of the rest of Section 11.2 is no longer necessary and has been deleted.

26. **Page 242, Section 13.1, Registration Timing:** A timeframe for beginning treatment after registration Step 2 (Re-Registration) has been inserted.

27. **Pages 243-244, Section 14.4, Data Submission Overview**: The section has been revised as follows:

    - Section 14.4b, has been inserted to provide information on forms to be submitted after registration Step 2 (Re-Registration). The subsequent section has been re-numbered accordingly.
    - Section 14.4d and 14.4f, a reference to the Re-Registration arm has been inserted.
    - Section 14.4.f, the **S1400C** Laboratory Values From has been inserted.
    - Section 14.4g: has been revised to clarify that time is measured from the time of registration.

28. **Pages 245-246, Section 15.2a.1, Peripheral Blood:** This section has been revised as follows:
    - The first bullet regarding peripheral blood has been revised for clarification purposes.
    - Arm 3 Palbociclib peripheral blood timepoints have inserted.
    - After Arm 1 Week 5, 7, 9, a sentence has been inserted to say that patients are not required to continue submitting specimens after they go off protocol treatment.
    - In the first full paragraph, in the third sentence, the statement "and the serum tube should be kept at room temperature until processing can be performed" has been removed to clarify which tube should be collected.

29. **Page 246, Section 15.2a.2, New Biopsy…:** This section has been reworded for clarification purposes.

30. **Page 246, Section 15.2b, Specimen Submission:** The timing of shipping in batches has been revised from 6 months to 3 months.

31. **Page 247, Section 15.3a, Radiology Review:** The last paragraph of this section has been revised to state that the central review of scans will not be triggered if the study will not be submitted for FDA approval. This paragraph previously stated that the review would be triggered should the study be stopped for efficacy based on objective response rate or investigator-assessed progression-free survival.

32. **Page 249, Section 16.1.e, Expedited reporting for investigational agents**: References to Arm 3 (Re-Registration) have been inserted since this arm includes palbociclib.

S1400D

1. **Page 255, Title Page:** The **S1400D** title page has been updated as follows:
   - Section 18.2d: "versus Docetaxel" has been removed
   - The **S1400** title has been revised as described above in the **S1400** section of this memo.
   - The **S1400D** title has been updated to reflect the new design modifications described at the beginning of this memo.
   - In the list of agents, an asterisk has been inserted after docetaxel. The accompanying footnote has been inserted to state that docetaxel is no longer a current study agent.
   - Jieling Miao has been added to the list of biostatisticians.

2. **Page 258, Schema:** A schema has been inserted to reflect the new study design described at the beginning of this memo. The "Old Schema" for patients registered prior to Revision #3 has been revised to show that after progression, patients on Arm 2 (docetaxel) may re-register to AZD4736. An accompanying footnote has been inserted to provide a reference to the definition of progression.

3. **Pages 259, Section 1.0, Objective:** This section has been replaced to include the "hybrid" master protocol design option #2 as follows:
   - Page X, Section 1.0: The first sentence of this section has been inserted to explain that **S1400D** will use Design #2 (sequential Phase II to Phase III) as described in **S1400**.

   - Section 1.1.a: The Phase II primary objective has changed from comparing investigator-assessed progression-free survival between AZD4547 and docetaxel to evaluating objective response rate for AZD4547.

   - Section 1.1.b: The Phase III primary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.

   - Section 1.2: The following sentence has been deleted from the beginning of this section: " The secondary objectives of the Phase II component of **S1400D** are:". The Phase II Secondary Objectives have been revised. Instead of comparing response rates between AZD4547 and docetaxel, the study will evaluate investigator-assessed progression-free survival and overall survival. The objective pertaining to toxicities has been revised to remove the docetaxel comparison. In addition, an objective to estimate the duration of response among FGFR positive patients has been inserted.

   - Section 1.2: The Phase III secondary objectives have been deleted. If the study moves on to include a randomized Phase III trial, objectives will be added at that time.

   - Section 1.0: The section formerly numbered Section 1.3 ("Treatment Arm Randomization Acceptance Rate Objective") has been deleted since patients will no longer be randomized.

   - Section 1.4.a: This section has been revised to delete reference to prognostic biomarkers and to specify that the biomarkers of interest would pertain to AZD4547.

4. **Page 262, Section 3.0, Drug Information**: The first sentence regarding docetaxel has been removed**.**

5. **Pages 263-266, Section 3.1c.1, AZD4547 (NSC 765338) (IND-119672):** The AZD4547 adverse effects section has been replace with a CTEP modified risk information Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.0, March 25, 2015. The section has been updated as follows:

- Added New Risk:

  Also Reported on AZD4547 trials but with the relationship to AZD4547 still undetermined:
  Fever, Alkaline phosphatase increased, Cardiac troponin T increased, Ejection fraction decreased, Musculoskeletal deformity, Acute kidney injury

- Increase in Risk Attribution:

  Less Likely: Eye disorders - Other (chorioretinopathy) (updated from Chorioretinopathy)

- Decrease in Attribution:

  Less Likely: Dry eye, Diarrhea, Dry mouth, Mucositis oral (updated from Epithelial and mucosal dryness), Dry skin, Skin and subcutaneous tissues disorders – Other (nail disorders)[3] (updated from Nail and nail bed changes), Creatinine increased, Alanine aminotransferase increased and Aspartate aminotransferase increased (updated from Liver transaminases, increased), Metabolism and nutrition disorders - Other (hyperphosphatemia) (updated from Hyperphosphatemia), Dysgeusia (updated from Dysgeusia/ageusia)

  Also Reported on AZD4547 trials but with the relationship to AZD4547 still undetermined: Anemia, Neutrophil count decreased (updated from Neutropenia), Cardiac troponin T increased (updated from increased troponin), Other (increase in LVEF) (updated from Left ventricular ejection fraction (LVEF) changes), Constipation, Nausea, Vomiting, Fatigue, Malaise, Sepsis, Blood bilirubin increased, GGT increased, Hyponatremia, Dehydration, Epistaxis, Respiratory failure, Dyspnea, Pleural effusion, Anorexia

- Removed Risks:

  Likely: Abdominal pain, Stomatitis, Asthenia, Lethary, Alopecia
  Less Likely: Eyelash disorder and trichomegaly, Hair disorder, Palmar-plantar erythrodysesthesia (hand-foot) syndrome,
  Rare but Serious: A trial fibrillation, Atrial flutter, Hypertension, Pericardial effusion, Hypotension, Ocular hyperemia, Esophageal achalasia, Gastroesophageal reflux disease, Mucosal inflammation, Peripheral edema, Pyrexia, Pneumonia, Bile duct obstruction, Hypokalemia, Neuralgia, Dizziness, Depression, Delirium, Rash, Renal failure

- Updated wording: Retinal detachment[2] (updated from Retinal pigmented epithelial detachment (RPED)),

- Specific Protocol Exceptions to Expedited Reporting (SPEER) column has been added.

6. **Page 268, Section 5.0, Eligibility Criteria:** The first paragraph of this section has been revised to reflect the addition of Section 5.3 ("Common Eligibility Criteria for all Sub-Studies") and Section 5.4 ("Step 2 Re-Registration ").

7. **Page 269, Section 5.2f, Eligibility Criteria**: This section has been revised for clarification purposes. Specifically, a URL has been provided to list the drugs known to prolong the QT interval.

8. **Pages 270-273, Section 5.3, Common Eligibility Criteria for all Sub-Studies:** This section, which is already included in Section 5.0 of the main study **S1400**, is now repeated here for convenience

9. **Pages 273-276, Section 5.4, Step 2 Re-Registration:** This section has been inserted for to register patients who progress on docetaxel to re-register to treatment with AZD4547.

10. **Page 277, Section 6.0, Stratification Factors:** This section has been updated as follows:
    - Section 6.0: The first paragraph has been inserted to state that patients will no longer be randomized or stratified.

11. **Page 277, Section 7.2, Treatment:** The first paragraph has been inserted to state that patients will no longer randomized. Arm 3: Re-Registration Treatment with AZD4547 has been added to define the treatment schedule.

12. **Page 278, Section 7.2c, Arm 3 Re-Registration:** This section has been inserted to provide the treatment plan for patients who progress on docetaxel and re-register to AZD4547.

13. **Page 278, Section 7.4b, Criteria for Removal from Protocol Treatment:** This section has been inserted to state that patients who progress on docetaxel and then re-register to AZD4547 and then progress must be removed from protocol treatment. The subsequent section has been re-numbered accordingly.

14. **Page 279, Section 7.6, Follow-Up Period**: This section has been updated to include the follow-up period for patients registered to Step 2 (Re-Registration).

15. **Page 280, Section 8.2e, General Considerations:** The phrase “or SRF” has been inserted in this section to clarify dose reduction exceptions.

16. **Page 281, Section 8.4, Dose Modifications – Docetaxel:** The following statement has been inserted “(Closed to accrual per Revision #3)”.

17. **Page 287, Section 9.1, Arm 1 AZD4547:** The calendar has been revised as follows:
    - In the Ω footnote, “while on treatment” has been removed.
    - The € footnote has been added to the laboratory tests and notes these tests should be performed within 14 days prior to treatment.
    - In the β footnote, at the end of the first sentence, the phrase "unless otherwise noted" has been inserted.

18. **Pages 288-289, Section 9.2, Arm 2 Docetaxel:** A watermark has been added to the section stating “DOCETAXEL ARM CLOSED”.

19. **Pages 290-292, Section 9.3, Arm 3 Re-Registration – AZD4547**: This calendar has been inserted for patients who cross over to AZD4547 after progressing on docetaxel.

20. **Page 293, Section 11.0, Statistical Considerations:** The first sentence has been inserted to state that this study will use Design #2 as described in the main study **S1400**.

21. **Page 293, Section 11.1, Primary Objective and Biomarker Prevalence**: In the first paragraph of this section, in the first sentence, the primary objective has been changed to remove the docetaxel comparison.

22. **Page 293, Section 11.2, Sample Size with Power Justification**: The first paragraph of this section has been inserted to state that this study will employ the Phase II design described in the main study **S1400**. As a result, the majority of the rest of Section 11.2 is no longer necessary and has been deleted.

23. **Page 294, Section 13.1, Registration Timing:** A timeframe for beginning treatment after registration Step 2 (Re-Registration) has been inserted.

24. **Pages 295-296, Section 14.4, Data Submission Overview**: The section has been revised as follows:

    - Section 14.4b, has been inserted to provide information on forms to be submitted after registration Step 2 (Re-Registration). The subsequent section has been re-numbered accordingly.
    - Section 14.4d and 14.4f, a reference to the re-registration arm has been inserted.
    - Section 14.4.f, the **S1400D** Laboratory Values From has been inserted.
    - Section 14.4g: has been revised to clarify that time is measured from the time of registration.

25. **Page 297, Section 15.2a.1, Peripheral Blood:** This section has been revised as follows:
    - The first bullet regarding peripheral blood has been revised for clarification purposes.
    - After the “Weeks 4, 7, 10, a sentence has been inserted to say that patients are not required to continue submitting specimens after they go off protocol treatment.
    - In the first full paragraph, in the third sentence, the statement "and the serum tube should be kept at room temperature until processing can be performed" has been removed to clarify which tube should be collected.

26. **Page 298, Section 15.2a.2, New Biopsy…:** This section has been reworded for clarification purposes.

27. **Page 298, Section 15.2b, Specimen Submission:** The timing of shipping in batches has been revised from 6 months to 3 months.

28. **Page 299, Section 15.3, Radiology Review:** The last paragraph of this section has been revised to state that the central review of scans will not be triggered if the study will not be submitted for FDA approval. This paragraph previously stated that the review would be triggered should the study be stopped for efficacy based on objective response rate or investigator-assessed progression-free survival.

29. **Pages 300-301, Section 16.1.e, Expedited reporting for investigational agents**: References to Arm 3 (Re-Registration) have been inserted since this arm includes AZD4547.

30. **Pages 307-308, Section 18.2 and 18.3, Figures 2 and 3:** These figures have been updated for the management of eye toxicity with and without symptoms.

S1400E

Page 309, Title Page: The **S1400E** title page has been updated as follows:

- The **S1400** title has been revised as described above in the **S1400** section of this memo.
- David Spigel has been removed from Sub-Study Chairs

S1400I

Pages 359-428, Section 18.2f, S1400I: A new sub-study, **S1400I**, has been inserted. S1400I is an immunotherapy non-match sub-study. This study will use the original design, Design #1 (Phase II/III Design) comparing nivolumab (anti-PD1) + ipilimumab with nivolumab monotherapy in checkpoint-inhibitor-naïve patients. This study will be replacing the current non-match sub-study, **S1400A**.

Model Consent Forms Changes

The following section refers to changes made to the Model Consent Form. Please refer to the IRB Review Requirements section on Page 1 of this memo.

1. The Version Date has been updated.

2. Throughout the consent form, typographical errors were corrected.

3. **Pages 3 [S1400] and 18 [S1400 Pre-Screening], 33 [S1400A], 46 [S1400B], 61 [S1400C], and 75 [S1400D], Model Consent Form Title Page**: The **S1400** title has been revised as described above in the **S1400** section of this memo and the sub-study specific title added.

4. **Pages 3 [S1400] and 18 [S1400 Pre-Screening], "What is the usual approach to my lung cancer?"**: This section has been replaced with the following: Squamous cell lung cancers make up about one-fourth of non-small cell lung cancer. Various chemotherapy drugs have been shown to improve survival for patients with advanced squamous lung cancer. Most patients will be treated at first with cisplatin or carboplatin in combination with a second chemotherapy drug such as gemcitabine, paclitaxel, docetaxel, or vinorelbine. In addition, an immunotherapy drug called nivolumab was recently FDA approved for patients with squamous lung cancer who previously received chemotherapy."

5. **Pages 3 [S1400], 18 [S1400 Pre-Screening] and 33 [1400A], "Why is this study being done**?": This section have been rewritten in a plan language for better patient understanding and the number of patients expected to be enrolled has been updated.

6. **Pages 4 [S1400] and 19 [S1400 Pre-Screening], "What are the study groups?":** The fourth paragraph of this section has been removed.

7. **Pages 13 [S1400], 28 [S1400 Pre-Screening], 43 [S1400A], 57 [S1400B], 71 [S1400C], and 84 [S1400D], "What if I have more questions?":** The italicized instructions "(include only applicable questions) have been removed

8. **Pages 31-44 [S1400A], Consent**: A watermark, "Closed effective 12/18/2015" has been added.

9. **Page 34 [S1400A], "What are the study groups?":** A third paragraph has been added and the Schema has been updated to reflect the addition of Re-treatment on MEDI4736.

10. **Page 35 [S1400A], "How long will I be in this study?":** This section has been revised to provide information to patients on the option to restart treatment on MEDI4736 should their cancer get worse.

11. **Pages 35 [S1400A], 49 [S1400B], 63 [S1400C], 76 [S1400D], "What extra tests and procedures…?": The following changes have been made to this section:** This section has been reworded for clarification purposes and template language added.

12. **Page 41 [S1400A], "What is involved":** The second bullet has been revised to include the additional correlative blood timepoints of before the study and at weeks 13 and 25**.**

13. **Pages 43 [S1400A], 57 [S1400B], 70 [S1400C], 84 [S1400D], "Are there any costs or payments?":** The first sentence has been revised to state that there are no costs to patients or insurance for the collection of testing of the tumor tissue and blood samples.

14. **Pages 46 [S1400B], 61 [S1400C], and 75 [S1400D], Model Consent Form Title Page:** The title has been updated to reflect the new design modifications and to remove the docetaxel comparison described at the beginning of this memo.

15. **Pages 46 [S1400B], 61 [S1400C], and 75 [S1400D], "Why is this study being done?"**: This section has been updated to reflect the re-design to a single arm sub-study and removal of the docetaxel comparison arm. In addition, the expected number of patients to enroll has been reduced.

16. **Pages 47 [S1400B], 62 [S1400C], and 76 [S1400D], "What are the study groups?"**: This section has been updated to reflect the re-design to a single arm sub-study and removal of the docetaxel comparison arm.

17. **Page 48 [S1400B], "What extra tests and procedures will I have if I take part in this study?":** The procedure EKG has been removed from extra tests prior to the beginning of the study.

18. **Pages 50 [S1400B], 65 [S1400C], and 80 [S1400D], "What possible risks..."**: The docetaxel side-effects section has been removed.

19. **Pages 64-65 [S1400C], "What possible risks…":** Patients currently receiving palbociclib **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. The following changes have been made to the palbociclib side effects information:

    Added New Risk to Occasional, some may be Serious (Less-Likely):
    a. **Dry eye**
    b. **Sores in the mouth which may cause difficulty swallowing**
    c. **Watering eyes**

    Increase in Risk Attribution Changed to Occasional, some may be Serious (Less-Likely) from Reported but Undetermined:
    d. Blurred vision
    e. Changes in taste

    Decrease in Risk Attribution Changed to Occasional may be Serious (Less-Likely) from Common:
    f. Diarrhea

    Decrease in Risk Attribution Changed to Reported But Undetermined from Occasional (i.e., removed from the Risk Profile):
    g. Pain
    h. Chills
    i. Cough
    j. Dry mouth
    k. Headache
    l. Muscle spasm

20. **Page 70 [S1400C], "What is involved?":** The third bullet regarding the collection of biospecimens for patients on the docetaxel arm has been removed.

21. **Pages 79-80 [S1400D], "What possible risks…":** Patients currently receiving AZD4547 **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. The following changes have been made to the AZD4547 side effects information:

Added to Occasional, some may be Serious (Less-Likely):
- **Change in or loss of some or all of the finger or toenails**

Decreased in Attribution to Occasional, some may be Serious (Less Likely):
- Dry eye, mouth, skin (updated from Dryness of the eye, Dry mouth, skin, and dryness of the tissue that lines body parts)
- Diarrhea
- Sores in mouth which may cause difficulty swallowing
- Changes in taste

Removed from Common, some may be Serious (Likely):
- Nose bleed
- Tiredness
- Constipation, nausea, vomiting
- Loss of appetite
- Hair loss
- Nail and nail bed changes
- Belly pain

Removed from Occasional, some may be Serious (Less-Likely):
- Hair and eyelash changes and/or loss
- Redness, pain or peeling of the palms and soles

Removed from Rare and Serious (Rare, but Serious):
- Kidney damage, kidney failure
- Anemia which may require blood transfusions
- Infection, especially when blood cell count and/or neutrophils are low
- Decreased heart function and/or abnormal heart rhythm, high or low blood pressure, fluid around the heart
- Change to eye color (red eye)
- Changes in vision can include blurred vision, seeing flashes of light, and loss of vision
- Swelling and infection of the lung
- Acid reflux (painful burning sensation in the throat and stomach)
- Swelling and redness of the arms, leg or face
- Fever
- Dehydration (severe loss of body water)
- Pain in nerves
- Dizziness
- Skin rash
- Depression
- Confusion
- Severe difficulties breathing and/or shortness of breath (may cause you to pass out, hospitalization may be required)
- Sores in internal organs
- Blockage of throat which may cause difficulty swallowing
- Yellowing of the skin and/or eyes

Updated wording only (no change in risk attribution):
- Swelling on the inside of the eye and Swelling and redness of the eye (updated from Swelling or discomfort of the eye)
- Visual loss (updated from Visual changes)

22. **Pages 102-116 [S1400I], New Sub-study Model Consent Form:** A new sub-study model consent form, S1400I, has been inserted.

Due to the extensive repagination, an entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of S1400.
This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Hossein Borghaei, D.O.
Jeffrey A. Engelman, M.D.,
Corey J. Langer, M.D.
Martin J. Edelman, M.D.
Charu Aggarwal, M.D., M.P
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Louise Highleyman
Kara Amber
MedImmune, LLC.
Genentech, Inc.
Pfizer, Inc.
AstraZeneca
Bristol Myers Squib
Foundation Medicine Inc.
Clarient, Inc.

Date: 12/18/2015

To: **S1400** Participating Investigators

From: Vassiliki Papadimitrakopoulou, M.D. – **S1400** Study Chair

Jeffrey Engelman, M.D., Ph.D.; Corey Langer, M.D. – **S1400B** Sub-Study Chairs
Martin Edelman, M.D.; Kathy Albain, M.D. – **S1400C** Sub-Study Chairs
Charu Aggarwal, M.D., M.P.H.; Primo Lara, M.D. – **S1400D** Sub-Study Chairs
Roy Herbst, M.D. Ph.D. – **S1400** Study Chair
David Gandara, M.D. – SWOG Lung Committee Chair

RE: **S1400**, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer ". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

Sub-studies: **S1400B** (P13K)/GENE; **S1400C** (CDK 4/6)/PFE; **S1400D** (FGFR)/AZN

Investigator Letter

The current Revision # 3 of **S1400** includes a design modification to a "hybrid" master protocol. The hybrid protocol allows for different statistical designs to be used for different sub-studies depending on the prevalence of the biomarker (or proportion of patients to be enrolled) and other factors for a given sub-study. Other changes to the protocol are outlined in the Memorandum – Revision # 3 accompanying the revision.

The modifications to the biomarker driven sub-studies (**S1400B, S1400C**, and **S1400D)** were made in response to the March 4, 2015, FDA approval of nivolumab (Opdivo®) for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response. The approval was based on superior overall survival (OS) for patients who were randomly allocated to either nivolumab or docetaxel in an open-label randomized trial in patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum-based chemotherapy regimen. Median OS was 9.2 months (95% CI: 7.3, 13.3) for patients assigned to nivolumab and 6 months (95% CI: 5.1, 7.3) for those assigned to docetaxel. In light of the nivolumab approval for second-line therapy, continuation of the current randomized Phase II/III sub-studies was considered no longer feasible. Therefore, the sub-studies have been modified to single arm Phase II studies. If sub-study of any specific investigational therapy demonstrates sufficient activity in the Phase II portion and an acceptable safety profile of the agent being tested, subsequent patients will be enrolled in a randomized Phase III portion of the study with the standard of care arm selected after it is determined a phase III trial will be started. The follow-on Phase III will be a pivotal proof of efficacy and safety study.[Note: The modified single arm Phase 2 leading to Phase 3 will enroll new patients after implementation of protocol Revision # 3.]

Investigators must notify their local Institutional Review Board (IRB) and must inform their patients of the information in the manner recommended by their local IRB. For patients currently registered to S1400B, S1400C, and S1400D and randomized to receive docetaxel, a "Patient Information Letter" is enclosed as a model for your use.

While this letter need not be provided verbatim, the information in the letter must be provided in a manner recommended by the local IRB. Documentation that this information was provided must be retained in the patient's research record on site and will be subject to verification at the time of a Quality Assurance audit. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

IRB Review Requirements:
SWOG considers the Model Consent Forms changes to represent a major modification to S1400. At the time of the distribution of this notice:

- **ALL PATIENTS ON S1400B, S1400C, and S1400D, ARM 2 DOCETAXEL**

A patient currently randomized to Arm 2, docetaxel, of **S1400B, S1400C, and S1400D** may continue to receive treatment with docetaxel if the patient is deriving clinical benefit, the patient agrees to continue treatment, and if their physician feels that it is in the patient's best interest to continue the treatment at this time. All patients will continue to be followed per protocol. However, since the docetaxel arms of **S1400B, S1400C and S1400D** are closing, the Off Treatment Notice should be submitted via Rave® for Arm 2 patients per **S1400B, S1400C, S1400D** protocol Section 7.4 and cycle-specific treatment and adverse event forms are no longer required after the final Treatment and Adverse Event forms are submitted per **S1400B, S1400C** and **S1400D** Section 14.4e. Since the secondary trial objectives are still ongoing, all patients are expected to continue with the protocol-specified follow-up. Patients will be given the option to re-register to the targeted therapy after progressing on docetaxel.

- IRB Requirements

SWOG considers the Model Consent Forms changes to represent a major modification to **S1400**. Therefore, accrual of new patients will be suspended to **S1400 and the sub-studies** at the time of this notice until the revised Model Consent Forms, in association with this revision, as approved by the site's IRB of record, **are implemented**, and proof of that IRB approval is received by CTSU. For sites using the CIRB as their IRB of record, the date of CIRB approval was received on 11/22/2015.

Please direct questions to:
Eligibility/Data Submissions: **S1400**Question@crab.org
Protocol/Regulatory: cmiwa@swog.org
S1400B Treatment-related/Medical: **S1400B**MedicalQuery@swog.org
S1400C Treatment-related/Medical: **S1400C**MedicalQuery@swog.org
S1400D Treatment-related/Medical: **S1400D**MedicalQuery@swog.org

Thank you for your continued participation in the **S1400** - Lung-MAP

[Patient Letter: For patients currently registered to S1400B, S1400C, and S1400D, and randomized to receive docetaxel]

PATIENT INFORMATION LETTER
For

S1400, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer". Study Chairs: V. Papadimitrakopoulou, F.R. Hirsch, P.C. Mack, R.S. Herbst, L.W. Schwartz, and D.R. Gandara.

Sub-studies: **S1400B** (P13K)/GENE; **S1400C** (CDK 4/6)/PFE; **S1400D** (FGFR)/AZN

You are participating in a SWOG research study to treat advanced squamous cell lung cancer in patients like you who have previously received chemotherapy. You were first assigned to a sub-study (**S1400B, S1400C, or S1400D**); then randomized to the 'standard of care' treatment arm, docetaxel. It was stated in your Consent Form that you would be given any new information that might affect your health or your willingness to continue in the study. We, the SWOG study investigators, have new information regarding the treatment for second line lung cancer.

In March 2015, the U.S. Food and Drug Administration (FDA) approved an immunotherapy drug called nivolumab (Opdivo®) for patients with squamous cell lung cancer who previously received chemotherapy. The approval was based on a study that found that patients treated with nivolumab lived longer than patients treated with the standard of care, docetaxel. Therefore, we decided that these sub-studies will be modified to include only investigational targeted treatment. There is no information that suggests that treatment with docetaxel is less effective than the investigational targeted therapy.

You will continue to receive treatment with docetaxel if you are deriving clinical benefit, and you agree to continue treatment, or if your physician feels that it is in your best interest to continue the treatment at this time. You will continue to be followed 'per protocol'. If your cancer gets worse on docetaxel, you will have the opportunity to crossover and receive the investigational targeted therapy.

We value the trust you have put in SWOG and regret any concern this may raise for you. You should discuss any questions you may have about this Patient Information Letter with your local study doctor. The results from this research study will contribute to the knowledge of how best to treat patients with advanced squamous cell lung cancer.

Thank you very much for your participation.

Sincerely,

Vassiliki Papadimitrakopoulou, M.D.
Jeffrey Engelman, M.D., Ph.D.
Corey Langer, M.D.
Martin Edelman, M.D.
Kathy Albain, M.D.
Charu Aggarwal, M.D., M.P.H.
Primo Lara, M.D.
Roy Herbst, M.D., Ph.D.
David Gandara, M.D.

18.2f **S1400I**: (Non-Match sub-study): Nivolumab plus Ipilimumab versus Nivolumab

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED SQUAMOUS CELL LUNG CANCER

A PHASE III RANDOMIZED STUDY OF NIVOLUMAB PLUS IPILIMUMAB VERSUS NIVOLUMAB FOR PREVIOUSLY TREATED PATIENTS WITH STAGE IV SQUAMOUS CELL LUNG CANCER AND NO MATCHING BIOMARKER (LUNG-MAP SUB-STUDY)

Bristol Myers Squibb Protocol #: CA209-489

NCT #02154490

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STUDY AGENTS:

Available from Pharmaceutical Collaborator:
Nivolumab (NSC 748726) (IND-119672)
Ipilimumab (NSC 732442) (IND-119672)

NURSE PRO/QOL STUDY COORDINATOR

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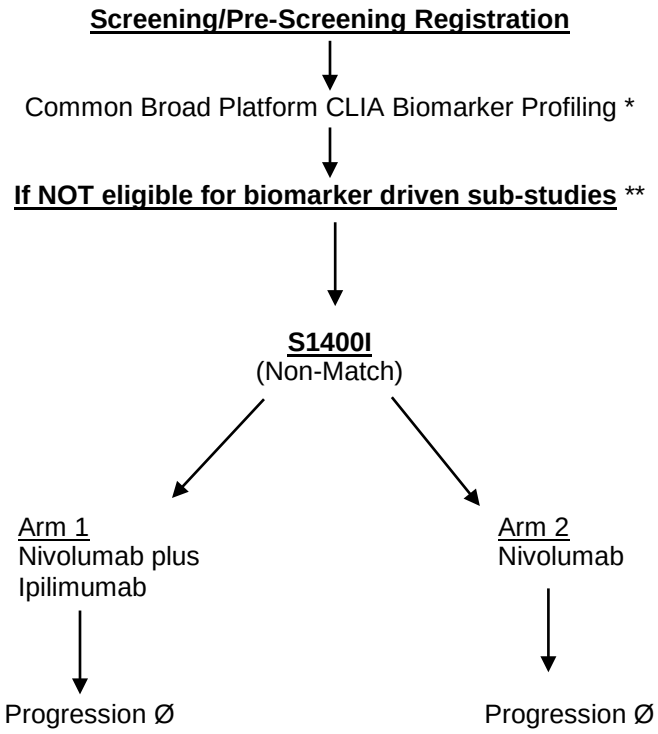
TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available to the SWOG Workbench. Access this by using your active CTEP-IAM USER ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. CTSU sties should follow procedures outlined in the protocol for site registration. Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement:		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 **S1400**question@crab.org **For treatment or toxicity related questions** contact S1400IMedicalquery@swog.org.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 888-823-5923 S1400contact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



* Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed

** Notification of sub-study assignment will be provided by the SWOG Statistical Center (see Section 11.0 in **S1400** for details).

Ø Upon progression (as defined in Section 10.2d in **S1400**), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistical Center. (see Section 14.6).

1.0 OBJECTIVES

1.1 Primary Objective

To compare overall survival (OS) in patients with advanced stage refractory SCCA of the lung randomized to nivolumab plus ipilimumab versus nivolumab.

1.2 Secondary objective(s):

a. To compare investigator-assessed progression-free survival (IA-PFS) in patients with advanced stage refractory SCCA of the lung randomized to nivolumab plus ipilimumab versus nivolumab.

b. To compare the response rates (confirmed and unconfirmed, complete and partial) per RECIST 1.1 among patients randomized to receive nivolumab plus ipilimumab versus nivolumab.

c. To compare the response rates (confirmed only, complete and partial) per RECIST 1.1 among patients randomized to receive nivolumab plus ipilimumab versus nivolumab.

d. To evaluate the frequency and severity of toxicities associated with nivolumab plus ipilimumab versus nivolumab.

1.3 Translational Medicine Objectives:

a. To evaluate if there is a differential treatment effect on OS, IA-PFS, and Response by tumor PD-L1 expression status.

b. To examine patient reported outcomes by treatment arm. (NOTE: Specific objectives for the **S1400I** Patient Reported Outcomes (PRO) are located in Section 18.2 of **S1400I**.)

2.0 BACKGROUND

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths. *(1)* Despite treatment with standard platinum-based doublet chemotherapy, patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of less than 5%. *(2)*

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer. *(3)* Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC. *(4)*

Nivolumab (Opdivo®) 3 mg/kg intravenously (IV) every 2 weeks was recently approved in the U.S. to treat patients with metastatic squamous cell NSCLC with progression on or after platinum-based chemotherapy. *(5,6)* The approval was based on the results of CA209017 (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation-017 [CheckMate-017]), a randomized trial of nivolumab 3 mg/kg IV every 2 weeks versus docetaxel 75 mg/m^2 IV every 3 weeks in 272 patients. The median OS for patients in the nivolumab arm was 9.2 months versus 6 months for those in the docetaxel arm (HR = 0.59). Improvement in survival was observed for nivolumab regardless of PD-L1 expression, though there was a trend for better efficacy for those with PD-L1+ tumors. *(7)* A single arm trial (CA209063, CheckMate-063) of 117 patients with metastatic squamous cell NSCLC, with progression after platinum-based chemotherapy and at least one additional systemic regimen, showed a 15% overall objective response rate (ORR), of whom 59% had response durations of 6 months or longer. *(8)*

A second Phase 3 study, CA209057 was recently stopped at a preplanned interim analysis by the independent Data Monitoring Committee (DMC), demonstrating superior overall survival of nivolumab 3 mg/kg IV every 3 weeks versus docetaxel 75 mg/m^2 IV every 3 weeks in patients with previously-treated non-squamous NSCLC with a 27% reduction in risk of death (HR = 0.73; P = 0.0015). *(9)* Interaction p-values reported for PD-L1 expression subgroups by each of the pre-defined expression levels suggested a clinically important signal of a predictive association. Nivolumab also significantly improved ORR versus docetaxel (P=0.0246), with ORR as high as 36% in subjects with PD-L1 expressing tumors. OS approximately doubled with nivolumab versus docetaxel across the PD-L1 expression continuum. In contrast, no difference in OS was seen between nivolumab and docetaxel when PD-L1 was not expressed in the tumor.

Nivolumab monotherapy has also been evaluated in first-line NSCLC, where it showed promising activity regardless of histology. *(10)* As in pretreated NSCLC, activity with nivolumab monotherapy is pronounced in PD-L1+ NSCLC.

In general, nivolumab also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action. *(11)*

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of a synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity.

Preclinical testing data confirmed that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone. *(12)*

Several clinical studies of the combination of nivolumab with ipilimumab have been conducted or are planned. In a Phase 1 clinical study of the combination of nivolumab plus ipilimumab in advanced melanoma (CA209004), there was a 41% response rate, including a 17% complete response rate (CR). *(13)* A randomized Phase 2 study (CA209069) comparing nivolumab plus ipilimumab versus ipilimumab showed an ORR of 61%, including a 22% complete response rate, in previously untreated, advanced melanoma patients with BRAF wild-type mutation status, versus 11 % for ipilimumab alone. *(14)* In addition, the combination regimen decreased the risk of melanoma progression or death compared to ipilimumab alone by 60%. Similar results were also observed in BRAF mutation-positive patients.

In a Phase 1 study in patients with NSCLC (CA209012), the combination of nivolumab plus ipilimumab is being evaluated at several different doses and schedules (see Rationale for Dose Selection and Schedule below). While the schedule evaluated in melanoma was not found to be tolerable in NSCLC, the study has identified alternative schedules with acceptable tolerability profiles.

CA209227 (CheckMate-227) is a randomized, open-label Phase 3 trial of nivolumab monotherapy or nivolumab plus ipilimumab versus platinum doublet chemotherapy in previously untreated subjects with Stage IV or recurrent PD-L1+ NSCLC, and nivolumab plus ipilimumab (2 different schedules) versus platinum doublet chemotherapy in subjects with Stage IV or recurrent PD-L1- NSCLC. The objectives of this study are to determine whether:

- nivolumab monotherapy or nivolumab plus ipilimumab improves OS and PFS compared with platinum doublet chemotherapy in subjects with PD-L1+ Stage IV or recurrent NSCLC, and
- nivolumab plus ipilimumab improves OS and PFS compared with platinum doublet chemotherapy in subjects with PD-L1- Stage IV or recurrent NSCLC.

Rationale for dose selections and schedules of nivolumab in combination with ipilimumab

Nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in patients with advanced NSCLC. In CA209012, early combination cohorts evaluated 2 dosing schedules.

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (n=24);
- nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (n=25)
-

These regimens resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related adverse event.

Thus, additional combination cohorts were initiated, using lower doses of both nivolumab and ipilimumab, or less frequent dosing of ipilimumab. Data from these cohorts demonstrate that both nivolumab 1 mg/kg + ipilimumab 1 mg/kg q 3 weeks with nivolumab maintenance 3 mg/kg q2w, as well as ipilimumab at 1 mg/kg q6w is tolerable, when given with nivolumab 3 mg/kg q2w.

Overall, the safety data are not dissimilar to what has been observed with nivolumab alone (i.e., in CA209012). Of particular note, the rate of discontinuation due to drug-related AEs was 13% and 11% in these combinations arms compared to 10% in the nivolumab monotherapy arm.

Table 1: Treatment-related adverse events from selected cohorts in CA209012

Arm	No. Subjects/ arm	Follow-up time (median, wks)	No. Subjects still on treatment	No. Subjects with drug-related AEs	No. Subjects with Grade 3-4 drug-related AEs	No. subjects d/c due to drug-related AEs (all grades
[a]	31	57	9 (29%)	23 (74%)	9 (29%)	4 (13%)
[b]	37	18	19 (51%)	20 (54%)	9 (24%)	4 (11%)
[c]	52	62	5 (10%)	37 (71%)	10 (19%)	5 (10%)

[a] nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks
[b] nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks
[c] nivolumab 3 mg/kg every 2 weeks

The significant toxicity observed in some of the other original cohorts resulted in limited exposure to treatment as demonstrated by the high discontinuation rate. Nonetheless, clinical activity was observed.

Table 2: Clinical Activity of Nivolumab/Ipilimumab Combination by Schedule and PD-L1 Status, using 1% Cutoff					
	ORR % (n/N)	**OS-12 mo**	**mOS (mos)**	**mPFS (wks)**	**PFS-24wk**
Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg q3w x4, followed by Nivolumab 3 mg/kg q2w (arms G/H)					
PD-L1+	17% (2/12)	83%	NR[a]	33.7	51%
PD-L1-	11% (1/9)	56%	19.8	12.4	38%
PD-L1 unk	0 (0/3)	33%	10.9	8.7	NC[b]
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg q3w x4, followed by Nivolumab 3 mg/kg q2w (arms I/J)					
PD-L1+	25% (4/16)	50%	16.5	14.4	33%
PD-L1-	0 (0/6)	33%	4.4	10.6	50%
PD-L1 unk	33%	33%	10.8	15.4	100%

[a] NR= not reached
[b] NC= not calculated

Based on these data, nivolumab (3 mg/kg every 2 weeks, i.e., the FDA approved dose in pretreated squamous NSCLC) with the highest dose and frequency of ipilimumab feasible (1 mg/kg every 6 weeks) will be evaluated.

HIV, HBV, and HCV Exclusion Rationale

Patients with known HIV/HBV/HCV infection will be excluded from this study. Immune checkpoint inhibition is a relatively new class of therapy. While HIV patients have been studied with anti-CTLA4 therapy, the unique interactions of PD-1/PD-L1 inhibitors and HIV may be difficult to predict and require further study. Since many of these patients may already be highly suppressed with antiretroviral therapy, standard assays may not be sensitive enough to detect a safety signal of increasing viral load. Thus, these patients may need to be studied in trials with access to such sensitive assays to better inform drug development in this particular population. The impact of PD-1/PD-L1 inhibition in HIV patients may be beneficial, which is of great interest in drug development in the field of chronic infections generally. We have elected not to complicate our trial with this added and important question at this time.

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this sub-study, nivolumab plus ipilimumab is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC # 748726) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: Nivolumab is human monoclonal antibody which targets the programmed death–1 (PD-1, cluster of differentiation 279

[CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

b. PHARMACOKINETICS

1. Distribution: Nivolumab has linear pharmacokinetics after single and multiple dosing within the range 0.1 mg/kg to 10 mg/kg. The volume distribution (Vd) is 8L.

2. Elimination: Clearance is independent of dose in the range 0.1 mg/kg to 10 mg/kg. The total body clearance is 9.5 mL/hr, and the elimination half-life of is approximately 26.7 days. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

Version 2.2, November 15, 2016[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
CARDIAC DISORDERS		
		Cardiac disorders - Other (cardiomyopathy)
		Myocarditis
		Pericardial tamponade[2]
		Pericarditis
ENDOCRINE DISORDERS		
	Adrenal insufficiency	
	Endocrine disorders - Other (hypophysitis)	
	Hyperthyroidism	
	Hypothyroidism	
EYE DISORDERS		
		Eye disorders - Other (diplopia)
		Eye disorders - Other (Graves ophthalmopathy)
		Eye disorders - Other (optic neuritis retrobulbar)
	Uveitis	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
		Colonic perforation
	Diarrhea	
	Dry mouth	
		Gastritis
	Nausea	
	Pancreatitis[3]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
	Infusion related reaction[4]	
	Injection site reaction	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Autoimmune disorder[5]
		Cytokine release syndrome[6]
		Immune system disorders - Other GVHD in the setting of allotransplant[7]
		Immune system disorders - Other (sarcoid granuloma)[5]
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	Creatinine increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)
		Myositis
NERVOUS SYSTEM DISORDERS		
		Encephalopathy
		Facial nerve disorder[5]
		Nervous system disorders - Other (demyelination myasthenic syndrome)
		Nervous system disorders - Other (encephalitis)
		Nervous system disorders - Other (Guillain-Barre syndrome)[5]
		Nervous system disorders - Other (meningoen-cephalitis)
		Nervous system disorders - Other (meningoradiculitis)
		Nervous system disorders - Other (myasthenia gravis)[5]
		Nervous system disorders - Other (myasthenic syndrome)
		Peripheral motor neuropathy
		Peripheral sensory neuropathy
RENAL AND URINARY DISORDERS		
		Acute kidney injury

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Pleural effusion	
	Pneumonitis	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)
		Erythema multiforme
	Pruritus	
	Rash maculo-papular	
	Skin hypopigmentation	
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[4] Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

[5] BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis,

endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[6] Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[7] Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (protein total decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation:

Pregnancy: Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use highly-effective contraception during therapy and for at least 23 weeks after treatment has been discontinued. Men receiving nivolumab and who are sexually active with women of child bearing potential should adhere to contraception for a period of 31 weeks after the last dose of nivolumab.

Lactation: It is not known if nivolumab is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends women to discontinue breastfeeding during treatment with nivolumab.

3. Drug Interactions: Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions. No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Nivolumab injection is to be administered as a 30 minute IV infusion through a 0.2 micron to 1.2 micron pore size, low-protein binding membrane in-line filter. DO NOT administer as IV push or bolus injection.

e. HOW SUPPLIED

1. Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous

solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

2. Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. . Nivolumab will be supplied as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

f. STORAGE, PREPARATION & STABILITY

1. Vials of nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking.

2. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to drug concentrations no less than 0.35 mg/mL. Note: Mix gently. Do not shake.

3. Compatibility: no incompatibilities between nivolumab and polyvinyl chlorie (PVC), nonPVC/non DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

4. Stability: Shelf-life stabilitiy studies of the intact vials are ongoing.

The administration of undiluted and diluted solutions of nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1400I**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that

institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <https://eapps-ctep.nci.nih.gov/iam/> and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

2. Drug Handling and Accountability (NCI logs or other)

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug return and/or disposition instruction (include forms if needed)

   a. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug expiration: (If packaging does not have expiration date, check with drug ordering designee and/or PI at site to confirm receipt of ongoing stability testing letter from NCI when internal drug audits are being performed on a quarterly basis. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first).

4. Contact Information

   Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

3.2 Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442) (IND-119672)

a. PHARMACOLOGY

Mechanism of Action: Cytotoxic T-lymphocyte antigen-4 CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a full human monoclonal immunoglobin (Ig) antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

b. PHARMACOKINETICS

1. Absorption: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes.

2. Distribution: Ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Based on population pharmacokinetic analysis, the mean volume of distribution (% coefficient of variation) at steady state was 7.47 liters (10%)

3. Metabolism: Not applicable. Monoclonal antibodies are usually degraded into amino acids and small peptides, independently from CYP450 or other drug-metabolizing enzymes.

4. Elimination: Clearance increased with body weight, but no dose adjustment is required with dosing on a mg/kg basis. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for CL was 16.8 mL/h (38%).

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2678 patients. Below is the CAEPR for Ipilimumab (MDX-010).

Version 2.8, December 21, 2016[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
		Blood and lymphatic system disorders - Other (acquired hemophilia)
CARDIAC DISORDERS		
	Atrial fibrillation	
		Myocarditis[2]
EAR AND LABYRINTH DISORDERS		
	Hearing impaired	
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
	Endocrine disorders - Other (hypopituitarism/ hypophysitis)[2]	
	Endocrine disorders - Other (testosterone deficiency)[2]	
	Hyperthyroidism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
	Eye disorders - Other (episcleritis)[2]	
	Uveitis[2]	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
		Colonic perforation[3]
	Constipation	
Diarrhea		
	Enterocolitis	
	Esophagitis	
		Ileus
Nausea		
	Pancreatitis[2]	
	Vomiting	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION		
	Chills	
Fatigue		
	Fever	
	Infusion related reaction	
		Multi-organ failure
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders – Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS		
	Autoimmune disorder[2]	
		Immune System Disorders-Other (GVHD in the setting of allotransplant)
INFECTIONS AND INFESTATIONS		
		Infections and infestations - Other (aseptic meningitis)[2]
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Neutrophil count decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Arthritis	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
NERVOUS SYSTEM DISORDERS		
	Facial nerve disorder	
	Headache	
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
	Nervous system disorders - Other (myasthenia gravis)[2]	
	Trigeminal nerve disorder	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pneumonitis	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Pruritus	
Rash maculo-papular		
	Skin and subcutaneous disorders – Other (Sweet's Syndrome)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	
VASCULAR DISORDERS		
	Hypotension	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3] Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4] Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5] In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[6]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia, Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: There are no adequate and well-controlled studies of Ipilimumab in pregnant women. Use of Ipilimumab during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from ipilimumab, a decision should be made whether to discontinue nursing or to discontinue ipilimumab, taking into account the importance of ipilimumab to the mother.

3. Drug Interactions: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

Ipilimumab injection is to be administered as an infusion with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not administer as IV push or bolus injection.

e. HOW SUPPLIED

1. Ipilimumab will be supplied free of charge by Bristol-Myers-Squibb (BMS) and distributed by NCI/DCTD/CTEP.

2. Ipilimumab injection is supplied as 200 mg/40 mL (5 mg/mL). It is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

	Process C
Component	**200 mg/ vial**[a]
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

[a] Includes 2.6 mL overfill.

[b] Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

f. STORAGE, PREPARATION& STABILITY

1. Store intact vials of ipilimumab refrigerated at (2^0 to 8^0C), protected from light. Do not freeze.

2. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride(PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2^0 to 8^0C) or at room temperature/room light.

3. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer).

4. Do not administer ipilimumab as an IV push or bolus injection.

5. Stability of prepared IV ipilimumab solution is stable up to 24 hours refrigerated at (2^0 to 8^0C) or at room temperature/ room light.

6. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1400I**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>.
Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account <https://eapps-ctep.nci.nih.gov/iam/> and the maintenance of an "active" account status and a "current" password. For questions

about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

2. Drug Handling and Accountability (NCI logs or other)

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug return and/or disposition instruction

   a. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug Expiration: Shelf life stability studies of the intact vials of ipilimumab are on-going

4.0 STAGING CRITERIA

See Section 4.0 of **S1400** for staging criteria.

5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria below to be eligible for **S1400I**. If the patient does not meet the eligibility criteria listed in Section 5.0 of **S1400I**, submit the **S1400** Notice of Intention Not to Register form and follow patient per Section 7.4 of **S1400**. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at S1400question@crab.org prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Sub-Study Specific Disease Related Criteria

_____ a. Patients must have been assigned to **S1400I**.

_____ b. Patients must not have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

_____ c. Patients must not have an active, known, or suspected autoimmune disease. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

5.2 Sub-Study Specific Clinical/Laboratory Criteria

_____ a. Patients must not have any known allergy or reaction to any component of the nivolumab and ipilimumab formulations.

_____ b. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to sub-study registration. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

_____ c. Patients must not have a known positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Patients with a positive hepatitis C antibody with a negative viral load are allowed. [*This criterion replaces common eligibility criteria in Section 5.3m.*]

_____ d. Patients must not have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). [*This criterion replaces common eligibility criteria in Section 5.3n.*]

_____ e. Patients must not have interstitial lung disease that is symptomatic or disease that may interfere with the detection or management of suspected drug-related pulmonary toxicity.

_____ f. Patients must also be offered participation in banking for future use of specimens as described in Section 15.0.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.2 Sub-Study Specific Clinical/LaboratoryCriteria (contd.)

_____ g. Patients must have a Lipase, Amylase, TSH with reflex Free T3/T4 performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar

_____ h. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see Section 18.1b).

1. Patients with a history of congestive heart failure (CHF) or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drug should have an EKG and echocardiogram performed to evaluate cardiac function as clinically indicated.
2. Patients with evidence of congestive heart failure (CHF), myocardial infarction (MI), cardiomyopathy, or myositis should have a cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, and echocardiogram.

_____ i. Patients who can complete PRO forms in English are required to complete a pre-study **S1400I** Patient Reported Outcomes (PRO) Questionnaire and a pre-study S1400I EQ-5D Questionnaire within 14 days prior to registration (see Section 18.2 of **S1400I**). NOTE: Patients enrolled to **S1400I** prior to 9/1/2016 are not eligible for the PRO study.

5.3 Common Eligibility Criteria for all Sub-Studies

The **S1400** Common Eligibility Criteria have been incorporated into Section 5.0 of each sub-study for ease of reference.

_____ a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	**Substitution**	**L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M**
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

_____ b. Patients must have progressed (in the opinion of the treating investigator) following the most recent line of therapy.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.3 Common Eligibility Criteria for all Sub-Studies (contd.)

_____ c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See 5.3e for criteria regarding therapy for CNS metastases).

_____ d. Patients must have measurable disease (see Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1400** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See Sections 15.0 and 18.1c for guidelines and submission instructions for required central radiology review.

_____ e. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment prior to regisitration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

_____ f. Patients must have fully recovered from the effects of major surgery at least 14 days prior to sub-study registration.

_____ g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

_____ h. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.

_____ i. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.3 Common Eligibility Criteria for all Sub-Studies (contd.)

_____ j. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})}{72 \times \text{serum creatinine}^*}\ \dagger$$

Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to sub-study registration.

†The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
*Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

_____ k. Patients must have Zubrod performance status of 0-1 (see Section 10.4) documented within 28 days prior to sub-study registration.

_____ l. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.2h. A place holder remains to keep consistency across all sub-studies*].

_____ m. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.2c. A place holder remains to keep consistency across all sub-studies*]

_____ n. [*This common eligibility criteria has been removed as it conflicts with the sub-study specific criteria in Section 5.2d. A place holder remains to keep consistency across all sub-studies*]

_____ o. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.

_____ p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

_____ q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.3 Common Eligibility Criteria for all Sub-Studies (contd.)

_____ r. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

_____ s. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

_____ t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

6.0 STRATIFICATION FACTORS

6.1 Patients will be randomized between nivolumab with or without ipilimumab using block randomization.

6.2 Randomization will be stratified by:

a. Gender (Male vs. Female)

b. Number of prior therapies (1 vs. 2 or more)

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Scott Gettinger and Lyudmila A. Bazhenova at **S1400I**MedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Supportive Care

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. Premedication for the use of prophylaxis for infusion reactions (e.g. diphenhydramine, acetaminophen, or other medications) may be given per institutional standard.

For patients that experience infusion reactions the following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combination, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab containing regimen.

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

Immunosuppressive agents

Immunosuppressive doses of systemic corticosteroids

Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)

7.2 Treatment – Non-Match **S1400I**

Patients will be randomized to one of the following treatment arms:

Arm 1: Nivolumab plus Ipilimumab

Arm 2: Nivolumab

a. **Arm 1: Nivolumab plus Ipilimumab**

Agent	Dose	Route	Day	Schedule*
Nivolumab (BMS-936558)	3 mg/kg	IV 30 minutes	1	Q 14 days
Ipilimumab (BMS-734016)	1 mg/kg	IV 60 minutes	1	Q 42 days (q 3 cycles) **

* NOTE: A cycle of treatment is 14 days.

** NOTE: Ipilimumab will be administered on Day 1 of every third cycle (i.e. Cycle 1, Cycle 4, etc.) see Section 9.0. Note that nivolumamb must be administered first. Ipilimumab to start 30 minutes after the end of nivolumab infusion.

Patients will be weighed prior to initiation of a new cycle of treatment. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the last-dosing weight. Following preparation of the dose, the entire contents of the IV bag should be administered (see Sections 3.1d and 3.2d).

Disease assessment are to take place every 6 weeks for the first year, then every 3 months. Treatment will continue until any of the criteria in Section 7.3 is met.

b. **Arm 2: Nivolumab**

Agent	Dose	Route	Day	Schedule*
Nivolumab (BMS-936558)	3 mg/kg	IV 30 minutes	1	Q 14 days

* NOTE: A cycle of treatment is 14 days.

Patients will be weighed prior to initiation of a new cycle of treatment. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the last-dosing weight. Following preparation of the dose, the entire contents of the IV bag should be administered (see Sections 3.1d).

Disease assessment are to take place every 6 weeks for the first year, then every 3 months. Treatment will continue until any of the criteria in Section 7.3 is met.

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2d in **S1400**. However, the patient may continue protocol treatment as long as the patient is continuing to clinically benefit from treatment in the opinion of the treating investigator. Patients should still be removed from protocol treatment for criteria below.

* Upon progression, the **S1400** Request for New Sub-Study Assignment Form may be submitted to receive a new sub-study assignment (see Section 14.0).

b. Symptomatic deterioration (as defined in Section 10.2e of **S1400**).

c. Unacceptable toxicity.

d. Treatment delay for any reason > 84 days (12 weeks) (or as noted in Section 8.0).

e. The patient may withdraw from this study at any time for any reason.

7.4 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.5 Follow-Up Period

All patients will be followed until death or 3 years after sub-study registration, whichever occurs first.

Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. No dose reductions are allowed.

b. The maximum dose delay for any reason is 84 days (12 weeks).

c. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

d. Cardiotoxic drugs should be avoided during the course of study treatment.

8.3 Dose Modifications – Nivolumab and Ipilimumab, Arm 1

See Section 8.8 for dose modification and management for cardiomyopathy myocarditis.

a. Dose Delay Criteria for Combination Therapy with Nivolumab and Ipilimumab
Nivolumab and ipilimumab administration should be delayed for the following:

1. Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities

2. Any Grade ≥ 3 skin drug-related AE

3. Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
   - Grade 3 lymphopenia does not require a dose delay
   - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
   - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade≥ 3 toxicity
   - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova at **S1400I**MedicalQuery@swog.org should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

1. Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
   Patients receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone. (Refer to Section 8.6 further details.)
2. Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
3. Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5 day window if needed to synchronize with the next nivolumab dose.
4. If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
5. A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 8.6.

b. Criteria to Resume Nivolumab and Ipilimumab Dosing

Patients may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

1. Patients may resume treatment in the presence of Grade 2 fatigue.
2. Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
3. Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
4. Patients with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Sections 8.5 and 8.6) should have treatment permanently discontinued.
5. Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
6. Patients who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ±10 mg/day.
7. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Study Chairs, Drs. Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org).
8. Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 6
9. In general, patients who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
10. One exception to note is when ipilimumab and nivolumab doses are delayed due to drug- related Grade ≥3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the patient's medical chart. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org) should be consulted prior to resuming

8.4 Dose Modifications – Nivolumab, Arm 2

See Section 8.8 for dose modification and management for cardiomyopathy myocarditis.

a. Dose Delay Criteria for Nivolumab

Nivolumab administration should be delayed for the following:

1. Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
2. Any Grade ≥ 3 skin drug-related AE
3. Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
   - Grade 3 lymphopenia does not require a dose delay
   - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
   - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade≥ 3 toxicity
   - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova at **S1400I**MedicalQuery@swog.org should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Patients who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (See below).

b. Criteria to Resume Nivolumab Dosing

Patient may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≥ 1 or baseline, with the following exceptions:

1. Patients may resume treatment in the presence of Grade 2 fatigue.

2. Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

3. Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.

4. Patients with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 8.5.) should have treatment permanently discontinued.

5. Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova at S1400IMedicalQuery@swog.org.

6. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova at (S1400IMedicalQuery@swog.org).

7. Patients who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova at S1400IMedicalQuery@swog.org should be consulted prior to resuming nivolumab in such patients.

8. Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 8.5.

8.5 Treatment Discontinuation Criteria Nivolumab and the Combination (Nivolumab with Ipilimumab

See Section 8.8 for dose modification and management for cardiomyopathy myocarditis.

Treatment with nivolumab should be permanently discontinued for any of the following:

a. Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

b. Any Grade $\geq$ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm);

c. Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration;

d. Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:

1. Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
2. Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
3. Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
4. Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
5. Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
   - AST or ALT > 5-10x ULN for > 2 weeks
   - AST or ALT > 10x ULN
   - Total bilirubin > 5 x ULN
   - Concurrent AST or ALT > 3 x ULN **and** total bilirubin > 2 x ULN

e. Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:

1. Grade 4 neutropenia <u>≤</u>7 days
2. Grade 4 lymphopenia or leukopenia
3. Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**<u>S1400I</u>**MedicalQuery@swog.org) should be consulted for Grade 4 amylase or lipase abnormalities
4. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
5. Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**<u>S1400I</u>**MedicalQuery@swog.org).

f. Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**<u>S1400I</u>**MedicalQuery@swog.org). Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

g. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a patient receiving combination therapy with nivolumab and ipilimumab meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue both nivolumab and ipilimumab.

8.6 Treatment Discontinuation Criteria Ipilimumab

See Section 8.8 for dose modification and management for cardiomyopathy myocarditis.

Ipilimumab should be permanently discontinued if any of the following criteria are met:

a. Any Grade ≥2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;

b. Any Grade ≥3 bronchospasm or other hypersensitivity reaction;

c. Any other Grade 3 non-skin, drug-related adverse with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);

d. Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

1. AST or ALT > 8x ULN
2. Total bilirubin > 5 x ULN
3. Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

e. Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:

1. Grade 4 neutropenia <7 days
2. Grade 4 lymphopenia or leukopenia
3. Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (S1400IMedicalQuery@swog.org) should be consulted for Grade 4 amylase or lipase abnormalities.

4. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
5. Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org).

f. Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 12 weeks, the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org) must be consulted. **Tumor assessments should continue as per protocol even if dosing is delayed.**

g. Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug- related reasons may be allowed if approved by the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org). Prior to re- initiating treatment in a patient with a dosing delay lasting > 12 weeks, the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova must be consulted. **Tumor assessments should continue as per protocol even if dosing is delayed.**

h. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a patient receiving combination therapy with nivolumab and ipilimumab meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue both nivolumab and ipilimumab.

8.7. Treatment of Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Study Chairs, Drs Scott Gettinger and Lyudmila A. Bazhenova (**S1400I**MedicalQuery@swog.org) and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

a. For Grade 1:
Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

b. For Grade 2

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

c. For Grade 3 or 4
Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

8.8 Dose Modification and Management for Cardiomyopathy Myocarditis

- Drug will be held for Grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for Grade 3 or 4 cardiac dysfunction and Grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

Cardiac *	**Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

8.9 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents such as nivolumab and ipilimumab are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: (I-O).

a. Pulmonary Adverse Event Management

Toxicity	Toxicity Management and Follow-up
Pulmonary (i.e., Pneumonitis)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Evaluate with imaging and pulmonary consultation.
Grade 1	- Monitor for symptoms every 2-3 days - Consider Pulmonary and Infectious Disease (ID) consults - Re-image at least every 3 weeks If worsens: - Treat as Grade 2 or 3-4
Grade 2	- Consider Pulmonary and ID consults - Monitor symptoms daily, consider hospitalization - 1.0 mg/kg/day methylprednisolone IV or oral equivalent - Consider bronchoscopy, lung biopsy - Re-image every 1-3 days If improves: - When symptoms return to near baseline, taper steroids over at least 1 month, consider prophylactic antibiotics If not improving after 2 weeks or worsening: - Treat as Grade 3-4
≥ Grade 3	- Hospitalize - Pulmonary and ID consults - 2-4 mg/kg/day methylprednisolone IV or oral equivalent - Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy If improves to baseline: - Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: - Add additional immunosuppression (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

b. Gastrointestinal Advers

Toxicity	Toxicity Management and Follow-up
Gastrointestinal (i.e., Diarrhea/Colitis)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.
Grade 1	- Close monitoring for worsening symptoms. - Educate patient to report worsening immediately - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. If worsens: - Treat as Grade 2 or 3/4
Grade 2	– Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. If persists > 5-7 days or recurs: - 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent - When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections If worsens or persists > 3-5 days with oral steroids: - Treat as Grade 3/4
≥ Grade 3	- 1.0 to 2.0 mg/kg/day methylprednisolone IV or oral equivalent - Add prophylactic antibiotics for opportunistic infections - Consider lower endoscopy If improves: - Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: - Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

c. Hepatic Adverse Event Management

Toxicity	Toxicity Management
Hepatic (Elevated LFTs – ALT, AST, Total Bilirubin)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Consider imaging for obstruction.
Grade 1	- Continue liver function tests (LFT) monitoring per protocol If worsens: - Treat as Grade 2 or 3/4
Grade 2	- Increase frequency of LFT monitoring to every 3 days until resolution to baseline. Resume routine monitoring If elevations persist > 5-7 days or worsen: - 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections
≥ Grade 3	- Increase frequency of LFT monitoring to every 1-2 days - 1.0 to 2.0 mg/kg/day methylprednisolone IV or oral equivalent. The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV. - Add prophylactic antibiotics for opportunistic infections - Consult gastroenterologist If returns to Grade 2: - Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: - Add mycophenolate mofetil 1 gram (g) twice daily (BID) - If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

d. Renal Adverse Event Management

Toxicity	Toxicity Management
Renal (i.e., Creatinine Increased)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.
Grade 1	- Monitor creatinine weekly until resolution to baseline; resume routine creatinine monitoring per protocol If worsens: - Treat as Grade 2 or 3/4
Grade 2-3	- Monitor creatinine every 2-3 days - 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent - Consider renal biopsy If returns to Grade 1: - Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: - Treat as Grade 4
≥ Grade 4	- Monitor creatinine daily - 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent - Consult nephrologist - Consider renal biopsy If returns to Grade 1: - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

e. Skin Adverse Event Management

Toxicity	Toxicity Management
Skin (i.e., Rash, Macula-papular)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.
Grade 1	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydrolyzine) and topical therapy (e.g., urea cream).
Grade 2	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydrolyzine) and topical therapy (e.g., urea cream). If persists > 1-2 weeks or recurs: - Consider skin biopsy - Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections If worsens: - Treat as Grade 3/4
Grade 3	- Consider skin biopsy - Dermatology Consult - 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent If improves to Grade 1: - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
Grade 4	- Consider skin biopsy - Dermatology Consult - 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent If improves to Grade 1: - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

f. Endocrinopathy Adverse Event Management

Toxicity	Toxicity Management
Endocrinopathy (Endocrine Disorders - adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance)	
Any Grade	- Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Consider visual field testing, endocrinology consultation, and imaging. - Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) - If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1	(including those with asymptomatic TSH elevation) Monitor patient with appropriate endocrine function test - If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider Endocrinology Consult.

Grade 2	(including those with symptomatic endocrinopathy)
	− Discuss with Study Chair
	− Initiate hormone replacement as needed for management
	− Evaluate endocrine function, and as clinically indicated, consider pituitary scan
	− For patients with abnormal lab/pituitary scan work up, consider short-term,1-2 mg/kg/day methylprednisolone IV or oral equivalent with relevant hormone therapy
	- For patients with normal endocrine work up (lab or MRI scans), repeat labs in 1-3 week/MRI in 1 month.
	- If improves (with or without hormone replacement):
	  - Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
	  - Patients with adrenal insufficiency may need to continue steroids with mineral corticoid component
	- Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)
	  - Discuss with Study Chair
	  - Rule out sepsis
	  - Administer stress dose of IV steroids with mineral corticoid activity
	  - Administer IV fluids
	  - Consult endocrinologist
	  - If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

Grade 3 Grade 4	−Discuss with Study Chair −Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or oral equivalent) at 1 to 2 mg/kg/day −Administer hormone replacement therapy as necessary −For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity −Consult endocrinologist - Once improving, gradually taper immunosuppressive steroids over ≥4 weeks

g. Neurological Adverse Event Management

Toxicity	Dose Modification	Toxicity Management
Neurological Toxicity (Nervous System Disorders)		
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.	
Grade 1	-Continue to monitor the patient. If worsens: -Treat as Grade 2 or 3/4	
Grade 2	−Treat symptoms per local guidelines −Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent If worsens: −Treat as Grade 3/4	
≥ Grade 3	−Obtain Neurology Consult −Treat symptoms per local guidelines −1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent −Add prophylactic antibiotics for opportunistic infections If improves to Grade 2: −Taper steroids over at least 1 month If worsens or atypical presentation: −Consider IVIG or other immunosuppressive therapies per local guidelines	

8.10 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Scott Gettinger and Lyudmila A. Bazhenova at **S1400I**MedicalQuery@swog.org. For dosing principles or questions, please consult SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

8.11 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Cycle 1 Wk 2	Cycle 2 Wk 3	Cycle 2 Wk 4	Cycle 3 Wk 5	Cycle 3 Wk 6	Cycle 4 Wk 7	Cycle 4 Wk 8	Cycle 5 Wk 9	Cycle 5 Wk 10	Cycle 6 Wk 11	Cycle 6 Wk 12	Subse-quent Cycles β	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
PHYSICAL																	
History & Physical Exam	X			X		X		X		X		X		X	X	X	
Weight & Performance Status	X			X		X		X		X		X		X	X	X	
Disease Assessment Ω	X							XΩ						X Ω		X Ω	
Toxicity Notation				X		X		X		X		X		X	X	Xđb	Xđb
Smoking Status Assessment	X														X		
S1400I PRO Questionnaire ☺	X			X		X		X		X		X		X☺		X☺	X☺
S1400I EQ-5D ☺	X					X		X		X				X☺		X☺	X☺
LABORATORY																	
CBC/Diff/Platelets/Hgb	X	X€		X		X		X		X		X		X	X	Xđb	Xđb
Serum Bilirubin	X	X€		X		X		X		X		X		X	X	Xđb	Xđb
ALT and AST	X	X€		X		X		X		X		X		X	X	Xđb	Xđb
Serum Creatinine/Calc CrCl	X	X€		X		X		X		X		X		X	X	Xđb	Xđb
Alkaline phosphatase	X	X€		X		X		X		X		X		X			
Blood urea nitrogen	X	X€		X		X		X		X		X		X			
Ca, Mg, Na, K, Cl	X	X€		X		X		X		X		X		X			
LDH ¥	X																
Glucose	X	X€		X		X		X		X		X		X			
Amylaseπ	X							X						Xπ			
Lipaseπ	X							X						Xπ			
TSH/w.reflex Free T3/T4 π	X							X						Xπ			
Albumin ¥	X																
Creatine phosphokinase (CPK)	X Ж							X Ж						X Ж			
Troponin	X Ж							X Ж						X Ж			
X-RAYS AND SCANS																	
CT or MRI for Disease Assessment Ω	X							XΩ						XΩ		X Ω	
Brain CT/MRI	X																
Image Submission Σ	X							X						X		X	
EKG	X Ж							X Ж						X Ж			
Echocardiogram (ECHO)	X Ж							X Ж						X Ж			

Calendar continued on next page. Calendar continued on next page. Click here for footnotes.

Calendar continued

REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Cycle 1 Wk 2	Cycle 2 Wk 3	Cycle 2 Wk 4	Cycle 3 Wk 5	Cycle 3 Wk 6	Cycle 4 Wk 7	Cycle 4 Wk 8	Cycle 5 Wk 9	Cycle 5 Wk 10	Cycle 6 Wk 11	Cycle 6 Wk 12	Subse-quent Cycles β	At Off Tx	Off Tx FU Prior to Prog Δ	Off Tx FU After Prog √
SPECIMEN SUBMISSION																	
Tissue for Banking																	X§
Blood for Banking ƒ	X			X				X		X							Xð
TREATMENT																	
Arm 1: Nivolumab/Ipilimumab																	
Nivolumab		X		X		X		X		X		X		X			
Ipilimumab		X						X						X ɯ			
Arm 2: Nivolumab																	
Nivolumab		X		X		X		X		X		X		X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

Footnotes for Calendar:

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.0 of **S1400I**) must be repeated every 6 weeks (± 7 day window) for the first year, then every 3 months until disease progression.

∑ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400I**.

☺ The **S1400I** Patient Reported Outcomes (PRO) Questionnaire administered at Pre-study (within 14 days prior to **S1400I** registration) and at **Weeks 3, 5, 7, 9, 11, 13, 24 and 36**. The **S1400I** EQ-5D Questionnaire is administered at Prestudy, **Weeks** 5, 7, 9, 13, 24, 36, and **Years** 1, 2, and 3. (see Section 18.2 of **S1400I**). For each timepoint, the Cover Sheet for PRO Questionnaires should also be completed. The scheduled PRO assessments should be completed even if the patient goes off treatment early. Note: Patients enrolled to **S1400I** prior to **9/1/2016** are not eligible for the PRO study.

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments are to take place every 6 weeks for the first year, then every 3 months. (± 7 days window). Treatment and evaluation will continue until any of the criteria in Section 7.3 is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated tests every 3 months for the first year, then every 6 months for up to 3 years from date of sub-study registration, unless otherwise noted.

√ After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of year 3 from date of sub-study study registration.

ƒ With patient's consent, additional research blood draws will be collected (see Section 15.0 of **S1400I**).

π Amylase, Lipase, and TSH w/ reflex Free T3/T4 are required at pre-study and must be repeated every 6 weeks while on treatment.

¥ Result of these tests do not determine eligibility but are recommended prior to sub-study registration.

§ With patients consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to protocol treatment (in the opinion of the treating physician) must be collected (see Section 15.0 of **S1400I**).

€ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated.

ȸ Assessments should continue until resolution of all acute adverse events.

ɯ Ipilimumab will be administered on Day 1 of every third cycle (i.e. Cycle 1, Cycle 4, Cycle 7 etc.).

ð Blood for Banking specimen must be collected at first progression after study treatment (see Section 15.0 of **S1400I**).

Ж CPK, troponin, EKG, ECHO are to be performed prestudy if clinically indicated (see Section 5.2) and are to be repeated every 6 weeks as clinically indicated while on treatment.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

See **S1400** Section 10.0 for criteria for evaluation and endpoint analysis

See **S1400I** Section 18.2 for criteria for evaluation and endpoint analysis of **S1400I** Patient Reported Outcomes (PRO).

11.0 STATISTICAL CONSIDERATIONS

This study will employ a modified version of Design #1: a Phase II/III design as described in **S1400** Section 11.1a. A complete description of the statistical design and analysis plan is included in Section 11.0 of **S1400**. This section includes details specific to **S1400I**.

11.1 Primary Objective

The primary objective is to compare overall survival (OS) with nivolumab in combination with ipilimumab versus nivolumab monotherapy in immune checkpoint-inhibitor naïve patients who are not eligible for the other biomarker-driven sub-studies in **S1400**

11.2 Sample Size with Power Justification

The expected proportion of patients assigned to **S1400I** is 50%. The estimated monthly accrual rate to **S1400I** is an average rate of 6-8 patients per month in the first year and 12-18 patients per month thereafter.

This study is using a modified version of the Phase II/III Design #1 (see **S1400** Section 11.1) Due the expected mechanism of action of checkpoint inhibitors and their effects on PFS, this study will not include the phase II interim analysis. The design of the study is a straight Phase III design.

The sample size for this study is based on a design that targets a 50% improvement in median OS (HR=0.67) with 90% power and a 2.5% 1-sided type I error rate. This design requires 256 deaths. The expected number of PFS at the final analysis is 290 IA-PFS events For this secondary objective, the analysis of IA-PFS will based on ruling out the null hypothesis of less than or equal to a 33% improvement (HR =0.75). With 290 IA-PFS events testing the IA-PFS null hypothesis of a HR equal to 0.75 at the 1-sided 0.05 level has 96.5% power. The approximate threshold for determining PFS is both clinically and statistically 47 significant is a 60% improvement in median PFS (HR = 0.62).

The total sample size is 332 eligible patients based on a median OS of 9 months. Assuming the ineligibility rate is 5%, the total accrual is 350 patients accrued over 27-36 months.

Accrual and time estimates assume a median 2-month delay between the **S1400** screening registration and sub-study registration for patients screened at progression and a median 9-month delay between screening and sub-study registration for patients pre-screened during prior treatment. Expected analysis times are stated from sub-study activation.

11.3 Analysis Plan

Primary analyses will be performed on an intent-to-treat basis. A stratified (using randomization stratification factors) log-rank test will be used to test the primary hypotheses related to OS comparing the two treatment arms at the levels specified below. A Cox proportional hazards (PH) model will be used to

estimate the hazard ratios and associated confidence intervals. Analysis of response rates and toxicities will be performed using a chi-square or Fisher's exact test, as appropriate. The analysis of IA-PFS for the Phase III component will be done using a PH model score test (or in other words, a modified log-rank test at the PFS null hazard ratio of 0.75 [the 33% improvement in median PFS]).

Interim Analysis Plan:
Formal interim analysis are planned when 50% and 75% of the expected deaths have been observed with rules specified on the fixed-sample p-value scale. Evidence suggesting early termination of the trial for futility/harm will be if the alternative hypothesis of at least 50% improvement in OS for the experimental arm is rejected at the one-sided level 0.0025, using a PH model score test evaluated at the alternative hypothesis (e.g. Ha: HR=0.67 for OS). However, if the hazard ratio is between 1.0 and 1.10 at the first interim analysis at 50% analysis, the decision to either continue accrual or stop early for futility should also consider the shape of the survival curves evaluating the presence of non-proportional hazards with more limited follow-up. In such a case, the hazard ratio estimate at that time could be greater than 1 when in fact the hazard ratio estimate with a longer follow-up duration would show benefit with the investigational therapy.

Evidence suggesting early termination of the trial for superiority will evaluated at the second interim analysis alone (75% of expected OS events) and will be if the hypothesis of no difference in OS is rejected at the one-sided 0.0025 level using a log-rank test. A full description of the interim analyses is included in the statistical design and analysis plan in Section 11.0 of **S1400**. The following table details the anticipated analysis times based on an accrual rate of 180 and 360 patients per year to **S1400I.**

Summary of interim and final analyses

				144 patients/year		216 patients/year	
	Events	Estimated HR Boundary		N (eligible)	Time	N (eligible)	Time
Phase III interim analyses:		Futility	Efficacy				
50% OS	128	1.03	N/A	267	26	309	20
75% OS	192	0.94	0.67	332	33	332	25
Final Analysis OS	256			332	48	332	39
Final Analysis PFS	290						

* See note above regarding the futility considerations if the HR is between 1.0 and 1.10

Sample size and analysis times for interim analyses are estimates. The actual numbers and timing will depend on the actual accrual rate and the event rates within the treatment arms. The analyses will occur upon the observation of the specified number of events.

If the study is closed for either futility or efficacy at any of the interim analyses, all secondary objectives will be evaluated.

11.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG. Group members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

11.5 Translational Medicine

The statistical considerations for the **S1400I** Patient Reported Outcomes (PRO) are described in Section 18.2 of **S1400I**.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

Patients must plan to begin treatment within 7 working days after sub-study registration.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3 for details.

14.3 Data Submission Procedures

a. All participating institutions must submit data electronically via the Web using Medidata Rave® at the following url:
https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.
2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on Page 5 of **S1400**.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF SUB-STUDY REGISTRATION, SUBMIT:

S1400I Onstudy Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in Section 15.4.

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0.

c. (For patients registered to **S1400I** after 9/1/2016 and participating in the **S1400I** PRO study) WITHIN 7 DAYS AFTER SUB-STUDY REGISTRATION AND AT WEEKS 3, 5, 7, 9, 11, 13, 24, AND 36, AND YEARS 1, 2, AND 3 SUBMIT:

S1400I Cover Sheet for Patient Reported Outcomes (PRO) Questionnaires*

S1400I Patient Reported Outcomes (PRO) Questionnaire*
(Required at Prestudy, Weeks 3, 5, 7, 9, 11, 13, 24, and 36)

S1400I EQ-5D Questionnaire*
(Required at Prestudy, Weeks 5, 7, 9, 13, 24, 36, and Years 1, 2, and 3)

* NOTE: In addition to completing electronic forms, upload the patient-completed questionnaires via the Source Documentation: PRO form in Rave®.

d. IMMEDIATELY AFTER EACH CYCLE (Cycle = 14 days) OF TREATMENT, SUBMIT**:**

S1400I Treatment Form

S1400I Adverse Event Form

S1400I Laboratory Values Form

For Cycle 1 only: submit the **S1400I** Pre-Treatment Laboratory Values Form

e. WITHIN 7 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO CONFIRMED DISEASE PROGRESSION [see **S1400I** Section 9.0 for Disease Assessment Schedule]), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.4.

f. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT, SUBMIT:

Off Treatment Notice documenting reasons for off treatment

S1400I Treatment Form

S1400I Adverse Event Form

S1400I Laboratory Values Form

Smoking Status Assessment Form

g. ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400I** REGISTRATION, THEN AT THE END OF YEAR 3 SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported.)

Note: Patients that enroll on a new sub-study following progression may discontinue follow-up on this sub-study and proceed per protocol of new sub-study. See Section 14.4j.

h. WITHIN 7 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in Section 15.4.

i. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in Section 14.4f or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

j. Data Submission FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 7 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1400** Request for New Sub-Study Assignment Form under **S1400** in Rave® Continue follow-up on **S1400I** per Sections 9.0 and 14.4g until registration to a new sub-study. See Section 14.6 of **S1400** for additional data submission requirements following request for new sub-study assignment.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Peripheral Blood:

Specimens must be collected at the following times:

- Prestudy (see Section 15.3 of**S1400I)**
  Note: If a patient provided blood at pre-screening at the time of progression on current treatment or screening (see Section 15.3 of **S1400**) and registration to **S1400** was within 42 days from sub-study registration, then that blood specimen can count as pre-study blood.
- Weeks 3, 7, 9. - Patients that go off treatment are not required to continue to submit specimens.
- First Progression after study treatment

Approximately 8-10 mL of blood must be collected in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, EDTA tubes that are not processed immediately should be refrigerated at 4˚C. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 g for 10 minutes at 4˚C for the collection of plasma. Plasma must be transferred to one 15 ml centrifuge tube and spun again at 800g for an additional 10 minutes. Plasma must then be pipetted into 1 ml coded cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present. Each buffy coat layer (the gray-white layer at the interface of blood cells and plasma, approximately 1 ml) from the blood tube must each be transferred into appropriately labeled 2-ml cryovials. Samples must be placed immediately in a -80˚C freezer to ensure long-term viability.

2. New Biopsy of Tumor at Time of Progression among responders to protocol treatment:

A new biopsy is strongly requested from patients who responded to protocol treatment (in the opinion of the treating physician) and then experienced disease progression for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy. The biopsy should be performed within one month after progression and should be processed as FFPE material. The minimum requirement is a block or 12 unstained sections.

b. Specimen Submission

Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.

Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 PD-L1 IHC Testing

With patient's consent, tissue will be sent from the SWOG Specimen Repository to University of Colorado Denver HSC. for PD-L1 Testing (see Section 18.1 for details).

15.4 Radiology Review (Required)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the following timepoints:

- Baseline
- Every 6 weeks for the first year, then every 3 months until progression

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks for the first year, then every 3 months until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see Section 10.1c). Each exam should be performed per **S1400** Section 18.1c. IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in **S1400** Section 18.1c.

b. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see **S1400** Section 13.2).
- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

Questions regarding image submissions, including TRIAD, should be directed to SWOG1400@irocohio.org or call IROC Ohio at 614-293-2929.

15.5 **S1400I** PRO Questionnaire Administration Instructions

Instructions for administration of the **S1400I** Patient Reported Outcomes (PRO) Questionnaire and the **S1400I** EQ-5D Questionnaire are described in Section 18.2 of **S1400I**.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 ADVERSE EVENT REPORTING REQUIREMENTS

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in Arm 1 and Arm 2 of this study are nivolumab and ipilimumab. [Please note – For this sub-study the post dosage expedited reporting requirement window has been extended to **100** days rather than the normal 30 day requirement.] If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 100 Days of the Last Administration of the Investigational Agent/Intervention[1] Nivolumab plus Ipilimumab, Arm 1 and Nivolumab Arm 2:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events (if applicable) are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 100 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

17.0 BIBLIOGRAPHY

1. Jemal A, Bray F, Center MM. et al. Global Cancer Statistics CA Cancer J Clin 61:69–90, 2011 [PMID: 21296855]

2. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. v.3.2014. www.nccn.org.

3. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 29:480-89, 2011. [PMID: 22193102]

4. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol 28:3167-3175, 2010. [PMID: 20516446]

5. Opdivo Prescribing Information, 2015. http://packageinserts.bms.com/pi/pi_opdivo.pdf.

6. Brahmer J, Reckamp KL, Baas P, et al. N Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. PMID [PMID: 26028407], 2015.

7. Spigel DR, Reckamp KL, Rizvi NA, et al. A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs. docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC). J Clin Oncol 33:5s, (suppl; abstr8009), 2015. http://meetinglibrary.asco.org/content/144815-156

8. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol Published online February 20, 2015. [PMID: 25704439]

9. Paz-Ares L, Horn L, Borghaei H, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). J Clin Oncol 33, (suppl; abstrLBA109), 2015.

10. Gettinger SN, Hellman MD, Shepherd FA, et al. First-line monotherapy with nivolumab (NIVO; anti-programmed death-1 [PD-1]) in advanced non-small cell lung cancer (NSCLC): Safety, efficacy and correlation of outcomes with PD-1 ligand (PD-L1) expression. http://meetinglibrary.asco.org/content/144603-156. J Clin Oncol 33:5s (suppl; abstr8025), 2015.

11. Amos S M., Duong CPM, Westwood JA, et al. Autoimmunity associated with immunotherapy of cancer. Blood 118:499-509, 2011.[PMID: 21531979]

12. Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 107: 4275-80, 2010.[PMID: 20160101]

13. Sznol M, Kluger HM, Callahan MK, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 32:5s (suppl; abstrLBA 9003).

14. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 372:2006-2017, 2015.[PMID: 25891304]

18.0 APPENDIX

18.1 Translational Medicine - PD-L1 IHC Testing

18.2 Translational Medicine – **S1400I** Patient Reported Outcomes (PRO)

18.1 Translational Medicine - PD-L1 IHC Testing

Objectives

1. To evaluate if PDL-1 protein expression as defined and used in previous nivolumab studies for NSCLC is associated with improved clinical outcomes (response, PFS, OS) in patients treated with PD-1 antibody (nivolumab).
2. To evaluate if PDL-1 protein expression as defined and used in previous nivolumab studies for NSCLC is predictive for improved clinical outcomes in patients treated with nivolumab + ipilimumab versus nivolumab alone.
3. To explore whether H-score assessment can be used as a predictive biomarker analysis in this setting.

Background

Treatment of patients with PDL-1 or PD-1 antibodies have demonstrated very encouraging effect in patients with advanced NSCLC and has led to FDA approval of nivolumab for 2nd Line therapy of patients with squamous lung cancer. Most recently superior outcome data has been presented in patients with non-squamous lung cancer with the same agents, and FDA approval is expected in this patient population, as well. However, conflicting data have been presented regarding the role of PDL-1 protein expression (IHC) as predictive biomarker for response and outcome (PFS/OS) for these new agents. Quite consistent in all studies is the fact that response and outcome seem to be better in patients with PDL-1 positive tumors compared to those with PDL-1 negative tumors, but not all the studies have shown statistical significant differences. In the nivolumab registration study for 2nd line therapy for squamous lung cancer some difference (not statistical significant) between the two groups was seen. However, no data yet is known for PDL-1 assay as a predictive biomarker for combination therapy, which will be studied in the current clinical trial.

No predictive data has yet been presented using an H-score system related to PDL-1, and this study provides an opportunity to also study alternating assessment methods using the same slides.

PD-L1 IHC testing will be performed on tumor specimens from patients registered to **S1400I** who consented to future testing in **S1400**. Tumor specimens will be shipped from the SWOG specimen repository at Nationwide to University of Colorado Denver HSC on a bi-weekly basis. The SWOG statistical center will provide Nationwide with the list of patient specimens to ship to University of Colorado Denver HSC. All specimens must be entered and tracked using the online SWOG Specimen Tracking System (STS). Shipments to University of Colorado Denver HSC will be accompanied by pathology report, SWOG patient ID, specimen ID, sample collection date, and sample type.

Experimental research techniques/tests employed and expertise

The DAKO assay previously used in nivolumab studies will be applied primarily with the use of the well-defined cut-offs (1%, 5%, 10%). In addition, an H-score evaluation will be applied as explorative. The H-score protein assessment for lung cancer was first described by the TM Study Chair (Dr. Hirsch) applied in EGFR in a publication in J clin Oncol in 2003. It has since been applied by other

investigators for different targets in multiple publications, including the Hirsch lab. Dr. Hirsch's lab is currently involved in an international "comparison" project of the available PDL-1 assays used in the clinical trials by the different companies. Dr. Hirsch's lab is also involved in a large PDL-1 project supported by BMS and performed through NCTN, which has the goal to understand this specific assay's performance on different types of specimens (i. e. large specimens versus small biopsies versus cytology). Dr. Hirsch is co-chair for that study, and as such has special experience with the DAKO/BMS PDL-1 assay, which is planned to be used in this TM study proposal.

Dr. Fred Hirsch is the key contact for questions regarding this translational medicine study:

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Statistical Plan

Based on current tissue submission data, it is estimated that approximately 60% of eligible patients enrolled on S1400I will have sufficient tissue leftover after FMI genetic profiling to have PD-L1 expression analyzed. Furthermore, based on Rizvi, et al [Lancet Oncol. 2015 Mar; 16 (3):257-65. doi: 10.1016/S1470-2045(15)70054-9. Epub 2015 Feb 20]. It is anticipated that for approximately 13% of these patients the specimens submitted will turn out not to be evaluable for PD-L1 testing. Therefore, with 332 patient enrolled on S1400I, we expect 174 patients in all of the analysis described below.

First we will evaluate if PD-L1 expression, as measured by the DAKO assay, is associated with improved clinical outcomes, overall survival (OS), progression-free survival (PFS), and response rate (confirmed and unconfirmed, complete and partial responses), in all patients treated with nivolumab (i.e. both study treatment arms combined). Using a definition of PD-L1 positivity as an IHC score of at least 5% (≥ 5%), it is expected, based on Rivzi et al, that of patients with evaluable specimens 35% will be PD-L1 positive and 65% will be PD-L1 negative.

Assuming that the median overall survival among PD-L1 negative patients is 9 months, with 174 patients enrolled over 36 months and an additional 12 months of follow-up, there will be approximately 83% power to detect a hazard ratio of 1.6, corresponding to a median OS of 14.4 months for PD-L1 positive patients, using a one-sided 0.05 level log-rank test.

Assuming a median PFS of 3.5 months in PD-L1 negative patients, there will be approximately 81% power to detect a hazard ratio of 1.5, corresponding to a median PFS of 5.25 months in PD-L1 positive patients, using a one-sided 0.05 level log-rank test.

In addition, we will assess whether patients who are PD-L1 positive have a better probability of response (confirmed and unconfirmed, complete and partial responses). With 174 patients we will have approximately 80% power to be able to detect a difference of 21% or greater using a one-sided 0.05 level test of proportions.

Next we will evaluate whether PD-L1 status is predictive for improved overall survival for patients receiving the combination of nivolumab + ipilimumab by fitting a cox model with an interaction term for treatment effect. If we assume no treatment effect in the single agent nivolumab arm, and no treatment effect for PD-L1 negative patients receiving the combination, and further assuming the null median OS is 9 months, there will be approximately 83% power, using a one-sided test at the 0.15 type-1 error level, to detect a OS hazard ratio of 2, corresponding to an improvement to a median OS of 18 months in PD-L1 positive patients receiving the combination of ipilimumab plus nivolumab.

We will evaluate a treatment interaction effect for PFS in the same manner as described above. Once again, we assume no treatment effect in the single agent arm and no treatment effect for PD-L1 negative patients in the combination arm. If we further assume the null median PFS is 3.5 months, there will be approximately 81% power, using a one-sided test at the 0.15 type-1 error level, to detect a PFS hazard ratio of 1.9, corresponding to an improvement in median PFS to 6.65 months for PD-L1 positive patients receiving the combination of nivolumab plus ipilimumab.

To evaluate if there is a treatment interaction effect on the probability of response, a logistic regression model will be fit. However, power for testing the interaction term at the 0.15 level will be at best modest (< 70%) to detect a very large difference (OR > 4).

All of the analyses previously described will be repeated using the alternative cut-offs for defining PD-L1 positivity as an IHC score of at least 1% (≥ 1%) and again for an IHC score of at least 10% (≥ 10%).

In addition, we will investigate in a preliminary manner whether PD-L1 expression by IHC is associated with improved clinical outcomes (OS, PFS, response) among all patients treated with nivolumab (i.e. both arms combined) as well as explore whether there is a treatment interaction effect for patients treated with the combination of nivolumab plus ipilimumab. The raw marker data (H score) will be rescaled to quantiles and a Cox regression model will be fit treating the rescaled data as a continuous variable.

Assuming 36 months accrual and 12 months of follow-up, there will be 86% power to detect a 1.5 hazard ratio (i.e. a 50% improvement in median PFS) between patients with H score levels in the third quantile versus patients with H score levels in the first quantile using a one-sided test with an alpha = 0.05.

To evaluate if patients receiving the combination of nivolumab + ipilimumab with PD-L1 expression by IHC have a better PFS than patients with PD-L1 expression treated on the control arm, we will fit a Cox regression model with a treatment interaction term to evaluate if there is a difference in treatment effect associated with marker values. The H Score data will be rescaled to quantiles. Assuming 36 months accrual and 12 months of follow-up, there will be 81% power to detect a 1.9 treatment interaction hazard ratio between the third quartile and the first quartile.

The association between PD-L1 expression and overall survival will be analyzed with Cox regression techniques in the same manner described above. The association between PD-L1 expression and response rates (confirmed and unconfirmed, complete and partial responses) will be evaluated by fitting logistic regression models to the rescaled data. Patients whose exact response cannot be determined due to inadequate follow-up assessments will be included in the analysis as non-responders.

Laboratory

University of Colorado Denver HSC will serve as the central laboratory for testing PD-L1 expression in patients who register to **S1400I** and have consented to additional testing beyond NGS.

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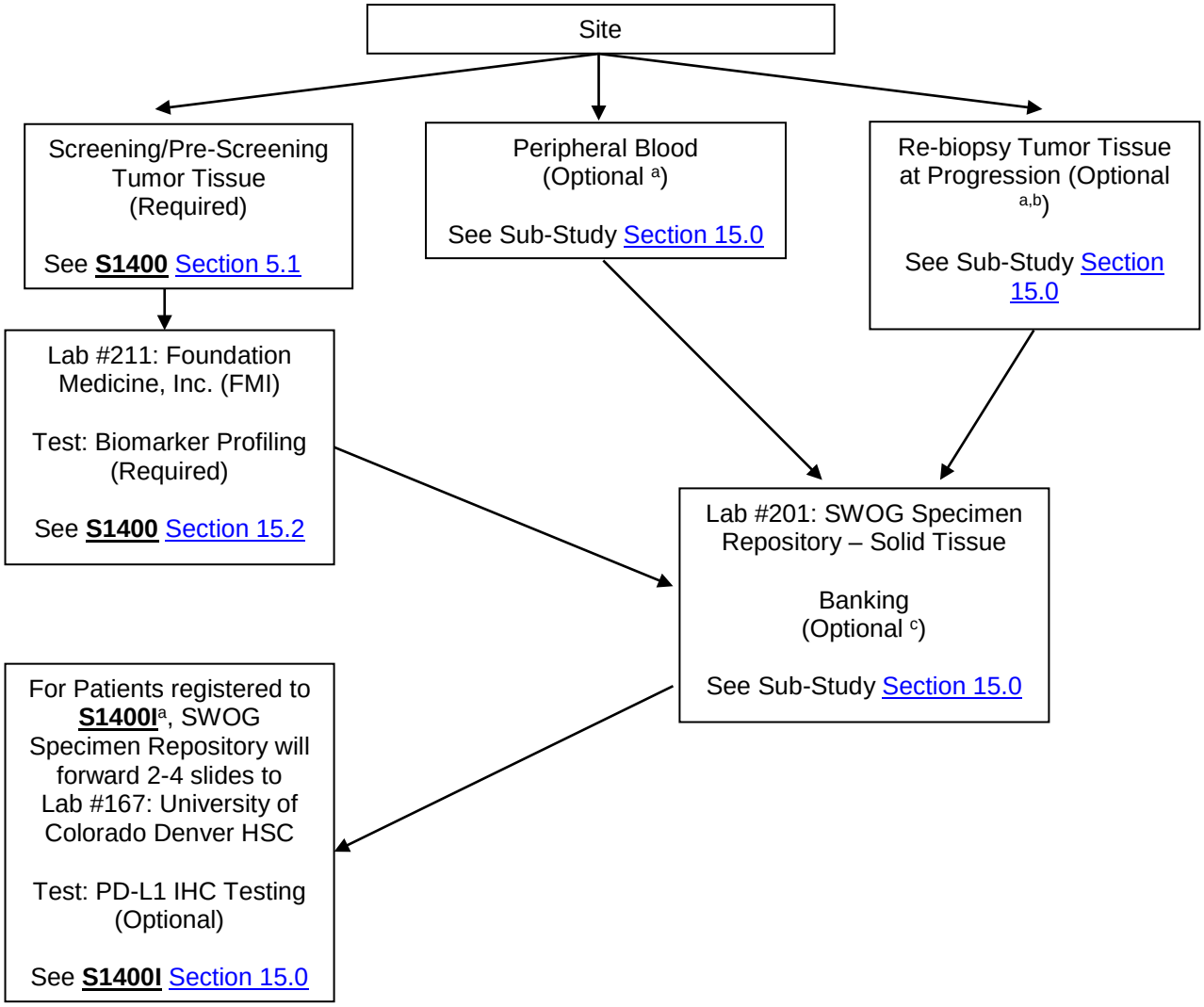
Specimen Requirements

The preferred thickness is 4 micron unstained tissue sections; although 5 micron unstained tissue sections are allowable. For patients with tumor blocks at Nationwide, Nationwide will prepare 4 micron unstained slides. At least 100 tumor cells is defined to be sufficient viable tumor tissue for PD-L1 IHC testing. Fine needle aspirates are not acceptable. A minimum of 3 unstained tissue sections along with a hematoxilyn-eosin (H&E)-stained slide or Aperio H&E-stained image will be sent to University of Colorado Denver HSC for PD-L1 IHC testing for consented patients with sufficient tissue.

Specimen Flow Diagram



a With patient's consent.

b Among patients who initiallyresponded to protocol treatment.

c With patient's consent, any remaining tissue will be sent to the SWOG Specimen Repository Solid Tissue, Myeloma and Lymphoma Division, Lab #201, for future exploratory analysis.

18.2 Translational Medicine – **S1400I** Patient Reported Outcomes (PRO)

Objectives

1. To compare symptom status by treatment arm using a validated PRO symptom measure, the M. D. Anderson Symptom Inventory (MDASI-LC) Severity Score

2. To identify PRO-based symptoms prognostic for time to progression

3. To develop a statistical model that identifies a PRO-based symptom score optimally prognostic for survival outcomes

4. To evaluate functional status/interference of symptoms with life as a prognostic variable for time to progression

5. To compare treatment-related toxicities by treatment arm at each assessment time

6. To compare EQ-5D Index scores by treatment arm.

7. To collect psychometric information (reliability and validity) data for the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ).

Background

Advanced squamous cell lung cancer (NSCLC) is associated with a significant symptom burden. Patients with NSCLC suffer from high levels of physical symptoms, the most common being cough, shortness of breath, and chest pain. *(1)* These symptoms can have serious consequences on patient functionality and quality of life and may serve as a predictor of performance status. *(2)* The ability to provide direct evidence reflecting the improvement, stabilization, or worsening of disease symptoms is invaluable to demonstrating clinical benefit, beyond survival, and informing decision making. *(3-6)*

Lung-MAP is a large scale, biomarker driven set of single arm trials for patients with advanced stage squamous cell lung cancer whose molecular profile matches a targeted therapy for that profile; it is an example of an umbrella trial. *(7)* Depending on results, some of these trials will progress to Phase III, randomized trials. Patients whose molecular profile does not match a targeted therapy will be assigned to a specific “non-match” sub-study and randomized to either treatment with a new drug or drug combination or standard of care (SOC); trials other than **S1400I** are in development. The endpoints used in Lung-MAP (PFS, OS, and RR), currently, do not adequately capture the complex symptom profile experienced by patients, which may result from the disease, the therapy, or both. We propose to fill this potential gap in the knowledge base through the addition of a set of patient-reported outcomes (PROs). Patients on **S1400I** are randomized to either SOC (Nivolumab) or the combination regimen (Nivolumab + Ipilimumab). This trial structure provides an ideal setting for evaluating the information provided by PRO measures and assessing how well PRO measures track with disease symptoms and other clinical outcomes. In addition, we have the opportunity to obtain preliminary survivorship status for this group of patients at the three yearly follow-up assessments for clinical status; we propose using the EQ-5D for this purpose.

PRO instrument:

The Lung-MAP PRO instrument for **S1400I** will include the following items that assess self-reported symptom and functional status of patients with squamous cell lung cancer. Patients will be asked to complete a total of 40 items.

1. **MDASI-LC***(3,8-11)*: **21 items**. The M. D. Anderson Symptom Inventory – Lung Cancer (MDASI-LC) asks patients to rate the severity of 13 core symptoms that are common in cancer patients once treatment begins: fatigue, sleep disturbance, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, dry mouth, distress, and sadness. Three additional lung-specific items were added for the MDASI Lung Cancer module (coughing, constipation, and sore throat). The MDASI-LC investigators *(10)* suggest elimination of the sore throat item if the treatment regimen does not include radiation therapy. As **S1400I** does not include radiation therapy, the MDASI-LC will not include this item. Patients rate each symptom's presence and greatest severity in the previous 24 hours on an 11-point (0–10) scale, with 0 representing “not present” and 10 representing “as bad as you can imagine.” The MDASI-LC questionnaire generates a mean Core symptom score for the 13 general symptoms and a mean Severity score for the Core plus two lung cancer symptom items for a total of 15 items. The MDASI-LC Interference score (six items) will also be included to address how symptoms interfere with the patient’s general activity/functional status in the last 24 hours; these items also use a 0 to10 response scale. *(3, 6, 9-11)* The MDASI-LC form will include 21 items for **S1400I**. Only the scores from the validated MDASI-LC questionnaire will be used to formally compare treatment arms in **S1400I**. This approach follows an accepted practice of only using validated PRO measures as endpoints in cancer clinical trials. *(12-14)*

2. **NSCLC-SAQ** *(15)*: **7 items.** The PRO Consortium’s NSCLC Working Group is developing the NSCLC-SAQ measure. Qualitative research has recently been conducted for this measure. An early report of qualitative research findings is available that addresses expert review to identify concepts as well as interviews with 51 patients to review draft concepts/items and patient understanding of these items; this report reflects data from the first of three waves of cognitive debriefing regarding the content validity of the NSCLC-SAQ. *(15)* To gather data that can be used in the validation of the new NSCLC-SAQ measure in the **S1400I**, we propose administering all seven items of the NSCLC-SAQ plus the MDASI-LC. There is conceptual overlap of the NSCLC-SAQ with the MDASI-LC, which generates some degree of patient response burden; this similarity in content will also increase the potential for a larger correlation between the two symptom measures. Allowing this redundancy is partly necessary in order to anchor the NSCLC-SAQ items to a known, validated instrument for documentation of psychometric properties of the new measure. The time frame does differ for these two measures, with the NSCLC-SAQ using a 7-day recall

period to address symptom severity or frequency whereas the MDASI-LC uses the past 24 hours for responses. The response option format also differs with the MDASI using a 0 to 10 scale and the NSCLC-SAQ using five response options for each item.

3. Single Items Used for Validation of New Measure: **2 Items**. A single item, patient-rating of performance status *(16-19)* based on the ECOG Performance Status measure *(20)* will be assessed as a surrogate for physical status. The MDASI-LC Interference score will also be used for this purpose. A second single item Global Rating of Change (GRC) in symptom status (Personal Communication, Charles Cleeland, February, 2016) will be obtained to identify minimally important differences in symptom status for both measures and to document the new measure's responsiveness to change. *(19, 21, 22)* The symptom severity GRC item will ask patients to rate change in the severity of symptoms "…since the last time you completed this questionnaire" (much better, better, nearly the same, worse, much worse). The GRC item is included in the **S1400I** Patient Reported Outcomes (PRO) Questionnaire; this item is not to be administered at PreStudy but should be completed starting at week 5 and at all subsequent assessments through week 36 post-registration.

4. **Four** Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) *(23)* will be included to address three toxicities (fatigue, pruritis, and diarrhea) common to the two agents used in this trial. *(24)* Fatigue treatment-related toxicity will be assessed with the PRO-CTCAE Fatigue severity item (What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK of ENERGY at its WORST [none/Mild/Moderate/Severe/Very severe]). . The degree to which fatigue interferes with daily functioning will also be assessed with one PRO-CTCAE item (How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?) Pruritis and dermatitis will be assessed with the PRO-CTCAE Itchy Skin item (What was the SEVERITY of your ITCHY SKIN at its WORST [None/Mild/Moderate/Severe/Very severe]). Diarrhea will be assessed with the PRO-CTCAE Diarrhea item (How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)[Never/Rarely/Occasionally/Frequently/Almost constantly/ Not applicable]). The time frame for these items is the last 7 days. Only Fatigue is assessed by the MDASI-LC, not the other two symptoms found to be associated with the two treatments. The MDASI-LC and the PRO-CTCAE response options differ, with the PRO-CTCAE options more tailored to the standard physician-rated CTCAEs. For this reason, we feel it is important to add these three symptoms and one fatigue interference item to the assessment package because of the interest in being able to separate disease- and treatment-related symptoms.

5. **S1400I** PRO study will also administer the EQ-5D health utility measure *(25-28)*: **6 Items**. These items addressing different health dimensions are rated with respect to no problems, some problems, or extreme problems. **S1400I** will include the single item visual analogue scale (VAS) to measure overall health status. We have used a version of the EQ-5D VAS in **S1007**. In this version, in addition to marking the point on the line reflecting the patient's "health state today", we ask the patient to write the number in the provided box on the form. This substantially

6. improves data capture and does not require staff time to record this information. Because the EQ-5D will be administered both early in follow up with the other cited measures, as well as later in follow-up (at years 1, 2, & 3) to assess survivorship status, it will be presented as a separate form.

Patient Questionnaires: Instructions for Administration

Method:
The **S1400I** Patient Reported Outcomes (PRO) Questionnaire will be administered to patients via paper-and-pencil at nine time points: Prestudy (prior to treatment initiation) and at the beginning of weeks 3, 5, 7, 9, 11, 13, 24, and 36 weeks after **S1400I** registration. In addition, the **S1400I** EQ-5D Questionnnaire will be administered at ten time points (Prestudy, weeks 5, 7, 9, 13, 24, 36, and at years 1, 2, and 3. Note: Patients registered to **S1400I** prior to 9/1/2016 are not eligible for the PRO study.

Frequency and timing:
In general, the assessment schedule emphasizes the early (first 3 months) assessments in order to minimize missing data given the advanced stage disease status of study patients who have a median survival of 9 months and to coincide with patient visits so as to link clinical assessments with patient symptom assessments. The administration of four PRO-CTCAE items will occur at the same times physicians are rating CTCAEs in order to allow for a mapping of symptom and disease progression status as well as to provide an opportunity to see if early change in symptom status is associated with clinical outcomes as reported by Eton et al. *(5)* However, we will also include PRO assessments at two later time points (24 and 36 weeks) in order to evaluate the extent of longer-term symptom and functional deterioration by treatment armExploratory analyses of the EQ-5D measure will also be conducted at years 1, 2, and 3 for preliminary data on survivorship outcomes at these later time points

As currently designed, the estimated time to administer the components of the PRO questionnaire is based on the estimate of 2-5 minutes for the MDASI and its module (21 items) *(11); a total of 10 minutes is estimated for* the addition of 7 more NSCLC-SAQ items and the inclusion of the additional items used for the NSCLC-SAQ validation. The time to complete the four PRO-CTCAE toxicity items will be very quick for patients, likely within one minute. *(29)* Also, patients were found to complete the EQ-5D in only a few minutes. *(25)* Therefore, we estimate that the inclusion of four PRO-CTCAE and the six EQ-5D items will add two to three minutes, so the total time to complete all 40 items will be approximately $\leq$ 15 minutes. The assessment schedule will also minimize data loss as collection will be linked with the timing of some clinical assessments and submitted simultaneously; staff and patient burden will also be minimized. For the Global Rating of Change (GRC) item, patients will be asked to respond with respect to change in symptom status since the last time the patient completed the questionnaire.

Four of the PRO sets of measures (MDASI-LC, NSCLC-SAQ, two single items measures to be used for validation of the NSCLC-SAQ, and the four PRO-CTCAE items) will be included in a separate, single form. This form, the **S1400I** Patient Reported Outcomes (PRO) Questionnaire will be administered only through week 36. In addition, the GRC item is not administered at PreStudy because it is addressing the patients's perception of change in symptom status. Patients are to be instructed to begin answering the GRC item at week 3.

We are also including longer term (years 1, 2, and 3) follow-up assessments using only the **S1400I** EQ-5D Questionnaire as a measure of survivorship status. The assessment times correspond to protocol-specified clinical outcome assessments. Patients will be asked to complete the **S1400I** EQ-5D Questionnaire in the clinic or by phone if the patient does not come to the clinic. The EQ-5D will be presented to patients in a separate form, the **S1400I** EQ-5D Questionnaire and this form will have a separate cover sheet, the **S1400I** Cover Sheet for the **S1400I** EQ-5D Questionnaire, because it is to be administered for a longer time period.

Recall period:
The recall period for the MDASI-LC is the last 24 hours; the recall period for the NSCLC-SAQ and the PRO-CTCAE items is the last seven days. Research staff should remind patients to answer questions accordingly. Note, studies have shown psychometric properties remain consistent independent of recall period. *(8)* The recall period for the EQ-5D is your health status on the day the measure is completed so its recall period is more similar to the MDASI-LC measure. *(25)*

Administration of Questionnaires:

1. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each section. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.
2. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note what assistance was required and indicate reason in the Comments section of the **S1400I** Cover Sheets for the two PRO forms (e.g., elderly, too sick, etc.). Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.
3. It is very important to review the questionnaires after completion by the patient to be sure all of the questions have been answered and that only one answer is marked. If the patient has marked more than one answer per question, ask the patient which answer reflects how he/she is feeling. If the patient skipped a question, tell the patient that a question was not answered and ask if he/she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.
4. If a patient refuses or cannot complete the questionnaire for some reason, then this must be documented in the Comments section of the **S1400I** Cover Sheets, depending on the form being completed by the patient; he/she should be asked to do so at the next scheduled administration time.
5. If a patient cannot be available on the scheduled date of assessment for any reason, follow the established protocol windows per Best Practices for SWOG Studies.
   http://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.
6. Alternatively, if a patient is too sick to complete the questionnaires in the clinic on the scheduled date, the questionnaire can be mailed to the patient or sent home with him/her. A telephone interview must be scheduled and completed within the allowed window (from the scheduled date of the assessment) per Best Practices for SWOG Studies. Patient responses to

questionnaire items are to be obtained during the telephone interview while the patient is looking at a copy of the questionnaire. The date of the telephone interview is to be noted in the Comments section of the **S1400I** Cover Sheets for the PRO forms.

Additional quality control procedures:

1. When a patient is registered to **S1400I**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed before receiving treatment. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this should be kept in the patient file.
2. If a patient goes off protocol treatment, continue to administer the patient completed questionnaires according to the protocol-defined assessment schedule (time from registration date).
3. The Nurse PRO/QOL Study Coordinator, will monitor compliance on a regular basis using the Expectation Report and the MediData RAVE system. Medidata RAVE will provide reminders of upcoming PRO assessments for a patient.

Anyone involved in the collection of quality of life/PRO data in SWOG trials should review the Patient Reported Outcome Training narrated slide program available on the SWOG website (www.swog.org, CRA Training, Tools of the Trade). This program is designed to standardize the way quality of life data are collected from patients. Contact cancercontrolquestion@crab.org for questions regarding the quality of life/PRO assessments OR the Nurse PRO/QOL Study Coordinator: Susan S. Tavernier, PhD, APRN-CNS, AOCN.

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Eligibility:

All patients must be eligible for the clinical component of **S1400I** and able to complete the PRO instruments in English. That is, the Prestudy PRO questionnaire forms are required for study eligibility if the patient can complete them in English. If a patient is deemed ineligible during the trial but continues protocol treatment, he/she should continue the PRO assessments as scheduled.

Endpoint(s) to be used in analyses:

For the **S1400I** protocol, progression free survival (PFS) and overall survival (OS) are the primary endpoints and the response rate (RR) is a secondary endpoint. The reduction of symptoms based on the validated PRO measures will also be considered a secondary endpoint. The PRO endpoints are described in the PRO Instrument section, above.

Experimental research techniques/tests employed and expertise of PI:

Research staff should be trained to administer PRO forms by viewing a training module available on the SWOG website [www.swog.org]; from the home page, the program can be found at the QUICKLINKS section as noted above. For example, this training program indicates that research staff should not influence the patient's responses to the questionnaires. Non-SWOG research staff can access the PRO training program directly on the SWOG home page. Research staff will need to enter the reported data into the online Medidata RAVE system.

Efforts to minimize missing data are critical to obtaining interpretable results. Again, the PRO training module addresses methods for reducing missing data.

Statistical Plan:

Primary Endpoints

PRO assessments will occur in conjunction with the clinical follow-up schedule already in place for **S1400I** and are scheduled for baseline and weeks 3, 5, 7, 9, 11, 13, 24, and 36. Two primary endpoints will be assessed, corresponding to an early assessment at week 7 when clinically meaningful differences by arm may first occur, and a late assessment at week 13 to identify potentially long-term differences.

The primary endpoint is the MDASI-LC Severity score. With respect to a minimally important difference (MID) between arms, Mendoza et al. *(10)* identified a difference of 1.06 points in the MDASI severity index (MDASI core 13 items plus the lung-specific items) between lung cancer patients with good vs. poor ECOG performance status, suggesting that such a difference is clinically meaningful. Also, prior literature in other disease settings suggests an MID for the MDASI in the range of 0.98 to 1.21 points. *(9-11)* Based on these data, we specify an average difference of 1.0 point in the MDASI severity score to be considered clinically meaningful.

Relying on the work by Mendoza et al. *(10)*, the standard deviation for assessment of the severity scale at 6 weeks of chemotherapy treatment was 1.88 points and at 12 weeks was 1.71 points.(Cleeland, personal communication; Mendoza, personal communication). For power calculations, we assume a higher (more conservative) standard deviation of 2.0 points for both time points, corresponding in general to an approach wherein the MID is half a standard deviation. *(30,31)*

The study specifies a median overall survival of 9 months on the standard arm, which suggests that approximately 10% of patients will have died by the time of their assessment at week 7 under exponential assumptions. In addition, conservatively, we assume another 10% will drop out due to worsening disease, and 10% will be non-adherent. Note that in power calculations, the 10% non-adherence rate reduces the nominal effect size of a 1.0 point target difference to 0.90, while the total 20% dropout rate inflates the estimated sample size by a factor of 1/(1-0.2) or 25%. The study anticipates enrolling n=332 eligible patients. Using a two-arm normal design, a two-sided alpha=.025 test (to account for multiple comparisons using Bonferroni), and the parameters specified above, a difference of 1.0 points between arms can be identified with 92% power.

For the week 13 endpoint, with a median overall survival of 9 months on the standard arm, approximately 20% of patients will have died. In addition, we assume 15% will drop out due to worsening disease and 15% will be non-adherent. With all other parameters the same, a difference of 1.0 points between arms can be specified with 81% power.

Power will vary as a function of the observed standard deviation, the total dropout, and non-adherence as shown in the table below.

Table: Power as a Function of Observed SD and Dropout

		Observed Standard Deviation				
Total Dropout*	**Non-Adherence**	**1.8**	**1.9**	**2.0**	**2.1**	**2.2**
15%	10%	98%	96%	94%	91%	88%
	15%	96%	94%	91%	88%	84%
20%	10%	97%	95%	**92%**	89%	86%
	15%	95%	92%	89%	85%	82%
25%	10%	96%	93%	90%	87%	84%
	15%	93%	90%	87%	83%	79%
30%	10%	94%	91%	88%	85%	81%
	15%	91%	88%	84%	80%	76%
35%	10%	92%	89%	86%	82%	78%
	15%	89%	85%	**81%**	77%	73%

* Includes dropout due to worsening disease and death.

Consistent with the design, the co-primary analyses of the week 7 and week 13 severity scores will be conducted using multiple linear regression analyses, adjusting for stratification factors and the baseline severity score as covariates. We will also conduct longitudinal modeling of the outcome measures over time. Power for the longitudinal analysis will be greater since the addition of all available MDASI severity scores over time will provide more information. For longitudinal modeling, linear mixed models will be used. The potential for differential dropout by arm will be mitigated by reminder notifications to site investigators to encourage proper assessment and submission of forms at every required time point for all patients. Dropout patterns will be monitored on an ongoing basis. Nonetheless the potential for non-random dropout exists. Cohort plots will be prepared to examine the extent to which missing data are informative (i.e., scores are higher (worse) for patients just before their data are missing for the subsequent assessment). If there is evidence of non-random dropout, pattern-mixture models will be utilized as a sensitivity analysis. *(32-34)* Covariates for longitudinal modeling will include intervention assignment, assessment time, their interaction, the baseline score, and a limited set of potential confounding variables (*e.g.,* age).

Secondary Endpoints

The following additional secondary endpoints will be examined:

A) Descriptive data will be presented, including the difference in the MDASI-LC mean Severity scores for the two treatment arms at baseline and weeks 3, 5, 7, 9, 11, 13, 24, and 36.

B) We will assess treatment differences at the remaining time points individually. That is, we will also assess the week 3, 5, 7, 9, 11, 13, 24, and 36 scores using a linear regression analysis adjusting for stratification factors and the baseline score.

C) We will examine the influence of treatment on the MDASCI total score (all 21 items) at the follow-up assessment times.

D) We will assess whether individual symptom items within the MDASI are prognostic for time to progression. The MDASI core item scale (13 total items), the MDASI Severity scale (core plus lung symptoms, 15 total items), and the MDASI total score (all 21 items) will also be examined for their potential to predict time to progression. First, we will examine whether each of the 21 individual items or the 3 index scores predicts progression in bivariate analyses, adjusted for treatment arm. Candidate items will be further explored in multivariable analyses adjusting for stratification and a limited number of additional covariates (e.g., age). Given that this objective is exploratory, candidate factors that are prognostic will rely on $p<.05$ and will not adjust for multiple comparisons.

Initial examinations will be based on baseline PRO measures. However, we will also consider the potential prognostic value of the difference between the baseline and Week 5 measures, since deterioration as reflected in the PRO measures may not have begun until after treatment initiation. A landmark approach will be used to avoid endogeneity between the predictor (PRO assessment) and outcome (progression).

E) We will develop a statistical model that identifies a PRO-based symptom scale that is optimally prognostic for survival outcomes. The first step will be identifying the individual items prognostic for progression at $p<.05$ as indicated above, with each variable considered on a continuous scale. We will use best subset selection, which determines the “best” model based on the global Chi-squared statistic. *(35)* The best 2, 3, 4, and 5 variable models will be identified. For final model determination, we will use the mean of the q variables and create an indicator variable, split at the median. We will then identify which of the q-variable models maximizes the hazard ratio in a Cox regression, adjusted for treatment and the stratification variables. We anticipate the model building process will incorporate resampled K-fold cross-validation to adjust for adaptive multiple model selection. This modeling approach will be repeated for overall survival.

F) We will examine three individual Interference items from the MDASI-LC that address physical function/functional status [General activity; Work (including work around the house); Walking]) to see if this PRO domain is prognostic for progression. Although we do not have a physical function scale as part of the **S1400I** PROs, the individual MDASI-LC items relevant to this domain can provide an exploratory examination of the value of early decline in physical function status for later clinical outcomes.

G) An exploratory analysis will compare the three treatment-related toxicities (fatigue, pruritis, and diarrhea) by treatment arm at each of the scheduled assessment times using the PRO-CTCAE item scores.

H) Additional exploratory analyses will describe differences in EQ-5D Index scores by treatment arm, including the examination of Index scores by arm at years 1, 2, and 3 to allow characterization of long term survivorship status for the different treatment groups.

DSMC approval will be required in any instance where early reporting of PRO results is sought.

VALIDATION

Analysis of Preliminary Validation Data for the Unvalidated NSCLC-SAQ Items: Phase II Trials

Undimensionality (36)*:* An exploratory factor analysis (EFA) will be done to identify the number of factors present in the NSCLC-SAQ. Support for a single factor measure will be examined with respect to commonly used criteria (e.g., scree test, the percent variance accounted for by the first factor, etc.); a confirmatory factor analysis (CFA) will fit a single factor model to the data to see fit statistics (e.g., CFI, RMSEA, etc.).

Internal Consistency Reliability: Coefficient alpha will be calculated for the either a single set of 7 NSCLC-SAQ items or for the number of scores based on the number of factors suggested by the EFA and CFA. Alphas ≥ 0.70 are of interest. (36)

Validity (36):
Construct Validity. Known groups comparisons will be made for mean scores by a set of variables where the levels of each variable can be hypothesized to generate different mean scores. The SWOG data will examine differences in patient-reported Zubrod performance status *(16-18)* (0-1, vs. 2) with respect to each item of the NSCLC-SAQ as well as the total score(s) if supported by the analyses above. Patients with performance status=2 would be expected to report worse symptom status on the NSCLC-SAQ that patients categorized as 0-1. We will also examine the comparisons using the patient-reported performance status item.

Criterion Validity. Given support for a total score, we expect the correlation between the MDASI-LC and the NSCLC-SAQ to be at least 0.35 (medium effect size for a correlation and 0.50 (large effect size for a correlation. *(30)* Given that the MDASI-LC is an established measure of lung cancer symptoms, it becomes the criterion measure. Reliability of each of the two measures being correlated is also a factor in their correlation.

Responsiveness: The effect size for the change in NSCLC-SAQ total scores between randomization and week 13 will be examined; effect sizes between 1/3 and ½ of a standard deviation will be of interest. *(37)* In addition, using the single item patient-reported global rating of change (GRC) in symptom severity status, we will examine the mean scores for patients who report different levels of

change (i.e., those who report much better, much worse, better, worse, nearly the same); we will also combine the much better and the better categories for a three-level measure of perceived change in symptom status. These latter analyses will allow preliminary identification of minimally important differences. *(19, 21, 22)*

Data analysis performed by: Joseph Unger, PhD

Disclosure of conflict of interest:
There are no conflicts of interest reported

Other considerations (including plan for financial support, grant submission, etc.): Additional support will be sought from the Lung-MAP PRO collaborating organizations to conduct analyses of the validation data and to transfer any data from the Statistical Center to any Lung-MAP PRO Working Group collaborators.

References

1. Iyer S, Roughley A, Rider A, Taylor-Stokes G. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer 22, 181-187, 2014. [PMID: 24026981]

2. Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, van Zandwijk N, Di Maio M, Martelli O, De Marinis F. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. Annals of Oncology 15, 419-426, 2004. [PMID: 14998843]

3. Barney BJ, Wang XS, Lu C, et al. Prognostic value of patient-reported symptom interference in patients with late-stage lung cancer. Qual Life Res 22, 2143-2150, 2013. [PMID: 23371797]

4. Gotay CC, Kawamoto CT, Bottomley A, et al The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 26(8), 1355-1363, 2008. [PMID: 18227528]

5. Eton DT, Fairclough DL, Cella D, Yount SE, Bonomi P, Johnson DH. Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: Results from Eastern Cooperative Oncology Group Study 5592. J Clin Oncol 21(8), 1536-1543, 2003. [PMID: 12697878]

6. Wang XS, Shi Q, Lu C, et al. Prognostic value of symptom burden for overall survival in patients receiving chemotherapy for advanced non-small cell lung cancer. Cancer 116(1), 137-145, 2010. [PMID: 19852033]

7. Kummar S, Williams PM, Lih CJ, et al. Application of molecular profiling in clinical trials for advanced metastatic cancers. J Natl Cancer Inst 107(4), djv003 [pages 001-006], 2015. [PMID: 25663694]

8. Shi Q, Trask PC, Wang XS, et al. Does recall period have an effect on cancer patients' ratings of the severity of multiple symptoms? Journal of Pain and Symptom Management 40(2), 191-199, 2010. [PMID: 20579835]

9. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients. Cancer 89(7), 1634-1646, 2000. [PMID: 11013380]

10. Mendoza TR, Wang XS, Lu C, et al. Measuring the symptom burden of lung cancer: the validity and utility of the Lung Cancer Module of the M. D. Anderson Symptom Inventory. The Oncologist 16, 217-227, 2011. [PMID: 21285393]

11. Cleeland CS. The M. D. Anderson Symptom Inventory. User Guide Version 1. Houston, TX: The University of Texas M. D. Anderson Cancer Center, 2014. https://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/MDASI_userguide.pdf

12. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res 22(6), 1161-1175, 2013. [PMID: 22987144]

13. Calvert M, Blazeby J, Altman DG, et al, Reporting of patient-reported outcomes in randomized clinical trials: The CONSORT PRO Extension. JAMA 309(8), 814-822, 2013. [PMID: 23443445]

14. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Quality of Life Research 22(8), 1889-1905, 2013. [PMID: 23288613]

15. Critical Path Institute, & Patient-Reported Outcome (PRO) Consortium Non-Small Cell Lung Cancer (NSCLC) Working Group. Preliminary development of the Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ). Tucson, AZ: Critical Path Institute, 2015. http://c-path.org/programs/pro/

16. Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy -- Lung (FACT-L) quality of life instrument. Lung Cancer 12(3), 199-220, 1995. [PMID: 7655830]

17. Basen-Engquist K, Bodurka-Bovers D, Fitzgerald MA, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Ovarian. Journal of Clinical Oncology 19(6), 1809-1817, 2001. [PMID: 11251013]

18. Yost KJ, Cella D, Chawla A, et al. Minimally important differences were estimated for the functional Assessment of Cancer Therapy--Colorectal (FACT-C) instrument using a combination of distribution- and anchor-based approaches. Journal of Clinical Epidemiology 58, 1241-1251, 2005. [PMID: 16291468]

19. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. Journal of Clinical Epidemiology 64(5), 507-516, 2011. [PMID: 21447427]

20. Zubrod CG, Schneiderman M, Frei E, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. J Chronic Diseases 11, 7-33, 1960. http://www.jameslindlibrary.org/zubrod-cg-schneiderman-m-frei-e-brindley-c-gold-gl-shnider-b-oviedo-r-gorman-j-jones-r-jonsson-u-colsky-j-chalmers-t-ferguson-b-dederick-m-holland-j-selawry-o-regelson-w-lasagna-l-ow/

21. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. Evaluation & The Health Professions 28(2), 172-191, 2005. [PMID: 15851772]

22. Yost KJ, Sorensen MV, Hahn EA, et al, Cella D. Using multiple anchor- and distribution-based estimates to evaluate clinically meaningful change on the Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) instrument. Value in Health 8(2), 117-127, 2005. [PMID: 15804320]

23. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's Patient-Reported outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncology 1(8):1051-1059, 2015. [PMID: 26270597]

24. Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. Nature Reviews Clinical Oncology 11(2), 91-99, 2014. [PMID: 24445516]

25. Cheung K, Oemar M, Oppe M, Rabin R. On behalf of the EuroQoL Group EQ-5D. User Guide. Basic information on how to use EQ-5D, 2009. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-Y_User_Guide_v1.0_2014.pdf

26. Luo N, Johnson JA, Shaw JW, et al. Self-reported health status of the general adult U. S. population as assessed by the EQ-5D and Health Utilities Index. Medical Care 43(11), 1078-1086, 2005. [PMID: 16224300]

27. Pickard AS, De Leon MC, Kohlmann T, et al. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Medical Care, 45(3), 259-263, 2007. [PMID: 17304084]

28. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health and Quality of Life Outcomes 5(70), 2007. [PMID: 18154669]

29. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminiology Criteria for Adverse Events (PRO-CTCAE). J Natl Cancer Inst 106(9), Published online September 29, 2014. [PMID: 25265940]

30. Cohen J. Statistical power analysis for the behavioral sciences (Second Edition ed.). Hillsdale, New Jersey: Lawrence Erlbaum Associates, Publishers, 1988.

31. Sloan JA, Dueck AC. Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. J Biopharm Stat 14(1), 73-96, 2004. [PMID: 15027501]

32. Little RJA. A class of pattern-mixture models for normal incomplete data. Biometrika 81, 471-483, 1994. http://biomet.oxfordjournals.org/content/81/3/471.abstract

33. Pauler DK, McCoy S, Moinpour C. Pattern mixture models for longitudinal quality of life studies in advanced stage disease. Stat Med 22(5), 795-809, 2003. [PMID: 12587106]

34. Fairclough DL. Design and analysis of quality of life studies in clinical trials, Second Edition (2nd ed.). Boca Raton, FL: Chapman & Hall/CRC, Taylor & Francis Group, LLC, 2010. http://file.zums.ac.ir/ebook/173-Design%20and%20Analysis%20of%20Quality%20of%20Life%20Studies%20in%20Clinical%20Trials,%20Second%20Edition-Diane%20L.%20Fa.pdf

35. Furnival GM, Wilson RW. Regressions by leaps and bounds. Technometrics 16, 499-511, 1974. http://www.stat.washington.edu/adobra/classes/536/Files/week3/leapsandbounds.pdf.

36. Nunnally J.C. Psychometric theory (Second ed.). New York, NY: McGraw-Hill Publishing Co, 1978.

37. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy -Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. Journal of Clinical Epidemiology 55, 285-295, 2002. [PMID: 11864800]

Informed Consent Model for S1400I

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making additions, deletions, or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	59.1 (targeted above 55)
Flesch-Kincaid Grade Level	9.2 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations

Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Study Title for Study Participants: Targeted Treatment for Advanced Squamous Cell Lung Cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

S1400, "A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer"
S1400I, "A Phase III Randomized Study of Nivolumab Plus Ipilimumab Versus Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarker (Lung-MAP Sub-Study)"

What is the usual approach to my lung cancer?

Squamous cell lung cancers make up about one-fourth of non-small cell lung cancer. Various chemotherapy drugs have been shown to improve survival for patients with advanced squamous lung cancer. Most patients will be treated at first with cisplatin or carboplatin in combination with a second chemotherapy drug such as gemcitabine, paclitaxel, docetaxel, or vinorelbine. In addition, an immunotherapy drug called nivolumab was recently FDA approved for patients with squamous lung cancer who previously received chemotherapy.

What are my other choices if I do not take part in this study?

Your other choices may include:

- **You may choose to have the usual approach described above**
- **You may choose to take part in a different study, if one is available**
- **You may choose to get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

Why is this study being done?

There are several investigational treatments that are being tested in various sub-studies as part of this study. You will have already received the information on your biomarker testing. You have been assigned to this treatment study because your tumor sample did not have a biomarker that matches one of the treatment studies or because you were not a candidate for a biomarker-matched treatment study. You have been assigned to a treatment study testing a drug that works with your immune system to fight your cancer. For this sub-study, you will be assigned to treatment with either nivolumab (the current standard of care) or to nivolumab combined with ipilimumab (the investigational therapy). The purpose of this sub-study is to learn if the study drug will improve the average time to cancer worsening by more than a month. Nivolumab combined with ipilimumab is investigational for this study. Nivolumab combined with ipilimumab may or may not shrink your cancer but it could also cause side effects. This study will allow the researchers to learn any good and bad effects of nivolumab combined with ipilimumab.

There will be about 350 patients taking part in this study.

What are the study groups?

You have been assigned to this sub-study because your tumor sample did not have any of the biomarkers being tested in the other sub-studies or you were not eligible to participate on the other sub-studies. This sub-study has two study groups (arms). A computer will by chance assign you to a treatment arm in the study. This is called randomization. This is done by chance because no one knows if one study arms is better or worse than the other. You have an equal chance of receiving the study drug or the standard treatment.

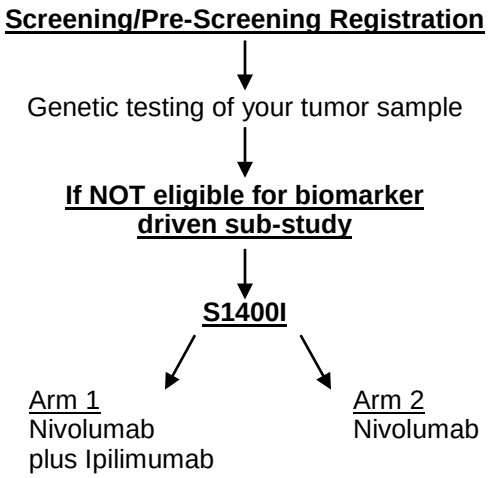
Patients assigned to Arm 1 will receive the study drug nivolumab combined with ipilimumab and nivolumab will be given via vein over 30 minutes on Day 1 of every 14 day cycle. Ipilimumab will be given via vein over 60 minutes on Day 1 of every **third cycle**. A cycle is 14 days.

Patients assigned to Arm 2 will receive the study drug nivolumab alone, one of the standard treatments for this cancer. Nivolumab will be given via vein over 30 minutes on Day 1 of every 14 day cycle. A cycle is 14 days.

The treatments on this study are described in the table below:

Arm	Drug	How often is it given?	How is it given?	What days is it given on?	What is the cycle duration?
1	Nivolumab	Once, every 14 days	Into a vein	Day 1	14 days
1	Ipilimumab	Once, every 42 days	Into a vein	Day 1 of every **third cycle**	14 days
2	Nivolumab	Once, every 14 days	Into a vein	Day 1	14 days

Another way to find out what may happen to you during the study is to read the chart below. Start reading at the top of the chart and read down, following the arrows.



How long will I be in this study?

You will receive treatment until your disease worsens. After you are finished taking study treatment, the study doctor will continue to watch you for side effects and follow your condition for 3 years from the time you started treatment. At the follow up visits you will have a physical exam, blood tests, and scans. Your doctor may give you other tests or procedures if they think they are needed.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra exams, tests, and/or procedures that you will need to have if you take part in this study.

Before you begin the study:

- Brain CT or MRI (to check if your cancer may have spread to your brain)
- (*Deleted 7/19/16*)
- Blood tests to assess your pancreas functions and your levels of hormones coming from your thyroid
- Questionnaires – You will complete questionnaires in English on how you are feeling physically and how you are performing your daily activities. You will also be asked questions about symptoms you may be having. Researchers will use this information to learn more about how cancer and cancer treatment affects people. *(Added 7/19/16)*

Note: You might receive the above tests even if you were not on the study as part of your cancer treatment.

You will have a CT or MRI done before you begin the study and then approximately every 6 weeks for the first year, then every 3 months until your disease worsens. Your doctor will review

the CT scans or other radiographic scans done to check on your tumors on a regular basis. These scans will also be sent to a central location for review. This central review is part of a total study analysis only. Information of your scans from the central review will not be sent back to you or your doctor.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests. They are not part of the usual approach for your type of cancer.

During the study:

- Blood tests to assess your pancreas functions and your levels of hormones coming from your thyroid
- Questionnaires – You will complete questionnaires in English, on how you are feeling physically and how you are performing your daily activities. You will also be asked questions about symptoms you may be having. Researchers will use this information to learn more about how cancer and cancer treatment affects people. *(Added 7/19/16)*

The blood test to assess your pancreatic functions will be done before you begin the study and approximately every 6 weeks. (*Revised 7/19/16*) The blood test to assess your levels of hormones coming from your thyroid will be done before you begin the study and approximately every 6 weeks.

You will be asked to complete forms before you start the study treatment, at weeks 3, 5, 7, 9, 11, 13, 24, 36, and at the end of years 1, 2, and 3. The forms will take about 15 minutes to complete. Some questions on the forms will ask about symptoms such as shortness of breath, itching, and diarrhea; you will also be asked if the symptoms interfere with your daily life. If you feel uncomfortable answering any of the questions, you can skip any you do not want to answer. *(Added 7/19/16)*

Neither you nor your health care plan/insurance carrier will be billed for the following tests for this study:

- Blood tests to assess pancreatic functions (Amylase and Lipase tests)
- Blood tests to assess for the thyroid tests (TSH, Free T3/T4)

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- **Lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **Be asked sensitive or private questions which you normally do not discuss**

The treatment used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Nivolumab

Special precautions
Side effects of nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.** *(Added 1/19/17)*

COMMON, SOME MAY BE SERIOUS

In 100 people receiving nivolumab, more than 20 and up to 100 may have:

- **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving nivolumab, from 4 to 20 may have: *(Table Replaced 1/19/17)*

- **Anemia which may require blood transfusion**
- **Swelling and redness of the eye**
- **Pain in belly**
- **Diarrhea, nausea, loss of appetite**
- **Dry mouth**
- **Fever**
- **Swelling and redness at the site of the medication injection**
- **Bruising, bleeding**
- **Pain or swelling of the joints**
- **Reaction during or following a drug infusion which may cause fever, chills, rash**

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.**
- **Skin: itching; rash, blisters including inside the mouth; loss of skin pigment**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting**

RARE, AND SERIOUS

In 100 people receiving nivolumab, 3 or fewer may have: *(Table Replaced 1/19/17)*

- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness**
- **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.**
- **Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.**
- **Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck**
- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.**
- **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.**

Possible Side Effects of Ipilimumab

Special precautions

Side effects of ipilimumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab is used in combination with nivolumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.** *(Added 1/19/17)*

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab, more than 20 and up to 100 may have: *(Table Replaced 1/19/17)*

- **Diarrhea, nausea**
- **Tiredness**

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Skin: itching; rash, blisters including inside the mouth (can be severe); hives**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab, from 4 to 20 may have: *(Table Replaced 1/19/17)*

- **Abnormal heartbeat**
- **Hearing loss**
- **Swelling and redness of the eye**
- **Pain in belly**
- **Difficulty swallowing, vomiting, loss of appetite**
- **Fever**
- **Dehydration**
- **Pain or swelling of the joints**
- **Reaction during or following a drug infusion which may cause fever, chills, rash**
- **Low blood pressure which may cause feeling faint**

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.**
- **Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine.**
- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.**

RARE, AND SERIOUS In 100 people receiving ipilimumab, 3 or fewer may have: *(Table Replaced 1/19/17)*
• **Bleeding** • **Blockage of the bowels which may cause constipation** • **Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion** **Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:** • **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma** • **Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.** • **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.**

*This is applicable for patients who have undergone a stem cell transplant. *(Added 3/3/16)*

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study as the drugs used in this study could be very damaging to an unborn baby. Women who receive these drugs should use effective contraception during the period of the trial and for at least 23 weeks (5 months) after completion of treatment. Men who receive these drugs should use effective contraception during the period of the trial and for at least 31 weeks (7 months) after completion of treatment. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drug/study approach is better than the usual approach, so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The nivolumab and ipilimumab will be supplied at no charge while you take part in this study. The cost of getting the nivolumab and ipilimumab ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the nivolumab and ipilimumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, SWOG, and the drug company supporting the treatment sub-study you are on.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration (FDA) and the National Cancer Institute (NCI) in the U.S., and similar ones if other countries are involved in the study
- TRIAD-Your medical images with clinical study data (e.g., the treatment Group you are assigned to, etc.) will be transferred to the Ohio State University in Columbus, Ohio. Your medical images will be reviewed by physicians at this organization as part of the study analysis for this trial. In addition, information gained from this study may be used in the future for additional research and only that data would be provided to other scientist for future research. Your name, and any other information that could be used to identify you personally, will not be included.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: The above paragraph complies with the new FDA regulation found at 21CFR50.25 (c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Optional Additional Biopsy and Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this part of the study, the researchers would also like to ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) Your specimens may be stored in the Biobank, along with samples from other people who take part. These specimens may include:
    - About 1 tablespoon of blood will be collected from a vein in your arm (at the same time as other study blood tests) on Weeks 3, 7, 9, and again if your cancer gets worse.
    - A sample of tissue will be collected from an optional extra biopsy if your cancer gets worse after treatment on this study. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain and bruising at the biopsy site, which can be treated with regular pain medications.

      Rarely, an infection can occur. Rarely, patients may experience partial lung collapse that may require a chest tube or breathing machine. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place. The samples will be kept until they are used up.
2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. (*Deleted 7/19/16*) The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The law prevents discrimination from health insurers and employers. This law does not cover life insurance, disability insurance and long-term care insurance. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

Neither you nor your health care plan/insurance carrier will be billed for the collection or testing of the tumor tissue or blood samples that will be used for this study. *(Revised11/18/15)* You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial).*

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR FUTURE RESEARCH STUDIES:

1. **My tumor tissue and related information may be kept in a Biobank for use in future health research.**

   YES NO

2. **My blood samples and related information may be kept in a Biobank for use in future health research.**

   YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled ‘yes’.

Participant’s signature_____

Date of signature_____