SWOG CANCER RESEARCH NETWORK

November 27, 2023

Larissa Korde, MD, MPH
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

RE: Amendment #27 of Protocol #S1404: "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma" Primary Study Chair: Sapna P. Patel, MD.

Dear Dr. Korde:

Thank you for your review of the above-referenced SWOG protocol. The following concerns were expressed in the letter of 10/24/2023. We would like to take this opportunity to respond to these concerns.

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	1.4	The translational medicine objectives must be stated in the body of the protocol. Please add these back to the Objectives Section. **PI Response: The section has been updated with the translational medicine objectives.**
2.	18.8 c	This section states, "No specimens, demographic data, or PHI will be provided to Thermo Fisher." However, the amended text of the section clearly states that the assays will now be performed at Thermo Fisher. Please reconcile. **PI Response: The section has been updated to clarify that the assays will now be performed at Thermo Fisher.**

II. Recommendations:

#	Section	Comments
3.	**CTSU Address and Contact Information Table** **Page 5**	**Revise the text in this section, as shown below, to reflect the updated CTSU template language.** **For patient enrollments:** Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is ~~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 by phone or email: 1-888-823-5923 or ~~a~~t ctsucontact@westat.com

#	Section	Comments
		PI Response: The section has been updated.
4.	**CTSU Address and Contact Information Table** **Page 5**	**Replace the text in this section with the following updated CTSU template language.** The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). 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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website. **PI Response: The section has beenwas updated.**
5.	**Section 13.2.a** **CTEP Investigator Registration Procedures Page 85**	**Replace this paragraph in this section with the following updated CTSU template language.** Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability. **PI Response: The section has beenwas updated.**
6.	**Section 13.2.a** **CTEP Investigator Registration Procedures Page 85**	**Revise the text in this section, as shown below, to reflect the updated CTSU template language.** ~~An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition,~~ IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

#	Section	Comments
		• Addition to a site roster; • Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN; • Ability to be named as the site-protocol Principal (PI) on the IRB approval; and • Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL). In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov. **PI Response: The section has been updated.**
7.	**Section 13.2.c** **CTEP Registration Procedures Page 86**	**Replace these paragraphs in this section with the following updated CTSU template language.** This study is supported by the NCI CTSU. **IRB Approval** As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations. Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically

#	Section	Comments
		communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878). *Include the following (highlighted) paragraph for trials that will include sites using their local IRB or REB as well as for trials with non U.S.-based NCTN and NCORP sites.* Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes: • Local IRB documentation; • IRB-signed CTSU IRB Certification Form; and/or • Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form. In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record: • Have an active CTEP status; • Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster; • If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record; • Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; • List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and • Have the appropriate CTEP registration type for the protocol. **Additional Requirements** Additional site requirements to obtain an approved site registration status include: • An active Federal Wide Assurance (FWA) number;

#	Section	Comments
		• An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); • An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and • Compliance with all applicable protocol-specific requirements (PSRs). **PI Response: The section has been updated.**
8.	**Section 13.2.c** **CTEP Registration Procedures Page 87**	**Revise the text in this section, as shown below, to reflect the updated CTSU template language.** **Downloading Site Registration Documents:** Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms: • Log in to the CTSU members' website (https://www.ctsu.org) ~~using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);~~ • Click on *Protocols* in the upper left of the screen: o Enter the protocol number in the search field at the top of the protocol tree; or o Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol number *S1404.* • Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.) **PI Response: The section has been updated.**
9.	**Section 13.4** **Registration Procedu**	**Replace the text in this section with the following updated CTSU template language.**

#	Section	Comments
	res Page 90	***Patient Enrollment*** The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave. Requirements for OPEN access: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; • To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type; • If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and • Have an approved site registration for the protocol prior to patient enrollment. To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL. Prior to accessing OPEN, site staff should verify the following: • Patient has met all eligibility criteria within the protocol stated timeframes; and • All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable). Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records. Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of

#	Section	Comments
		the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. **PI Response: The section has been updated.**
10.	**Section 14.3** **Data Submission Requirements Page 91**	**Replace the text in this section with the following updated CTSU template language.** Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: • Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; • Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and • Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an

#	Section	Comments
		eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the *Data Management* section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response: The section has been updated.**
11.	13.4 b	**Include this language in the protocol, as applicable.** • *If this is a study with a radiation and/or imaging (RTI) component, add the following to the protocol if applicable.* This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website. • *If IROC Houston will conduct RT modality credentialing, add the following to the protocol:* IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process. • *If this study uses the IROC integration suite to document that the enrolling site is associated with a radiation or imaging (RTI) provider credentialed for the study modalities, add the following to the protocol:*

#	Section	Comments
		To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals. Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist. **PI Response: The section has been updated.**
12.	**Section 15.6.a** **TRIAD Digital Image Submission** **Page 106**	**Replace the text in this section with the following updated CTSU template language.** Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred. TRIAD Access Requirements: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; • Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and • TRIAD Site User role on an NCTN, ETCTN, or other relevant roster. All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

#	Section	Comments
		TRIAD Installation: To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/. This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration. For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858. **PI Response: The section has been updated.**
13.	14.3 d	**Our records indicate that this study uses the Data Quality Portal (DQP). Please confirm and include the following CTSU template language.** ***Data Quality Portal*** • *Include only if study will use Data Quality Portal.* • *Include within the data submission/reporting section of the protocol.* The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

#	Section	Comments
		To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. *Include the following (highlighted) only if study is **not** using the Calendaring functionality in Rave:* This study does not use the Rave Calendaring functionality, and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count. **PI Response: The section has been updated.**

III. Other Edits

#	Section	Comments
1.	Protocol and Consent	The version date was updated.
2.	13.3h	Removed the sentence "Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)"

SWOG CANCER RESEARCH NETWORK

Version Date: November 27, 2023

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: SWOG Operations Office (protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chair: Dr. S. Patel.

REVISION # 17

Study Chair: Sapna Pradyuman Patel, M.D.
Phone number: 713/792-2921
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Other: Additional Translational Medicine
(√) Editorial / Administrative changes

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.

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.

REVISION #17

The above-referenced protocol has been updated as follows to incorporate additional translational medicine details:

1. Protocol and Model Consent Form: The version date of these documents has been updated. No additional changes were made to the Model Consent Form.

2. Kenneth F. Grossman, M.D., Ph.D. has been removed as a study chair and has been replaced by Sapna Pradyuman Patel, M.D. throughout the protocol document and contact information updated accordingly.

3. Table of Contents: The Table of Contents has been updated.

4. Contact Information Table: Sapna Pradyuman Patel, M.D was replaced Kenneth F. Grossmann, M.D., Ph.D. as the contact person for treatment or toxicity related questions.

5. Cancer Trials Support Unit (CTSU) Address and Contact Information: The CTSU Contact Information has been updated throughout.

6. Section 13.2, 13.3, and 13.4 :These sections have been updated to reflect new CTSU template language.

7. Section 13.3h: This section has been revised per CTSU updates to the protocol template. The following sentence was removed "Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)"

8. Section 14.2 Master forms location has been updated.

9. Section 14.3 and 15.15.6a.:Throughout this section the CTSU template language has been updated.

10. Appendix 18.8c-d.: This section has been updated, Retrospective T-Cell Receptor Beta Chain Sequencing assays will be performed at Thermo Fisher, replacing MD Anderson laboratory.

11. Appendix 18.8 f.: This section has been updated. Thermo Fisher mailing address, contact information has been added, and The University of Texas MD Anderson Cancer Center contact information was updated.

12. Section 18.9 b: This section has been updated, the bank instructions for distribution has been changed to Thermo Fisher and MD Anderson laboratory was removed.

The updated protocol and model informed consent form can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace with the updated versions. Please contact melanomaquestion@crab.org or 206/652-2267 with any questions.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Teresa Petrella, M.D. – CCTG
Karen Favata – Merck
Maria Edwards – PPD
TaNisha Evans – PPD
Loni Pickle-Thermo Fisher Scientific

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated October 15, 2015

SWOG

A PHASE III RANDOMIZED TRIAL COMPARING PHYSICIAN/PATIENT CHOICE OF EITHER HIGH DOSE INTERFERON OR IPILIMUMAB TO MK-3475 (PEMBROLIZUMAB) IN PATIENTS WITH HIGH RISK RESECTED MELANOMA.

NCT#02506153

This is an FDA Registration Trial. Additional site requirements include maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf) and additional monitoring (see Appendix 18.6).

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NCI Supplied Investigational Agents (DCTD-sponsored):

MK-3475 (Pembrolizumab) (NSC 776864)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal:

(Sign in at www.ctsu.org , and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

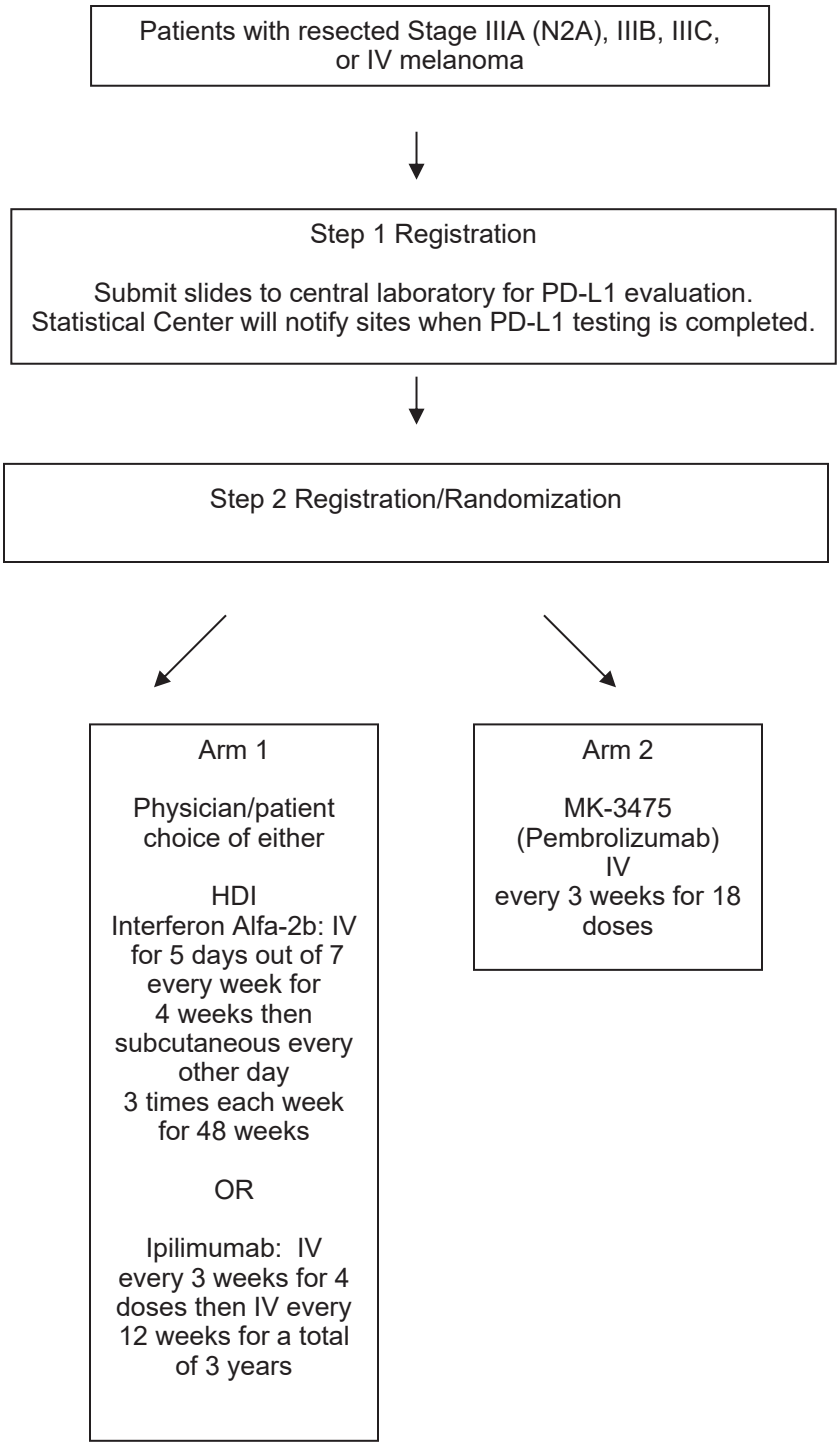
Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https ://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923 or at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org).

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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.</td></tr>
<tr><td colspan="3"><u>For patient eligibility or data submission questions</u> contact the SWOG Data Operations Center by phone or email206/652-2267
melanomaquestion@crab.org

<u>For treatment or toxicity related questions</u> contact the Study Chair by phone or email:
Sapna Pradyuman Patel, M.D.
Phone: 713/792-2921
E-mail: S1404SCquestion@swog.org</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org .</td></tr>
</table>

SCHEMA


Patients with resected Stage IIIA (N2A), IIIB, IIIC, or IV melanoma
Step 1 Registration
Submit slides to central laboratory for PD-L1 evaluation.
Statistical Center will notify sites when PD-L1 testing is completed.
Step 2 Registration/Randomization
Arm 1
Physician/patient choice of either
HDI
Interferon Alfa-2b: IV for 5 days out of 7 every week for 4 weeks then subcutaneous every other day 3 times each week for 48 weeks
OR
Ipilimumab: IV every 3 weeks for 4 doses then IV every 12 weeks for a total of 3 years
Arm 2
MK-3475 (Pembrolizumab) IV every 3 weeks for 18 doses

1.0 OBJECTIVES

1.1 Primary Objectives

a. To compare overall survival (OS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab)

b. Among patients who are PD-L1 positive, to compare OS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

c. To compare relapse-free survival (RFS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab to MK-3475 (pembrolizumab).

1.2 Secondary Objectives

a. To estimate OS and RFS for patients who are PD-L1 negative or PD-L1 indeterminate in this population.

b. To compare OS and RFS of patients between the two arms within PD-L1 positive and negative subgroups and to look at the interaction between PD-L1 (positive versus negative) and treatment arm.

c. To assess the safety and tolerability of the regimens.

1.3 Additional Objectives

a. To bank tissue and whole blood in anticipation of future correlative studies in this patient population.

b. To evaluate PD-L1 expression through immunohistochemistry assay.

c. To evaluate the effect of treatment-related side effects that may have an impact on the health-related domains of quality of life (QOL) using the FACT-BRM, EQ-5D-3L, and FACIT-D between patients treated with physician/patient choice of either high-dose interferon alfa-2b or ipilimumab and MK-3475 (pembrolizumab).

d. Pharmacokinetic (PK) and anti-drug antibody (ADA) testing will be performed on all patients receiving MK-3475 (pembrolizumab). These analyses will evaluate exposure-response analyses for activity and efficacy, potential pharmacodynamic biomarkers, and the safety of MK-3475 (pembrolizumab).

1.4 Other Objectives

a. Translation Medicine Objective Related to T-Cell Receptor Beta Chain Sequencing

1. To evaluate the association between TCRβ variable gene (TRBV) haplotype and Grade 3-4 immune-related adverse events (irAEs) among Stage III melanoma patients treated with adjuvant Ipilimumab or Pembrolizumab.
2. To describe the TRBV haplotype distribution among this cohort of patients studied.

b. Translational Medicine Objective Related to Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients
c. To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms.
d. To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms.
e. To evaluate associations between pretreatment ctDNA and relapse within 2 years of randomization in a case-control analysis within each treatment arm (after treatment arm data are unblinded to investigators).
f. To evaluate associations between "early-on treatment" ctDNA levels and relapse within 2 years of randomization.
g. To describe ctDNA levels at end of therapy and time of relapse.

2.0 BACKGROUND

Although the long term RFS for most patients with low risk Stage I and II melanoma is excellent following surgery, patients who have high risk features such as tumor-involved lymph nodes (Stage III) have poorer outcomes with an average 5-year OS of Stage III patients approximating 50%. *(1)* Although modern therapy has significantly improved outcomes for patients with Stage IV melanoma such that 20% of patients achieve survival beyond 4 years, this still reflects a minority of patients. *(2)* Furthermore, relapses in this disease can be severely detrimental to quality of life with distant relapses accounting for greater than 50% of the relapse events in Stage III patients. *(3)* Adjuvant therapy is currently considered for patients with Stage III melanoma and selected patients with resected Stage IV melanoma.

Adjuvant treatment for Stage III melanoma – Rationale for Physician/Patient Choice of either High Dose Interferon alfa-2b or Ipilimumab as the Control Arm (Arm 1):

Multiple studies have investigated adjuvant immunotherapy alone or in combination with other treatments for high-risk melanoma. The first trial to demonstrate an OS advantage compared high dose interferon-alfa-2b (HDI) to observation. *(4)* This study established HDI as the standard of care for the adjuvant treatment of melanoma, and HDI remains the most widely used adjuvant treatment option in the US today. Subsequent studies involving differing doses, schedules, and preparations of interferon have been extensively reviewed and taken together have shown consistent relapse-free survival (RFS) and OS benefit in large meta-analyses. *(5,6,7)* Pegylated interferon has also been studied by the EORTC in a single large Phase III trial in Stage III melanoma that showed a RFS advantage compared to observation, but no OS advantage was demonstrated. *(8)* Based upon the RFS advantage of this EORTC study, the FDA granted approval for pegylated interferon for the adjuvant treatment of Stage III melanoma. Biochemotherapy consisting of interferon, interleukin-2, dacarbazine, vinblastine, and cisplatin has also been studied in the adjuvant setting (**S0008**) and results show a RFS advantage compared to HDI but no OS difference. *(9)*

Unfortunately, the toxicity of this regimen limits the use of biochemotherapy to institutions with sufficient expertise in its administration, and the lack of an OS advantage compared to HDI argues against this becoming a community-based standard for the adjuvant treatment of melanoma.

Ipilimumab, administered intravenously, was originally approved in 2011 to treat late-stage melanoma that cannot be removed by surgery. Ipilimumab is a monoclonal antibody that blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen). CTLA-4 may play a role in slowing down or turning off the body's immune system, and affects its ability to fight off cancerous cells. Ipilimumab may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors.

In October 2015, based on preliminary results from **EORTC 18071**, the U.S. Food and Drug Administration expanded the approved use of ipilimumab to include a new use as adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will return following surgery. The safety and effectiveness of ipilimumab for this new use were studied in 951 patients who received ipilimumab or a placebo as adjuvant therapy following complete surgical removal of melanoma. The study measured recurrence-free survival and overall survival. Forty-nine percent of participants taking ipilimumab had their cancer return after an average of 26 months, compared to 62 percent of those receiving a placebo, whose cancer returned after an average of 17 months. The analysis of overall survival data has not yet occurred. *(10)*

The most common side effects of ipilimumab in this study were rash, diarrhea, fatigue, itching, headache, weight loss and nausea. Ipilimumab can also cause autoimmune disease in the digestive system, liver, skin, nervous system (which would each require treatment with corticosteroids), as well as in the hormone-producing glands (which requires life-long hormone replacement therapy). Women who are pregnant should not take ipilimumab because it may cause harm to a developing fetus. *(11)* In addition, the relative adjuvant therapeutic impact of ipilimumab as compared to HDI is currently unknown. Similarly, given the toxicity profile of ipilimumab at 10 mg/kg, there is a need to better assess the risk-benefit ratio relative to the standard 3 mg/kg dose currently approved for inoperable metastatic melanoma.

The benefits described above for HDI, though statistically significant, remain modest with the most recently published meta-analysis showing an OS advantage with a hazard ratio of 0.91 (95% CI 0.85 to 0.97; P value = 0.003). *(12)* Additionally, the toxicity of HDI can be significant and prolonged over the course of one year of administration.

The current landscape of other studies ongoing in high-risk melanoma:

Ongoing adjuvant clinical trials in patients with melanoma include a study investigating ipilimumab at either 10 mg/kg or 3 mg/kg compared to HDI (U.S. Intergroup **E1609**). The co-primary endpoints of this study are RFS and OS. **E1609** completed accrual of adult patients August 15, 2014 (remains open for pediatric/adolescent patients). Results of **E1609** are not expected until after completion of accrual to the present trial, and until that time there is insufficient evidence to consider ipilimumab at either dose as a standard form of adjuvant therapy for high risk melanoma patients.

Two additional ongoing adjuvant studies are industry-sponsored BRAF inhibitor-based studies, investigating vemurafenib or dabrafenib/trametinib compared to observation. Results of these studies are not expected until after completion of accrual to the present trial, and until that time there is insufficient evidence to consider BRAF inhibitors alone or in combination with MEK inhibitors as a form of adjuvant therapy for high-risk melanoma patients.

Clinical Rationale for PD-1 blockade for the adjuvant treatment of high-risk melanoma:

Novel therapies have been developed recently targeting the programmed cell death – 1 (PD-1) inhibitory co-receptor on T-cells. *(13)* Monoclonal antibodies directed at the PD-1 co-receptor, or the cognate PD-L1 receptor on tumor cells, have robust activity in advanced melanoma. *(14,15)* The drug MK-3475 (pembrolizumab) is a member of this class of medications and targets the PD-1 receptor. A recently reported Phase I study in 411 patients defined safe and effective dosing regimens (10 mg/kg IV q 2 weeks, 2 mg/kg IV q 3 weeks, 10 mg/kg IV q 3 weeks) and showed the highest confirmed response rate yet observed for any single agent immunotherapy in Stage IV melanoma (41% objective responses across all cohorts). *(16)* Furthermore, the safety and tolerability of pembrolizumab (12% Grade 3/4 toxicities) appears superior to both HDI (64% Grade 3/4

toxicities in **S0008**) and ipilimumab (43% Grade 3/4 toxicities in **EORTC 18071**), making it ideally suited for evaluation as adjuvant therapy. *(17)* Ongoing studies, including Phase III studies for Stage IV patients, are confirming the high response rate and the favorable toxicity profile of pembrolizumab such that an adjuvant Phase III study is warranted.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator Brochure). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (> 21 days). This early PK and pharmacodynamic data provided a scientific rationale for evaluating the Q3W dosing schedule.

The choice of the 200 mg Q3W as an appropriate dose for fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that is well-tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Rationale for one year of dosing with pembrolizumab

Adjuvant therapy for melanoma with HDI or pembrolizumab is aimed at inducing an immune response that eradicates micrometastatic tumor deposits that may lead to a future melanoma relapse. Based on the experience with HDI it is postulated that one year of adjuvant therapy would be able to induce the desired antitumor effects and eradicate small metastatic lesions.

Biological rationale for the study population based on the anticipated mechanism of action of pembrolizumab:

PD-L1 is known to be expressed by cells in the tumor microenvironment and engages PD-1 on T cells to subsequently trigger inhibitory signaling downstream of the T-cell receptor (TCR), blocking effect or functions and reducing T-cell killing capacity. PD-L1 can be constitutively expressed on the surface of melanoma cells through poorly characterized oncogenic signaling pathways or alternatively, expressed in response to the presence of T cells producing immune-stimulating cytokines such as interferons. *(18,19,20)* This process has been termed “adaptive immune resistance” and represents a mechanism by which cancer cells attempt to protect themselves from immune-cell mediated cell killing. Based on this conceptual framework, pre-existing tumor-infiltrating CD8+ T-cells with associated PD-1/PD-L1 engagement within tumors represented a key factor in determining clinical response to PD-1 blocking therapy. Emerging evidence from the analysis of samples from 46 patients with metastatic melanoma obtained before and during anti-PD-1 therapy with pembrolizumab (24 responders and 22 non-responders) using quantitative immunohistochemistry, quantitative multiplex immunofluorescence, and next generation sequencing for T-cell receptors (TCR), supports the concept that the pre-requisite for responses to pembrolizumab is the presence of clonal CD8 T cells expressing PD-1 and closely interacting with PD-L1 expressed by melanoma cells. *(21)* These data indicate the requirement for the presence of CD8 cells interacting with adaptive immune resistance-mediated PD-L1 expression by melanoma cells to lead to responses to PD-1 blockade.

Rationale for PD-L1 status blinding

Although patients will be stratified based on PD-L1 status, they and the investigator will be blinded to this result at randomization. Presently there is no indication that PD-L1 status

predicts response to PD-L1 antibody treatment in the adjuvant setting so this will not impact patient care during treatment on the study. PD-L1 expression is dynamic and PD-L1 expression of primary or lymph node tissue is not necessarily indicative of PD-L1 status in other sites. Thus, at relapse we recommend that patients have the biopsy confirming relapse tested for PD-L1 expression with a CLIA certified test. We recommend against using the **S1404** baseline PD-L1 expression for subsequent treatment decisions. Only in the event that tissue is limited in the relapsed setting and that there is no other reasonable alternative to attain PD-L1 expression for the patient, should the **S1404** baseline PD-L1 expression be used. **S1404** baseline PD-L1 expression will be provided to patients on study at report of relapse.

FDA approval of MK-3475 (pembrolizumab) for Stage IV and unresectable Stage III melanoma

MK-3475 (pembrolizumab) has recently received accelerated approval by the FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if B-RAF V600 mutation positive, a B-RAF inhibitor. This approval is based on the high response rate and durability of response seen in the clinical studies conducted so far with MK-3475 as described above. We anticipate extensive use of MK-3475 among the patients who relapse on HDI, and also anticipate the use of other PD-1, and PD-L1 targeted antibodies in both groups. Data regarding post-relapse therapy will be collected as part of this study.

Rationale for collecting quality of life (QOL) data and the potential impact of the trial on QOL

An important issue in the adjuvant treatment of patients with high-risk melanoma is the how patients weigh the benefits of overall survival and QOL. Adjuvant HDI has been demonstrated to provide relapse-free survival and overall survival benefits for this patient population but it is also known to be associated with major Grade 3-4 toxicities. *(22)* Patients treated with MK-3475 (pembrolizumab) can also experience Grade 3-4 drug-related toxicities and immune-related adverse events (irAEs). The Functional Assessment of Chronic Illness Therapy Diarrhea (FACIT-D) utilizes the four primary domains of the FACT-BRM (Physical Well-Being, Social Well-Being, Emotional Well-Being, and Functional Well-Being). *(23)* The additional measure of the FACIT-D instrument includes 11 questions tailored to bowel symptoms. It is appropriate for patients with any form of cancer, and content was determined and validated by experts with patient input. We therefore plan to collect QOL data utilizing the FACT-BRM, FACIT-D and EQ-5D-3L health questionnaires to evaluate health-related quality-of-life outcomes between the two arms.

Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, samples will be collected for analysis of anti-drug antibodies (ADA) and pharmacokinetics (PK).

Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis will be performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) as endpoints and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic samples will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately from the primary results of this trial.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. To date, studies of MK-3475 (pembrolizumab) and similar agents have not shown evidence of significant gender or race-based differences in efficacy. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	6	0	0	6
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	4	0	0	4
Black or African American	10	3	0	0	13
White	359	840	4	10	1213
More Than One Race	0	0	0	0	0
Total	369	855	4	10	1238

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	41	96	0	0	137
More Than One Race	0	0	0	0	0
Total	41	99	0	0	140

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, MK-3475 (pembrolizumab) is investigational and is being provided under an IND held by the National Cancer Institute. The current version of the Investigator Brochure (IB) will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed via email to IBcoordinator@mail.nih.gov or by phone (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET). Interferon alfa-2b and ipilimumab are commercially available drugs.

3.1 Interferon alfa-2b (Intron® A)

a. PHARMACOLOGY

Mechanism of Action: Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. In vitro studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

b. PHARMACOKINETICS

1. *Absorption: Time to peak, serum: IM, SubQ: ~3-12 hours; IV: by the end of a 30-minute infusion*

2. Distribution: Volume of distribution = 31 L, but has been noted to be much greater, (370-720 L) in leukemia patients receiving continuous infusion. Interferon alfa-2b does not penetrate the CSF.

3. Metabolism: Primarily renal

4. Elimination: Half-life IV: ~2 hours; IM, SubQ: ~2-3 hours

c. ADVERSE EFFECTS

1. Possible Side Effects of Interferon alfa-2b

Common (>20%): infection, diarrhea, nausea, vomiting, flu-like symptoms including fever, chills body aches, and muscle pain, fatigue, loss of appetite, disorder of taste, headache, confusion, depression, suicidal thoughts, alopecia, rash, and/or pain.

Less common (4 to ≤ 20%): cardiomyopathy, cirrhosis of liver, hepatotoxicity, thrombocytopenia, organ damage and/or failure, edema, injection site extravasation, erythema of injection site, generalized exfoliative dermatitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, transient ischemic attack (TIA),

cerebral infarction, cerebrovascular accident, and/or ischemic stroke.

Rare (≤ 3%), and serious: anemia, arrhythmias, ischemic heart disease, myocardial infarction, NSTEMI, hypersensitivity reaction, anaphylaxis.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse effects.

2. Pregnancy and Lactation: Pregnancy category C. There are no adequate and well-controlled studies in pregnant women. Breastfeeding is not recommended

3. Drug Interactions: Interferon alfa-2b drug interactions have not been fully evaluated. Caution should be exercised when combining with other potentially myelosuppressive agents such as: aldesleukin, clozapine, dipyrone, methadone, ribavirin, telbivudine, theophylline derivatives, and zidovudine. Due to potential drug interactions, a complete patient medication list, including interferon alfa-2b, should be screened prior to initiation of and during treatment with interferon alfa-2b. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. DRUG SUPPLY:

Interferon alfa-2b is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. DOSAGE FORMS:

Interferon alfa-2b is available in vials as powder for reconstitution and in vials containing solution for injection.

NOTE: Intron® A (interferon alfa-2b) formulation must be consistent with the approved product labeling for the intended route of administration.

1. Interferon alfa-2b powder for injection

a) Interferon alfa-2b powder for injection appears white to cream-colored. The powder for injection must be reconstituted prior to injection using the diluent (sterile water for injection USP) provided with the vial. Refer to the package insert for current reconstitution and infusion solution preparation.

b) Available vial strengths include 10 million units, 18 million units or 50 million units per vial. Refer to the package insert for current available formulations.

c) Interferon alfa-2b powder for injection vials do NOT include a preservative. Reconstituted vials must be

discarded immediately after the appropriate dose is withdrawn from the vial.

d) All powder for injection vials may be used for intravenous, intramuscular or subcutaneous injection.

Vials containing 10 million units may be used for intralesional injection.

e) Ingredients in the formulation include purified sterile recombinant interferon product, glycine, sodium phosphate dibasic, sodium phosphate monobasic, and human albumin.

2. Interferon alfa-2b solution for injection

a) Interferon alfa-2b solution for injection appears clear or colorless and is available in 18 million units per vial or 25 million units per vial. Please refer to the package insert for current available formulations.

b) Solution for injection vials containing 18 million units or 25 million units may be used for subcutaneous or intramuscular injection. Solution for injection vials containing 25 million units may be used for intralesional injection.

The Intron® A (interferon alfa-2b) formulation must be consistent with the approved product labeling for the intended route of administration.

c) Ingredients in the formulation include purified sterile recombinant interferon product, sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, edetate disodium, polysorbate 80, and cresol as a preservative.

g. STORAGE AND STABILITY

1. Interferon alfa-2b powder for injection

a) Vials should be stored in a refrigerator at 2ºC - 8ºC (36ºF-46ºF) until the expiration date indicated on the vial or packaging has been reached or until immediately prior to use. Vials should be allowed to come to room temperature prior to use.

b) Reconstituted vials may be stored refrigerated at 2ºC - 8ºC (36ºF - 46ºF) for no longer than 24 hours. However, the reconstituted vial must be discarded after one dose has been withdrawn from the vial.

c) Interferon alfa-2b powder for injection vials do not contain a preservative. Reconstituted vials containing leftover medication should not be re-used, as the sterility is not guaranteed. Bacterial contamination may occur in reconstituted vials used for more than a single dose.

2. Interferon alfa-2b solution for injection

a) Vials should be stored in a refrigerator at 2ºC - 8ºC (36ºF - 46ºF) until the expiration date indicated on the vial or packaging has been reached.

Multidose solution for injection vials contain preservatives and can be stored refrigerated for up to one month. Unused doses remaining in the vial must be discarded after one month.

b) Vials should not be frozen or exposed to excessive heat.

3.2 Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442)

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

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 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 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]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism [2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS])	
		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]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders – Other (immune-mediated encephalitis) [2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
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 receving 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 - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
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; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
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; 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.

1. 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.

2. 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

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL (5 mg/mL). Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

Ipilimumab is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

1. Store intact vials of ipilimumab refrigerated at (2˚ to 8˚C), protected from light. Do not freeze.

2. Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion. Refer to package insert for complete preparation and dispensing instructions

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˚ to 8˚C) 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.

3.3 MK-3475 (Pembrolizumab) (NSC-776864)

a. PHARMACOLOGY

MK-3475 (Pembrolizumab) is a humanized MAb of the IgG4/kappa isotype. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells expressing PD-1 ligands to suppress immune control. MK-3475 blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands and thereby promoting the host immune system to recognize tumor cells as foreign bodies to be eliminated.

b. PHARMACOKINETICS

The pharmacokinetic profile of MK-3475, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Elimination half-life after IV administration was approximately 14 to 21.6 days. Steady state concentration levels were achieved within 16 weeks of treatment when tested at 3 and 10mg/kg dosing as administered at 2 week intervals. During repeated dosing of 2 or 10mg/kg Q3W, steady state in trough concentrations appeared to have been achieved after approximately three months. Furthermore, MK-3475 has a low potential of eliciting the formation of anti-drug antibodies.

c. ADVERSE EFFECTS

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864) 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 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

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 2.5, December 27, 2019[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[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] Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3] Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

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

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) 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.

1. Pregnancy and Lactation: MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Patients are excluded from this study if pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

   Men and non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two

birth control methods can be barrier method or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Pregnancy: If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is a serious adverse experience (*e.g.*, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn.

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

2. Drug Interactions: No studies on pharmacodynamic drug interactions have been performed. Due to potential drug interactions, a complete patient medication list, including MK-3475, should be screened prior to initiation of and during treatment with MK-3475. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

MK-3475 is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

f. PREPARATION

MK-3475 solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

g. STORAGE

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box. If a storage temperature excursion is identified, promptly return MK-3475 to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

h. STABILITY

Stability testing of the intact vials is on-going.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 20 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

i. ROUTE OF ADMINISTRATION

IV infusion only. Do not administer as an IV push or bolus injection.

j. METHOD OF ADMINISTRATION

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

k. PATIENT CARE IMPLICATIONS

Refer to Section 8.3a for information on evaluation and management of potential immune-related adverse events.

I. DRUG ORDERING AND 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 (**S1404**) 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 at 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)

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Electronic logs are allowed as long as a print version of the log process has the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

b. Drug Disposition: 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).

c. *Drug Expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.*

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 or email at PMBAfterHours@mail.nih.gov.

4.0 STAGING CRITERIA (AJCC 7TH Edition, 2010)

Pathologic Staging included in this trial:

Stage IIIA	T1-T4a	N2a	M0
Stage IIIB	T1-4a	N1-N2b	M0
	T1b (ulcerated)	N1-N2a	M0
	T2b-4b	N1-N2a	MO
	T1-4a.b	N2c	M0
Stage IIIC	T1-4b	N1-N2b	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

See Section 18.5 for TNM Definitions for Pathologic Staging.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the **S1404** Eligibility Checklist to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at melanomaquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 42 or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1 REGISTRATION

Disease Related Criteria

a. Patients must have completely resected melanoma of cutaneous origin or of unknown primary in order to be eligible for this study. Patients must be classified as Stage IIIA (N2a), IIIB, IIIC, or Stage IV melanoma. Patients with non-ulcerated T1b N1a disease are not eligible. Patients with melanoma of mucosal or other non-cutaneous origin are eligible. Patients with melanoma of ocular origin are not eligible. Patients with a history of brain metastases are ineligible.

b. Patients are eligible for this trial either at initial presentation of their melanoma or at the time of the first detected nodal, satellite/in-transit, distant metastases, or recurrent disease in prior lymphadenectomy basin or distant site. Nodal, satellite/in-transit metastasis, distant metastases or disease in a prior complete lymphadenectomy basin must have been confirmed histologically by H & E stained slides.

c. Patients with multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted.

d. Patients at initial presentation of melanoma must undergo an adequate wide excision of the primary lesion, if present. (See Section 18.1 for guidelines on surgical management.) Patients with previously diagnosed melanoma must have had all current disease resected with pathologically negative margins and must have no evidence of disease at the primary site or must undergo re-resection of the primary site. A full

lymphadenectomy meeting the criteria outlined in Section 18.1 is required for all node-positive patients including those with positive sentinel nodes. Patients with recurrent disease who have had a prior complete lymphadenectomy fulfill this requirement as long as all recurrent disease has been resected. For all patients, all disease must have been resected with negative pathological margins and no clinical, radiologic, or pathological evidence of any incompletely resected melanoma. **Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.**

Specimen Submission Criteria

e. Patients must have available and be willing to submit a minimum of five unstained slides from primary, lymph node, or metastatic site to determine PD-L1 expression as described in Section 15.2. The tumor tissue must be adequate for PD-L1 testing (defined as ≥ 100 tumor cells as confirmed by the treating institution's local pathologist). This must be documented by having a pathologist sign the **S1404** Local Pathology Review form (see Section 18.4) prior to Step 1 registration. The specimens may come from an archived block but must be submitted within 20 days from cutting the slides.

f. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.3.

g. Patients must be willing to have blood draws for PK/ADA analysis as outlined in Section 15.4, should the patient be randomized to the MK-3475 arm.

Prior/Concurrent Therapy Criteria

h. Patients may have received prior radiation therapy, including after the surgical resection. All adverse events associated with prior surgery and radiation therapy must have resolved to ≤ Grade 1 prior to registration.

i. Patients must not have received neoadjuvant treatment for their melanoma. Patients must not have had prior immunotherapy including, but not limited to ipilimumab, interferon alfa-2b, high dose IL-2, PEG-IFN, anti-PD-1, anti-PD-L1 intra-tumoral or vaccine therapies. Patients must not be planning to receive any of the prohibited therapies listed in Section 7.2 during the screening or treatment phases of the study.

j. Patients must not be planning to receive concomitant other biologic therapy, radiation therapy, hormonal therapy, other chemotherapy, surgery or other therapy after Step 2 registration.

Clinical/Laboratory Criteria

k. Patients must be ≥ 18 years of age.

l. All patients must have disease-free status documented by a complete physical examination and imaging studies within 42 days prior to registration. Imaging studies must include a total body PET-CT scan that is of diagnostic quality (with or without brain) or a CT of the chest, abdomen and pelvis. For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with IV contrast or PET-CT through the region) is required. If the patient has had unknown primary with disease in the axilla, neck imaging is required to assure region is clear of cancer. CT imaging should be done with intravenous contrast if there are

no contraindications for it. Any other clinically-indicated imaging studies if performed (e.g. bone scan) must show no evidence of disease.

m. All patients must have a CT or MRI of the brain within 90 days prior to registration. The brain CT or MRI should be performed with intravenous contrast (unless contraindicated).

n. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500 microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 10 g/dL. These results must be obtained within 42 days prior to registration.

o. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and SGOT (AST) and SGPT (ALT) and alkaline phosphatase ≤ 2 x IULN. These results must be obtained within 42 days prior to registration.

p. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ IULN OR measured or calculated creatinine clearance ≥ 60 mL/min. This result must have been obtained within 42 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

q. Patients must have LDH performed within 42 days prior to registration.

r. Patients must have Zubrod Performance Status ≤ 1 (see Section 10.4).

s. Patients must have a baseline ECG performed within 42 days of registration that is normal or considered not clinically significant by the site investigator.

t. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

u. Patients must not have an active infection requiring systemic therapy.

v. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

w. Patients must not have received live vaccines within 42 days prior to registration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

x. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts (≥ 350 mm^3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off anti-viral therapy so long as they meet the CD4 count criteria.

y. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.

z. Patients must not have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the trial results, interfere with the patient's participation for the full duration of the trial, or indicate that participation in the trial is not in the patient's best interests, in the opinion of the treating investigator.

aa. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, lobular carcinoma of the breast in situ, atypical melanocytic hyperplasia or melanoma in situ, adequately treated Stage I or II cancer (including multiple primary melanomas) from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

bb. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. 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. Patients must not be pregnant or nursing due to unknown teratogenic side effects.

cc. Patients who are able to complete questionnaires in English, Spanish or French must participate in the quality of life assessments. (Those patients who cannot complete the quality of life questionnaires in English, Spanish or French can be registered to **S1404** without contributing to the quality of life studies.)

Regulatory Criteria

dd. Patients must be informed of the investigational nature of this study and must sign and give written informed consent for this protocol in accordance with institutional and federal guidelines.

ee. 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.

5.2 STEP 2 REGISTRATION (Randomization)

An e-mail notification from the SWOG Statistical Center should be received within 10 business days of submitting tissue as described in Section 15.2.

The following additional criteria must be met in order for a patient to be considered eligible for registration to the randomized trial. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at melanomaquestion@crab.org prior to registration.

a. Patients must not be registered until receiving confirmation from the SWOG Statistical Center that the patient's tissue specimen was adequate for PD-L1 testing. Patients must be registered within 7 working days of receiving the e-mail notification.

b. Women of childbearing potential must plan to have a urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a negative serum pregnancy test will be required.

c. No tests or exams are required to be repeated for Step 2 registration (Randomization). However, patients who are known to have a change in eligibility status after Step 1 registration are not eligible for Step 2 registration. For example, ANC is not required to be repeated between Step 1 and Step 2 registration, but the most recent ANC performed before Step 2 registration is required to be ≥ 1,500 mcL.

6.0 STRATIFICATION FACTORS

Patients will be randomized between Arm 1 – physician/patient choice of either high dose interferon or ipilimumab and Arm 2 – MK-3475 (pembrolizumab) in a 1:1 fashion, using a randomized block design. Stratification is based on:

1) surgically resected AJCC stage:

IIIA (N2a) versus IIIB versus IIIC versus IV

2) PD-L1 status (see Section 15.2): positive versus negative versus indeterminate

(NOTE: Institutions will be blinded to the patient's PD-L1 status.)

3) Planned control arm regimen *: high dose interferon versus ipilimumab.

* NOTE: The intended control arm regimen must be declared prior to randomization for all patients.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Sapna Patel at 713/792-2921 (or S1404SCquestion@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 Procedures" under the "About" menu and choose Policy 38).

7.1 Treatment

a. Pretreatment Labs:

Blood samples collected for pretreatment laboratory tests must be collected and analyzed no more than 3 days prior to dosing. Albumin, glucose, and electrolytes (Na, K, HC03 or CO2) are required within 3 days prior to dosing to obtain baseline data for future toxicity assessments.

b. Arm 1: **Physician/Patient Choice of Either High Dose Interferon or Ipilimumab**

1. High Dose Interferon

Induction Therapy

Agent	Dose Schedule	Route	Days
Interferon Alfa-2b	20 MU/m^2/d* Weeks 1 - 4	IV over 20 min	1-5 5 days a week

* Dose rounding ± 10% is allowable per institutional standards.

For the purpose of data reporting, 1 cycle = 6 weeks (4 weeks of HDIFN plus first 2 weeks of IFN maintenance.).

If possible, on the days when patients are required to come in for a clinic visit, Interferon treatment should be administered after all questionnaires, procedures and assessment have been completed.

Interferon doses must be rounded to the nearest 1 million unit. Interferon is given over a 20 minute infusion. Day 1 of each week of induction therapy should be administered at the registering institution. Days 2 – 5 of interferon administration for Weeks 1 - 4 may be administered at an institution other than the registering institution provided that during treatment to-date, the patient has not encountered any life-threatening or unusual toxicities and that the registering physician still retains primary responsibility for the patient's treatment. Documentation concerning all drugs administered, side effects, and tests performed must be forwarded to the registering institution. Home Health Agencies (HHA) may be used to treat patients. The registering institution must document any care given at an outside institution.

Maintenance Therapy

Agent	Dose Schedule	Route	Days
Interferon Alfa-2b	10 MU/m^2/d* Weeks 5 - 52	SC	1, 3, 5 M,W,F

For the purpose of data reporting, Cycle 2 (Weeks 7-12) is 6 weeks, and all subsequent cycles are 12 weeks.

Self-Administration of Subcutaneous Doses

Interferon doses must be rounded to the nearest 1 million unit. Patients who are deemed competent to self-administer the subcutaneous maintenance doses of Interferon alfa-2b may do so following the first 4 weeks of treatment. Patients must complete compliance documentation (Section 7.3) for self-administered doses. If patient cannot self-administer, a nurse, or qualified HHA staff may administer the injections. The registering institution must document any care given at an outside institution.

* Dose rounding ± 10% is allowable per institutional standards.

2. Ipilimumab

Induction Therapy

Agent	Dose Schedule	Route	Days
Ipilimumab	10 mg/kg* Weeks 1-10;	IV infusion over 90 minutes	1 Q 3 weeks for a total of four doses

For the purpose of data reporting, 1 cycle = 6 weeks.

* Dose rounding ± 10% is allowable per institutional standards.

If possible, on the days when patients are required to come in for a clinic visit, treatment should be administered after all questionnaires, procedures and assessment have been completed.

The final concentration must be between 1-2 mg/mL.

Maintenance Therapy

Agent	Dose Schedule	Route	Days

Ipilimumab 25-145;	10 mg/kg*	IV infusion over 90 minutes	1	Weeks Q 12 weeks for 11 doses ending at 3 years)

For the purpose of data reporting, 1 cycle = 12 weeks.
* Dose rounding ± 10% is allowable per institutional standards.

If possible, on the days when patients are required to come in for a clinic visit, treatment should be administered after all questionnaires, procedures and assessment have been completed.

The final concentration must be between 1-2 mg/mL.

c. Arm 2: **MK-3475 (Pembrolizumab)**

Agent	Dose	Route	Schedule
MK-3475 (Pembrolizumab)	200 mg	IV over 30 minutes	Day 1, Q 3 weeks for 52 weeks

For the purpose of data reporting, Cycle 1 and Cycle 2 are 6 weeks and all subsequent cycles are 12 weeks.

MK-3475 (pembrolizumab) treatment should be administered after all questionnaires, procedures and assessments have been completed. MK-3475 (pembrolizumab) treatment may be administered up to 3 days before or after the protocol-specified Q 3 weeks due to administrative reasons.

MK-3475 (pembrolizumab) treatment will be administered on an outpatient basis.

MK-3475 (pembrolizumab) will be administered as a 30 minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 25-40 minutes).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chairs. The reason for interruption should be documented in the patient's study record.

All planned doses must be administered. Missed doses must be made up.

7.2 Prohibited and Cautionary Medications

Radiation therapy must be completed at least 1 day prior to starting ipilimumab or MK-3475 and must be completed at least 7 days prior to starting interferon.

Patients are prohibited from receiving the following therapies after registration to Step 1 and through completion of protocol therapy:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Any non-study anti-cancer agent (investigational or non-investigational).
- Investigational agents other than MK-3475.
- Live vaccines: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and **are allowed**; however, intranasal influenza vaccines (*e.g.* Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids (defined as 10 mg prednisone) are acceptable, however site investigators should consult with the Study Chair for any dose higher than 10 mg prednisone.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol treatment. Patients may receive other medications that the investigator deems to be medically necessary.

7.3 Drug Compliance Documentation

Patients who self-administer interferon alfa-2b, may complete the **S1404** Patient Interferon Diary which can be found in Section 18.3. Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. The completed patient diary should be kept in the patient's clinic chart. Note that the diary is provided only as a tool for tracking patient compliance. Do not submit patient diaries to the SWOG Data Operations Office. Sites may utilize institutional diaries or other source documentation in place of the **S1404** Patient Interferon Diary at the discretion of the treating physician. The completed Interferon Diary, institutional diary, or other source documentation in place of the **S1404** Interferon Diary must be available for upload if requested as part of the risk based monitoring.

7.4 Criteria for Removal from Protocol Treatment

a. Recurrence of disease (as defined in Section 10.0).

b. Unacceptable toxicity.

c. The patient may withdraw from the study at any time for any reason.

d. The investigator may discontinue treatment if they determine that the patient's continued treatment on the study is detrimental to their long-term health, or due to poor compliance with the study's required visits and treatments.

e. Positive pregnancy test.

f. Completion of protocol treatment.

g. Patients will be removed from protocol treatment if there is a treatment delay > 84 consecutive days for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period, End of Study

Randomized patients will be followed until death or 10 years after randomization, whichever occurs first.

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 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 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 5.0.

8.2 Dose Modification Considerations for Patients Receiving Interferon (Arm 1)

a. General

Induction therapy by the IV route in Weeks 1-4 shall be evaluated separately from Maintenance therapy in Weeks 5-52. A patient requiring dose modification(s) in the first 4 weeks will therefore commence Week 5 at full dose. **Doses missed during treatment due to toxicity, patient compliance, holiday, etc. should not be made up.**

b. Arm 1 – IFN Dose Modification Table

	Full Dose	Dose mod 1	Dose mod 2	Dose mod 3
Induction (Weeks 1-4)	20 MU/m^2	13.3 MU/m^2	6.6 MU/m^2	Remove from protocol treatment
Maintenance (Weeks 5-52)	10MU/m^2	6.6 MU/m^2	3.3 MU/m^2	Remove from protocol treatment

PLEASE NOTE: If a patient experiences any of the toxicities listed below, the patient must have a dose modification as follows: treatment must be held until the toxicity returns to institution's normal limits, patient's baseline, or normal limits per CTCAE or as listed in the table under Section 8.2c, then reduced per above.

EXCEPTIONS: For Grade 3 proteinuria without creatinine or BUN elevation, dose should be held until return to Grade 2 toxicity. For Grade 2 weight loss observed over a period of one month, dose should be held until weight gain or stabilization.

Dose modifications outside of the guidelines prescribed below are allowed at the discretion of the treating physician if:

- The modification is being performed due to toxicity related to HDI therapy; and,
- After consideration of the patient's safety and overall clinical status, the treating physician feels that the modification is in the patient's best interest.

Any modifications outside of the prescribed guidelines must be documented in the comment section of the **S1404** Treatment Form.

c. ARM 1 (IFN) TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS *(24)*

TOXICITY	GRADE 2	GRADE 3	GRADE 4
<u>Blood/Bone Marrow</u> Thrombocytopenia	Full Dose	Hold therapy*; Reduce one dose level	Remove from protocol treatment
Anemia	Hold therapy* until return to Grade 1 or baseline; reduce one dose level	Hold therapy* until return to Grade 1 or baseline; reduce one dose level	Remove from protocol treatment
Neutropenia	Full Dose	Full Dose	Reduce one dose level
<u>Cardiovascular</u> Arrhythmia Cardiac-Other	Hold therapy until return to normal*; reduce one dose level after formal cardiologic evaluation and clearance	Removal from protocol treatment	Removal from protocol treatment
<u>Gastrointestinal</u> Nausea, vomiting and/or diarrhea	Administer supportive care; if persistent for more than 2 weeks, reduce one dose level	Hold therapy*; reduce one dose level	Removal from protocol treatment
Weight loss	Hold therapy for weight loss observed over a 1 month period until weight gain or stabilization*		
<u>Hepatic</u> ALK PHOS. Bilirubin or SGOT(AST)/SGPT (ALT)	Full Dose	Hold therapy until return to ≤ Grade 1*; reduce one dose level	Removal from protocol treatment
<u>Neurology</u> Cognitive disturbance Mood alteration Neuropathy – motor	Full Dose	Hold therapy *; reduce one dose level (evaluation by specialist)	Removal from protocol treatment

TOXICITY	GRADE 2	GRADE 3	GRADE 4
Neuropathy - sensory			
<u>Renal/Genitourinary</u> Proteinuria Creatinine	Full Dose Hold therapy*; reduce one dose level	Hold therapy until return to ≤ Grade 2*; reduce one dose level Removal from protocol treatment	Removal from protocol treatment Removal from protocol treatment

***PLEASE NOTE:** If a patient experiences any of the toxicities listed in the above table, the patient must have a dose modification as indicated (unless otherwise specified). Treatment must be held until the toxicity returns to institution's normal limits, patient's baseline, or normal limits per the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov, then reduce as indicated above. Dose re-escalation will not be attempted following resolution of toxicity that required dose interruption or attenuation.

8.3 Dose Modification Considerations for Patients Receiving Ipilimumab (Arm 1)

a. Dose and schedule modifications for ipilimumab

There will be no dose reductions for ipilimumab. The dose of ipilimumab will either be given or delayed/discontinued. Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs. Details of how to dose study medication in the presence of adverse drug reactions that may or may not be IRAEs are addressed below.

Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be **definitely**, **probably**, or **possibly** related to ipilimumab treatment unless otherwise specified. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab. For an adverse event, review the following criteria in a stepwise manner: First, assess the dose delay criteria and decide whether a scheduled dose should be delayed. Second, determine whether the permanent discontinuation criteria apply to the adverse event in question as well.

NOTE: Due to the possible effect of treatment with ipilimumab on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) 1 week before or after any dose of ipilimumab.

b. Criteria to delay/skip one dose of ipilimumab

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Delay ipilimumab dosing for any of the following definitely, probably, or possibly treatment related adverse events, unless otherwise specified:

- Grade ≥ 1 diarrhea and/or colitis **regardless of attribution**. Grade ≥ 2 diarrhea and/or colitis, definitely, probably, or possibly related to ipilimumab, requires permanent discontinuation.
- Any other ≥ Grade 2 non-skin related adverse event (including IRAEs) except for laboratory abnormalities.
- Grade ≥ 2 laboratory abnormalities that are secondary to an immune-related adverse event or autoimmune phenomenon (e.g., Grade ≥ 2 TSH associated with a CTCAE v.4 grade 2 thyroid dysfunction induced by ipilimumab, anemia, neutropenia, amylase, lipase, CPK, hyperglycemia, or elevated LFTs) should also lead to an ipilimumab dosing delay/skipping.
- Any other ≥ Grade 3 laboratory abnormality.
- Any ≥ Grade 3 skin-related adverse event (including IRAEs) **regardless of attribution**.

c. Criteria to resume ipilimumab treatment

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Ipilimumab **may not** be restarted while the patient is being treated with oral or intravenous corticosteroids for the management of immune related adverse events except for patients on stable doses of hormone replacement therapy for adrenal insufficiency such as hydrocortisone. In addition, patients must be off and have no requirement for oral/I.V. corticosteroids for at least 1 week and meet the other criteria for retreatment as outlined below.

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 3 weeks of last dose administration:

- If the adverse event has resolved (to ≤ Grade 1 severity or returns to baseline), restart ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window, the next scheduled dose will be omitted.
- Patients with Grade 1 diarrhea and/or colitis who require steroid therapy must have resolution to Grade 0 (or baseline) before resuming dosing with ipilimumab. Patients with Grade ≥ 2 related diarrhea and/or colitis must have ipilimumab permanently discontinued.

d. Criteria for permanent discontinuation of ipilimumab for Related Adverse Events

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Ipilimumab administration must be permanently discontinued for any of the following definitely, probably, or possibly treatment related adverse events, unless otherwise specified:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any ≥ Grade 2 diarrhea and/or colitis related to ipilimumab. Any ≥ Grade 2 diarrhea/colitis should be considered RELATED unless immune related colitis is definitely ruled out (including by endoscopy and biopsy.)
- Any ≥ Grade 2 hypophysitis, pneumonitis, nephritis, and/or sarcoid-like lesions.
- Any new motor or sensory neurologic toxicity ≥ Grade 2 regardless of attribution (including Guillain-Barré syndrome and myasthenia gravis).
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other ≥ Grade 3 non-skin adverse event with the exception of events listed under “Exceptions to Permanent Discontinuation”
- AST or ALT > 5 x ULN.
- Total Bilirubin > 3 x ULN.
- Any other ≥ Grade 4 laboratory abnormalities except for specified exceptions
- Any other ≥ Grade 4 adverse event.
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations.
- 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 dosing.
- Patients who require high dose steroids, other immune suppressants or anti-TNF drug therapy for the management of immune related adverse

events as described in the Toxicity Management Guidelines/Algorithms should have ipilimumab permanently discontinued.

e. 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.	

f. Exceptions to permanent discontinuation of ipilimumab

Ipilimumab administration may be resumed in the following cases:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Laboratory abnormalities that are rapidly reversible, not life threatening, do not reflect underlying organ system dysfunction, and are not related to the study treatment, such as transient elevations of uric acid, hypocalcaemia, hypophosphatemia.
- Hospitalization for ≤ Grade 2 adverse events (not including Grade 2 events that require permanent discontinuation) where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy and has improved to ≤ Grade 1 severity within 2 weeks of starting therapy.
  - Patients without a diagnosis of hypophysitis who have Grade 2 hypothyroidism, Grade 2 low testosterone or Grade 2 adrenal insufficiency where clinical symptoms are controlled with appropriate hormone replacement therapy.

8.4 Dose Modification Considerations for Patients Receiving MK-3475 (pembrolizumab) (Arm 2)

a. General MK-3475 Dose Modifications

Missed doses of MK-3475 must be made up.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1 below. See Section 8.4b for supportive care guidelines, including use of corticosteroids.

NOTE: Due to the possible effect of treatment with MK-3475 on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) within 1 week before or after any dose of MK-3475.

Dose Modification

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as

bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 1.

Table 1 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroi-dism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroi-dism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table Y.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chair. The reason for interruption should be documented in the patient's study record.

b. Management of Infusion Reactions

- Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion

Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475 (pembrolizumab).

Table 2 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g.	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

8.5 Use of Transfusion and/or EPO

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications on the S1404 Concomitant Medication Form. Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

8.6 Use of G-CSF

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

8.7 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Document on the **S1404** Concomitant Medication Form.

8.8 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Sapna Patel at 713/792-2921. 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 Procedures" under the "About" menu and choose Policy 38).

8.9 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 Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDARS

9.1 Arm 1: Interferon alfa-2b

REQUIRED STUDIES	Pre-study screening	Ran-domiza-tion	Induction Phase[a] Days 1-5 (M-F) of Weeks 1-4				Maintenance Phase[a] Days 1, 3, 5 (M, W, F) of Weeks 5-52										End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse	Relapse /Recu-rrence	F/U post relapse[d]
			Cycle 1						C2	C3		C4		C5		C6				
			W 1	W 2	W 3	W 4	W 5	W 6	W7-12	W 13	W 19	W 25	W 31	W 37	W 43	W 49				
PHYSICAL	Reg Step 1	Reg Step 2																		
History & Physical (w/BSA, BP, Height & Weight) [s]	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
PS & Tox Notation	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																				
Cover Sheet for Patient-Completed Questionnaires			X			X				X		X		X		X		X[p]	X[q]	
FACT-BRM, EQ-5D-3L and FACIT-D Questionnaire			X			X				X		X		X		X		X[p]	X[q]	
LABORATORY[e]																				
ANC, platelets, Hgb	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
LDH [f]	X																		X[f]	
AST and ALT, Alkaline Phosphatase	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Alb, Glu, Na, K, HCO3 (or CO_2) [a]			X[a]	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Triglycerides [g]	X											X[g]					X[g]			
Free T_3, TSH, Free T_4 [r]	X									X[r]		X[r]		X[r]			X[r]			
Pregnancy Test [i]	X		X[i]						X[i]	X[i]		X[i]		X[i]		X[i]				

Calendar continued on next page. Click here for footnotes.

9.1 Arm 1: Interferon alfa-2b (contd.

REQUIRED STUDIES	Pre-study screening	Ran-domiza-tion	Induction Phase[a] Days 1-5 (M-F) of Weeks 1-4				Maintenance Phase[a] Days 1, 3, 5 (M, W, F) of Weeks 5-52										End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse [c]	Relapse /Recu-rrence	F/U post relapse[d]
			Cycle 1						C2	C3		C4		C5		C6				
			W 1	W 2	W 3	W 4	W 5	W 6	W7 -12	W 13	W 19	W 25	W 31	W 37	W 43	W 49				
X-RAYS AND SCANS	Reg Step 1	Reg Step 2																		
Whole Body PET/CT or CT neck [j], chest abdomen & pelvis [k]	X									X		X		X		X		X [j k]		
Brain MRI or CT with Contrast [k]	X															X[k]		X[k]		
EKG [h]	X																			
Image Submission [o]		X								X		X		X		X		X		
SPECIMEN SUBMISSION																				
Slides for PD-L1 Expression [l]	X																			
E-mail confirmation tissue was adequate for PD-L1 analysis [l]		X																		
Tissue[m] for banking		X																	X	
Serum[m] for banking		X[n]								X		X					X		X	
Plasma & Buffy Coat[m] for RNA/DNA for banking		X[n]								X		X					X		X	
TREATMENT																				
Interferon alfa-2b			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form 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, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Study Calendar 9.1: Arm 1 (Interferon alfa-2b)

a. The following exams and labs are done weekly during induction (Weeks 1-4 of Cycle 1), the first week of maintenance (Week 5 of Cycle 1), then every first and seventh week of each subsequent cycle until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at Week 53 or whenever patient comes off treatment.
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: If a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of IFN treatment and at the end of IFN treatment.
h. To be performed at baseline, then as clinically indicated throughout treatment.
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months(± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized on Step 2 until e-mail confirmation has been received indicating that the specimen was adequate for determining PD-L1 status.
m. If patient consents, submit specimens for banking as specified in Section 15.0.
n. Blood needs to be drawn prior to treatment.
o. Submit scans as outlined in Sections 14.0 and 15.0.
p. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks(± 2 weeks) after the date of last treatment.

q. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.

r Thyroid function tests need to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post-treatment follow-up. Additional testing to be done as clinically indicated.

s History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.

9.2 Arm 1: Ipilimumab

REQUIRED STUDIES	Pre-screen-ing	Rand-dom-ization	ON TREATMENT [a]																End of treat [b]	Post treat F/U pre-re-lapse[c]	Re-lapse /Rec ur-rence	F/U post re-lapse[d]
PHYSICAL	Reg Step 1	Reg Step 2	Induction				C 3	C 4	C 5	C6	C 7	C 8	C 9	C 10	C 11	C 12	C 13	C 14				
			Cy 1		C 2																	
*			W 1	W 4	W 7	W 10	W 13	W 25	W 37	W 49	W 61	W 73	W 85	W 97	W 109	W 121	W 133	W 145				
History & Physical (w/ BSA, BP, Height & Weight) [t]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PS & Toxicity Notation	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																						
Cover Sheet for Patient-Completed Questionnaires			X	X			X	X	X	X										X[r]	X[s]	
FACT-BRM, EQ-5D-3L and FACIT-D Questionnaire			X	X			X	X	X	X										X[r]	X[s]	
LABORATORY[e]																						
ANC, platelets, Hgb	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
LDH [f]	X																				X[f]	
AST and ALT, Alkaline Phosphatase	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Albumin, Glucose, Na, K, HCO3 (or CO_2) [a]			X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Triglycerides[g]	X							X[g]											X[g]			
Free T_3, TSH, Free T_4 [o]		X					X[o]	X[o]	X[o]											X		
Cardiac Function [u]			X		X		X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy Test[i]	X		X[i]				X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]			

Study Calendar 9.2 continued on next page. Click here for footnotes.

9.2 Arm 1: Ipilimumab (contd.)

	Pre-StudyScreening	Randomization	ON TREATMENT [a]															End of treat [b]	Post treat F/U pre-relapse [c]	Relapse/Recurrence	F/U post relapse [d]
	Reg Step 1	Reg Step 2	Induction				C 3	C 4	C 5	C6	C 7	C 8	C 9	C 10	C 11	C 12	C 13	C 14				
			Cy 1		Cy 2																	
*			W 1	W 4	W 7	W 10	W 13	W 25	W 37	W 49	W 61	W 73	W 85	W 97	W 109	W 121	W 133	W 145				
X-RAYS AND SCANS																						
Whole body PET/CT or CT neck [j], chest, abdomen & pelvis [k]	X						X	X	X	X	X	X	X	X	X	X	X	X		X [j k]		
Brain MRI or CT with contrast [k]	X									X[k]					X[k]					X [k]		
EKG[h]	X																					
Image Submission [p]		X					X	X	X	X	X	X	X	X	X	X	X	X		X		
SPECIMEN SUBMISSION																						
Slides for PD-L1 expression [l]	X																					
E-mail confirmation tissue was adequate for PD-L1 analysis		X																				
Tissue [m] for banking		X																			X	
Serum [m] for banking		X [n]					X	X											X		X	
Plasma & Buffy Coat [m] for RNA/DNA for banking		X [n]					X	X											X		X	
TREATMENT																						
Ipilimumab			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X				

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form 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, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Study Calendar 9.2: Arm 1 Ipilimumab

a. The following exams and labs are performed prior to receiving first dose and at the start of every cycle until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at the 15th infusion or whenever patient comes off treatment (treatment stops at the end of Year 3, even if the patient has not received all 15 infusions).
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first 2 follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse event assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation date, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: if ipilimumab was delayed per the dose delay/scheduling criteria or if a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of treatment and the end of treatment.
h. To be performed prior to Registration Step 1, then as clinically indicated. Also see footnote “u”.
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease. Patients may still be on treatment until 3 years from randomization.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized to Step 2 until e-mail notification has been received indicating that the specimen was adequate for determining PD-L1 status.
m. If patient consents, submit specimens for banking as specified in Section 15.0.
n. Blood needs to be drawn prior to treatment.
o. Thyroid function tests to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post treatment follow-up. Additional testing to be done as clinically indicated.

p. Submit scans as outlined in Sections 14.0 and 15.0.
r. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks (± 2 weeks) after the date of last treatment.
s. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.
t History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.
u Patients with history of CHF or who are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs should have an ECHO prior to treatment and an ECHO and EKG at the start of each cycle, as clinically indicated. Patients who have evidence at baseline (or subsequently) of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, ECHO cardiogram, as clinically indicated.
* These are the corresponding weeks if there are no dose delays.

9.3 Arm 2: MK-3475 (Pembrolizumab)

REQUIRED STUDIES	Pre-study Screen	Random-ization	ON TREATMENT [a] The first two cycles consist of 2 infusions, subsequent cycles consist of 4 infusions. Infusions to be given q 3 weeks for 18 total infusions (5.5 cycles).											End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse[c]	Re-lapse/ Recur-rence	F/U post relapse[d]
PHYSICAL	Reg Step 1	Reg Step 2	Cycle 1		Cycle 2		C3		C4		C5		C6				
			*W 1	*W 4	*W 7	*W 10	*W 13	*W 19	*W 25	*W 31	*W 37	*W 43	*W 49				
History & Physical (w/ BSA, BP, Height & Weight) [t]	X		X		X		X	X	X	X	X	X	X	X	X		
PS & Toxicity Notation	X		X		X		X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																	
Cover Sheet for Patient-Completed Questionnaires			X	X			X		X		X		X		X[r]	X[s]	
FACT-BRM, EQ-5D-3L, and FACIT-D Questionnaire			X	X			X		X		X		X		X[r]	X[s]	
LABORATORY[e]																	
ANC, platelets, Hgb	X		X		X		X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X		X		X	X	X	X	X	X	X	X	X		
LDH [f]	X															X[f]	
AST and ALT, Alkaline Phosphatase	X		X		X		X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X		X		X	X	X	X	X	X	X	X	X		
Albumin, Glucose, Na, K, HCO3 (or CO_2) [a]			X [a]		X		X	X	X	X	X	X	X	X	X		
Triglycerides [g]	X								X[g]					X[g]			
Free T_3, TSH, Free T_4 [o]	X						X [o]		X [o]		X [o]			X [o]	X		
Pregnancy Test[i]	X		X [i]		X [i]		X [i]		X [i]		X [i]		X [i]				
Cardiac Functiont[v]			X		X		X		X		X		X				

Study Calendar 9.3 continued on next page. Click here for footnotes.

9.3 Arm 2: MK-3475 (Pembrolizumab) (contd.)

	Pre-study Screen	Random-ization	ON TREATMENT [a] The first two cycles consist of 2 infusions, subsequent cycles consist of 4 infusions. Infusions to be given q 3 weeks for 18 total infusions (5.5 cycles).											End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse[c]	Re-lapse/Recur-rence	F/U post relapse[d]
	Reg Step 1	Reg Step 2	Cycle 1		Cycle 2		C3		C4		C5		C6				
			*W 1	*W 4	*W 7	*W 10	*W 13	*W 19	*W 25	*W 31	*W 37	*W 43	*W 49				
X-RAYS AND SCANS																	
Whole body PET/CT or CT neck [j], chest, abdomen & pelvis [k]	X						X		X		X		X		X [j k]		
Brain MRI or CT with contrast [k]	X												X [k]		X [k]		
EKG[h]	X																
Image Submission [p]		X					X		X		X		X		X		
SPECIMEN SUBMISSION																	
Slides for PD-L1 expression [l]	X																
Serum for PK/ADA [q]			X	X		X		X	X				X		X [q]		
E-mail confirmation tissue was adequate for PD-L1 analysis		X															
Tissue [m] for banking		X														X	
Serum [m] for banking		X [n]					X		X					X		X	
Plasma & Buffy Coat [m] for RNA/DNA for banking		X [n]					X		X					X		X	
TREATMENT																	
MK-3475 (Pembrolizumab)			X	X	X	X	X	X	X	X	X	X	X				

Study Calendar 9.3 continued. Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form 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, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Study Calendar 9.3: Arm 2 MK-3475 (Pembrolizumab)

a. Following exams & labs are performed prior to receiving first dose & prior to every other infusion until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at the 18th infusion or whenever patient comes off treatment.
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: if MK-3475 was delayed per the dose delay/scheduling criteria or if a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of treatment and at the end of treatment.
h. To be performed prior to Registration Step 1, then as clinically indicated. Also see footnote “v”.
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized to Step 2 until e-mail notification has been received indicating that the specimen was adequate for determining PD-L1 status.
m. If patient consents, submit specimens for banking as specified in Section 15.0.

Footnotes for Study Calendar 9.3: Arm 2 MK-3475 (Pembrolizumab) (contd. on next page)

n. Blood needs to be drawn prior to treatment.
o. Thyroid function tests to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post treatment follow-up. Additional testing to be done as clinically indicated.
p. Submit scans as outlined in Sections 14.0 and 15.0.
q. Serum for PK and anti-MK-3475 antibody testing must be submitted for all patients randomized to the MK-3475 arm as described in Section 15.4. Pre-dose trough PK and anti-MK-3475 samples will be collected before the first infusion Cycle 1 (Week 1), before second infusion Cycle 1 (Week 4), before second infusion Cycle 2 (Week 10), before third infusion Cycle 3 (Week 19), before first infusion Cycle 4 (Week 25), before infusion Cycle 6 (Week 49) and 30 days after discontinuation of study drug (or until patient starts new anti-cancer therapy). **All pre-dose trough samples should be drawn within 24 hours before infusion of MK-3475. (AS OF 12/11/2017 PK/ADA SAMPLING HAS BEEN DISCONTINUED. SPECIMENS ALREADY COLLECTED MUST STILL BE SHIPPED.)**
r. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks (± 2 weeks) after the date of last treatment.
s. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.
t History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.
* These are the corresponding weeks if there are no dose delays.
v Patients with history of CHF or who are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs should have an ECHO prior to treatment and an ECHO and EKG at the start of each cycle, as clinically indicated. Patients who have evidence at baseline (or subsequently) of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, ECHO cardiogram, as clinically indicated.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Measurement of Effect

10.1 Progression/Relapse

Appearance of any new lesion/site. Death due to disease without prior documentation of progression.

- Appearance of a new melanoma in-situ or Stage I melanoma which can be treated curatively by wide excision does not constitute recurrence. If this does occur, upload pathology and operative reports via the Source Documentation: Follow-Up Form in Rave.

- In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms persist beyond 4 weeks or there must be additional evidence of progression.

- For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

- Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, X-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

10.2 Relapse-Free Survival

Measured from date of randomization to date of first documentation of relapse or death due to any cause. Patients last known to be alive and relapse-free are censored at date of last contact.

10.3 Overall Survival

Measured from date of randomization to date of death due to any cause. Patients known to be alive are censored at date of last contact.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual goals

Based on **E1609**, an intergroup accrual rate of at least 45 patients per month is assumed.

It is assumed that up to 10% of patients will be ineligible. It is expected that 1378 registered patients will be required to accrue 1,240 eligible patents (see below for sample size calculations). Including time to ramp up accrual, it is anticipated that it will take less than 2.5 years to complete accrual for this trial.

11.2 Overall survival (OS) and relapse-free survival (RFS) objectives

There are three primary objectives of this study: 1) to test whether OS is improved with pembrolizumab compared to a control arm of physician/patient choice of high-dose interferon (HDI) or ipilimumab in this patient population, 2) to test whether among patients who are PD-L1 positive OS is improved with pembrolizumab compared to this control arm in this patient population, 3) to test whether RFS is improved with pembrolizumab compared to this control arm in this patient population.

11.3 Overall survival (OS) and relapse-free survival (RFS) design assumptions

OS and RFS estimates from **S0008** indicate that a proportion of patients may be long-term survivors in the sense that they will not be observed to relapse or die during the follow-up period planned for the study. It is further assumed that there are no differences in OS or RFS between the treatment regimens in the control arm.

An exponential cure rate model fit to OS on the HDI arm of **S0008** indicated that 40% of patients were long-term survivors and that median OS for patients who were not long-term survivors was 3.01 years (null hypothesis). The null OS model is written that the OS at year t is equal to 0.40+0.60*exp(-0.23t). For sample size calculations, it is assumed that OS with pembrolizumab will also follow an exponential cure rate model, but with 45% of patients long-term survivors and a median OS for non-long term survivors of 3.96 years (alternative hypothesis). The alternative OS model is written that the OS at year t is equal

to 0.45+0.55*exp(-0.175t). This corresponds to an average hazard ratio (HR, average of 10,000 simulated hazard ratios from the Cox model) of 0.73 from a Cox proportional hazards model at 100% OS events (374 events at Study Year 5).

An exponential cure rate model fit to RFS on the HDI arm of **S0008** indicated that 35% of patients were long-term survivors and that median RFS for patients who were not long-term survivors was 1.03 years (null hypothesis). The null RFS model is written that the RFS at year t is equal to 0.35+0.65*exp(-0.67t). For sample size calculations, it is assumed that RFS with pembrolizumab will also follow an exponential cure rate model, but with 41% of patients long-term survivors and a median RFS for non-long term survivors of 1.44 years (alternative hypothesis). The alternative RFS model is written that RFS at year t is equal to 0.41+0.59*exp(-0.48t). This corresponds to an average hazard ratio (HR) of 0.70 from a Cox proportional hazards model at 100% RFS information.

We assume a total two-sided alpha of 5% (one-sided alpha of 2.5%) allocated between the four co-primary objectives as detailed below. We assume 1:1 randomization, 2.5 years of accrual, 2.5 years of follow-up after accrual completes. We assume 48.2% of patients will be PD-L1 positive, (based on the lower limit of the 95% confidence interval of the prevalence from ClinicalTrials.gov trial NCT 01704287), 46.8% will be PD-L1 negative, and 5% will be PD-L1 indeterminate. All testing will be stratified by the randomization stratification. Tests of the null hypothesis will be done using the log-rank test. Futility analysis testing will be performed using a modified log-rank test modified for testing non-null hypotheses (a score test of the alternative hazard ratio).

11.4 Alpha allocation between Overall survival (OS) and Relapse-free survival (RFS)

Using a Bonferroni split, 4.6% (two-sided) of the alpha will be allocated to the OS endpoint (overall population and PD-L1+ subgroup) and 0.4% (two-sided) of the alpha will be allocated to the RFS endpoint (overall population). For OS, 80% of the alpha will be allocated to the overall population and the remaining alpha will be allocated to the PD-L1 positive subgroup using the method described in the next paragraph.

Under the null hypothesis, the test statistics for the overall population and the PD-L1 positive subgroups are multivariable normal with correlation equal to the proportion of events the PD-L1 positive subgroup relative to the whole population. *(25)* The residual alpha for the PD-L1 population can be calculated using this relationship. For clarity in the exposition of the design we will assume the PD-L1 positive subgroup has 48.2% of the total OS events of the study (based on the lower limit of the 95% confidence interval of the prevalence from ClinicalTrials.gov trial NCT 01704287). For the final analyses involving the PD-L1 positive subgroups, the actual alpha level will be calculated using the multivariate normal relationship based on the PD-L1 positive proportion observed in the trial

Under these assumptions, the alpha allocation is expected to be as follows: the OS overall population with 3.7% (two-sided) and the PD-L1 + subgroup OS with 1.52% (two-sided). Accounting for the correlation between the subgroup and overall group, the overall alpha is 4.6% (two-sided) for OS and 0.4% (two-sided) for RFS.

- OS overall population 3.7%
- OS PD-L1 + subgroup 1.52%
- RFS overall population 0.4%

11.5 Interim and final analysis plans

The primary analysis will be intent-to-treat population.

All testing will be stratified by the randomization stratification factors. Tests of the null hypothesis will be done using the log-rank test. Futility analysis testing will be performed using a modified log-rank test modified for testing non-null hypotheses (a score of the alternative hazard ratio).

100% of expected RFS is 536 events. One formal interim analysis of the overall population RFS endpoint is scheduled at approximately 75% of RFS events (402 RFS events calculated across both arms under the alternative). At the interim analysis, an efficacy test will be done (test of null hypothesis HR=1) with a one-sided alpha=0.09%. At the interim analysis a futility test will evaluate if the HR from a Cox regression model stratified by the randomization factors favors the control arm (HR>1). If an efficacy or futility boundary is crossed at the interim analysis, the DSMC will consider early release of the RFS results. The final analysis of the overall population RFS will test of the null hypothesis (HR=1) at the two-sided 0.32% level (one-sided 0.16% level) in order to account for the interim analysis.

Up to two formal interim analyses of the overall population OS will be completed at approximately 55% and 80% events (206 and 399 events, respectively, events calculated across both arms under the alternative). At both interim analyses, an efficacy test will be done (test of null hypothesis HR=1) with a one-sided alpha=0.125%. At the first interim analysis a futility test will evaluate if the HR from a Cox regression model stratified by the randomization factors favors the control arm (HR>1). At the second interim analysis a futility test will be done testing the alternative hazard ratio (HR=0.73) with a one-sided alpha of 2.5%. If a boundary for futility is crossed at an interim analysis, the DSMC will consider the toxicities on each arm. Considering the magnitude of the survival difference between the two arms along with the relative toxicities, the DSMC can choose not to recommend reporting results early if additional data on the potential non-inferiority of pembrolizumab is warranted. The final analysis of the overall population OS will test of the null hypothesis (HR=1) at the two-sided 3.6% level (one-sided 1.8% level) in order to account for interim analyses. At the final analysis for the overall population OS, a two-sided test of the null hypothesis of OS in the PD-L1 positive subgroup will be performed at the two-sided alpha=1.52% level[2] (one-sided 0.76% level).

The final OS superiority test will be performed in a stepwise fashion following an OS non-inferiority test using a margin of 1.045. An upper limit of a one-sided 98.15% confidence interval less than 1.045 will be considered evidence of non-inferiority of pembrolizumab compared to the control arm.

At the final analysis for OS, results for RFS with updated follow-up will be presented. We note that because of the expected survival patterns with this population, the average hazard ratio is expected to become more null (closer to 1) over time. Under the alternative hypothesis, at 3.5 years since the first patient is randomized the hazard ratio is 0.70, while at 5 years since the first patient is randomized the hazard ratio is 0.73.

There will be no formal interim testing of RFS (overall or PD-L1 positive subgroup) or of OS in the PD-L1 positive subgroup.

If 100% RFS or OS events has not been reached by 3.5 years after the last eligible patient is randomized, the final RFS and OS analyses will be performed at this time.

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[1] Alpha to be calculated based on observed proportion of total OS events in the PD-L1 positive group.

The sample size of this trial was determined to ensure appropriate power to detect meaningful OS differences. As such, the trial is overpowered for RFS, and may therefore detect small RFS differences of uncertain clinical benefit. Hence, regardless of the statistical significance of the RFS results, the clinical benefit of pembrolizumab will be

assessed by the magnitude of the relative and absolute RFS improvement of the pembrolizumab arm over the control arm, and by the comparisons of overall survival and toxicity between the treatment arms.

Under this design and assuming PD-L1 positive patients have the same OS on the control arm as the whole population, the alternative OS survival model for 80% power is model is written that OS at year t is equal to 0.44+0.56*exp(-0.13t) [44% long-term survivors and median OS of 5.3 years for non-long-term survivors]. This corresponds to an average HR of 0.58 from a Cox proportional hazards model at 100% OS events. The alternative OS survival model for 90% power is model is written that OS at year t is equal to 0.45+0.55*exp(-0.13t) [45% long-term survivors and median OS of 5.3 years for non-long-term survivors]. This corresponds to an average HR of 0.56 from a Cox proportional hazards model at 100% OS events.

Design properties were determined via simulation with 100,000 replications. Properties of the design are summarized in the tables below.

Table 1 Overall population OS Interim and final analysis summary. Events calculated across both arms. Actual analysis timing may vary.

Percent OS events	Study Year	N events	Tests done
55%	3	206	Efficacy and futility
80%	4	299	Efficacy and futility
100%	5	374	Efficacy

Table 2 Characteristics of interim and final overall population OS analyses

OS Scenario	Probability under alternative	Probability under null
Probability stop for futility at 1st interim analysis	1%	50%
Probability stop for efficacy at 1st interim analysis	28%	<1%
Probability stop for futility at 2nd interim analysis	1%	17%
Probability stop for efficacy at 2nd interim analysis	19%	<1%
Probability stop early for futility	2%	67%
Probability stop early for efficacy	48%	1%
Probability of positive result	86%	2.1%[a]

[a] Ignoring futility monitoring two-sided, alpha level=3.7%

Table 3 Overall population RFS Interim and final analysis summary. Events calculated across both arms. Actual analysis timing may vary.

Percent RFS events	Expected time	N events	Tests done
75%	Mid-2018	402	Efficacy and futility
100%	Late 2018	536	Efficacy

Table 4 Characteristics of interim and final overall population RFS analyses

RFS Scenario	Probability under alternative	Probability under null
Probability stop for futility at interim analysis	<1%	50%
Probability stop for efficacy at interim analysis	69%	<1%
Probability of positive result	90%	0.22%[a]

[a] Ignoring futility monitoring two-sided, alpha level=0.4%

Table 5 Additional characteristics of overall population OS analyses. Events calculated across both arms. Actual analysis timing may vary.

Analysis	Alpha level	HR threshold	OS Events
Year 3 interim efficacy	0.125% (one-sided)	0.67	206
Year 3 interim futility	NA	1	206
Year 4 interim efficacy	0.125% (one-sided)	0.70	299
Year 4 interim futility	2.5%	0.92	299
Year 5 final efficacy	3.6% (two-sided)	0.81	374

HR threshold = HR that will correspond to a significant p-value based on alpha level. For efficacy analyses HRs less than the threshold will be significant, for futility analyses HRs larger than the threshold will warrant early closure of the study.

Table 6 Characteristics of overall population RFS analyses. Actual analysis timing may vary.

Analysis	Alpha level	HR threshold	RFS Events
interim efficacy	0.09% (one-sided)	0.66	402
Interim futility	NA	1	402
Final efficacy	0.32% (two-sided)	0.78	536
Year 5 follow-up	NA	NA	668

HR threshold = HR that will correspond to a significant p-value based on alpha level. For efficacy analyses HRs less than the threshold will be significant.

Table 7 PD-L1 positive subgroup analysis details, N = 596 (48.2% prevalence)*

Endpoint	Time point	Alpha-level (two sided)*	HR threshold	Design HR	Power
OS	Year 5	1.52%	0.66	0.57	80%
OS	Year 5	1.52%	0.68	0.56	90%

* These calculations assume a 48.2% event fraction in the PD-L1 positive subgroup. For the final analysis, calculations will be based on the observed fraction of events in the trial. HR threshold = HR that will correspond to a significant p-value based on alpha level. Design HR = HR that provides stated level of power.

How to interpret the first line of Table 7: If 48.2% of patients are PDL1-positive (and making all the assumptions about survival in the protocol), at Year 5 we will have 80% power to detect a true hazard ratio of 0.57 for OS. In other words, if the true hazard ratio between the arms is 0.57 and we ran the trial many times, 80% of the trials would have an observed hazard ratio of 0.62 or less or a two-sided p-value less than 0. 0152.

11.6 Anticipated stage distribution.

Eligibility for SWOG trial **S0008** included Stages IIIA(n2), IIIB, and IIIC. Eligibility for ECOG trial **E1609** included Stages IIIB, IIIC, M1a, and M1b. Eligibility for this trial **S1404** includes Stages IIIA(n2), IIIB, IIIC, M1a, M1b, and M1c. Null (historical) survival estimates for **S1404** are based on **S0008** data. We note that compared to **S0008**, **S1404** will also include M1a, M1b, and M1c patients. In **E1609** 6% of patients were Stage M1a and 2% were M1b. We expect approximately 1% of randomized patients to be Stage M1c. We expect less than 10% of randomized patients in **S1404** to be Stage M1, and because of modest differences in expected survival we have used **S0008** survival patterns as a historical reference for this trial.

11.7 Analyses of other objectives

a. **Estimation of OS and RFS in PD-L1 negative subgroup:** Cox regression models will be used to estimate hazard ratios and calculate confidence intervals to compare treatment arms in the PD-L1 negative subgroup. In addition Cox regression models for OS and RFS will be used to estimate interaction terms between PD-L1 status and treatment arm.

b. **Analysis of toxicity:** On the MK-3475 (pembrolizumab) arm, six hundred and twenty eligible patients will be sufficient to estimate toxicity rates within ± 4% (95% confidence interval). Any toxicity occurring with at least a 0.8% probability is likely to be observed at least once (99% probability). Assuming that on the Control Arm 310 patients receive HD-IFN and 310 patients receive ipilimumab, this will be sufficient to estimate toxicity rates for these regimens to within ± 6% (95% confidence interval). Under this assumption any toxicity occurring on a particular control arm regimen with at least a 1% probability is likely to be observed at least once (96% probability).

c. **Analysis of post-relapse therapy:** Data on therapy after relapse will be collected for three years after relapse (or until 10 years after registration maximum). Therapies will be categorized into one of two categories: systemic or local. Specific therapies after relapse will be tabulated and summarized. Therapy after relapse will be analyzed as a time-dependent variable in Cox regression analyses for the endpoint of OS after relapse.

d. **Analysis of BRAF mutation data:** Prestudy BRAF mutation status on patients will be collected. BRAF mutation status will be analyzed as a covariate in Cox regression analyses and exponential-logistic cure regression models. *(26)* In addition, the interaction between BRAF mutation status and treatment arm will be

analyzed in Cox regression models and in exponential-logistic cure regression model.

e. **Analysis of long-term survivors/cured patients:** Exponential-logistic cure regression models will be used to examine the association between known prognostic factors (including stage) and long-term survivor/cure status, and survival for patients who are not long-term survivors/cured. *(27)*

f. **Other analyses of OS and RFS:** A restricted mean survival time analysis will be done as a supportive analysis.

g. **T-cell Receptor Beta Chain sequencing:** The statistical plan for the T-cell receptor beta chain sequencing objectives is included in Appendix 18.8

11.8 Quality of life (QOL data)

This pre-specified statistical analysis plan (SAP) is intended to describe the strategy, rationale, and statistical techniques that will be used to assess the patient-reported outcomes (PROs) data gathered in the **S1404** trial.

a. **Objectives:** The key objective of the PRO analysis is to evaluate overall health-related quality of life (QOL) for patients with melanoma treated with physician/patient choice of either high-dose interferon alfa-2b or ipilimumab and MK-3475 (pembrolizumab).

b. **Instruments:** The FACT-BRM measures quality of life domains important to patients treated with biological response modifiers (BRMs). The domains are represented by six sets of response items, four of which comprise the FACT-General (FACT-G) subscales including Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being; and two additional subscales specific to the FACT-BRM instrument, the BRM Physical Subscale, and the BRM Cognitive/Emotional subscale. Each subscale is derived from 6-7 items on the questionnaire, with responses given on a five-point Likert-type scale ranging from 0 to 4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much). The six subscales are also combined to form a single FACT-BRM total score. In addition, the FACT-BRM Trial Outcome Index (TOI) is derived from a subset of four of the subscales (Physical Well-Being, Functional Well-Being, BRM Physical, and BRM Cognitive/Emotional). Each FACT BRM subscale, the FACT BRM total score, and the FACT BRM TOI will all be analyzed. Scoring of the scales will follow the standard published metrics. For the FACT BRM, the higher the score, the better the quality of life.

The FACIT-D comprises the FACT-G and a symptom-specific subscale that measures quality of life specific to diarrhea. Like the FACT-BRM, the FACIT-D subscales is scored on a 5-point Likert-type scale ranging from 0 to 4, with higher scores indicating better quality of life. The FACIT-D subscales (distinct from the FACT-BRM subscales) and FACT-D total score will all be analyzed.

The EQ-5D-3L has two systems. The descriptive system measures three functional domains (mobility, self-care, usual activities) and two symptom domains (pain/discomfort and anxiety/depression). Each domain has three levels (no problems, some problems, extreme problems). A visual analog system (VAS) records self-rated global health between “best imaginable health state” and “worst imaginable health state” and can be used as a quantitative measure of health outcome as judged by individual patients. The three functional and two symptom domains can be summarized categorically, and the VAS global health rating can be summarized quantitatively. The measures can then be combined into a single summary index. Utility scoring will follow the US and European algorithms.

c. **Endpoints**: PRO endpoints are measured by the FACT-BRM, FACIT-D, and EQ-5D-3L. These endpoints are affected by both disease progression and treatment tolerability.

The Trial Outcome Index (TOI) from FACT-BRM is the primary PRO endpoint for this study. The TOI combines four subscales: Physical Well-Being, Functional Well-Being, the BRM Physical Subscale, and the BRM Cognitive/Emotional Subscale. The primary TOI endpoint will be the TOI score at Cycle 3.

Secondary PRO endpoints from the FACT-BRM are the six individual FACT-BRM subscales and the FACT-BRM total score. Secondary PRO endpoints from the FACIT-D are symptom-specific subscale and specific items and the FACIT-D total score. Secondary PRO endpoints from the EQ-5D-3L include the summary index as well as each of the six individual EQ-5D-3L domains.

For PRO endpoints, the baseline score will be accounted for as a covariate in multivariable regression models. The change between the baseline and Cycle 3 scores will also be examined as a sensitivity analysis. In addition, the changes over all time points in the TOI endpoint as well as all of the secondary PRO endpoints will be analyzed using longitudinal data analytic approaches described below.

d. Schedule for PRO data collection:

Table 11.8.1 PRO Data Collection Schedule

Treatment Cycle	Baseline	Cycle 1	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Follow-up	Recurrence
Study Time*	Before first day of treatment	4 weeks	13 weeks	25 weeks	37 weeks	49 weeks	24 and 48 weeks after protocol treatment discon-tinuation	See below [a, b]

* assuming no treatment delays
a) Once patient has disease recurrence, no subsequent PRO data will be collected.
b) If recurrence occurs more than 48 weeks after protocol discontinuation, then PRO data collection at the time of recurrence is not required.

With the exception of the recurrence time point, at each time point the FACT-BRM, FACIT-D, and EQ-5D-3L will be administered prior to all other study procedures. At the time of recurrence, the FACT-BRM, FACIT-D, and EQ-5D-3L will be administered after the patient sees the treating investigator. At each time point, if

a patient does not complete one or both PRO instruments, the site staff will record the reason on the PRO Coversheet from predefined choices.

e. **Analysis Populations:** The primary analysis population will be based on an intent-to-treat (ITT) approach, incorporating data from all eligible randomized patients. To be evaluable, patients must have completed both the baseline and the Cycle 3 assessments.

f. PRO instrument completion and compliance:

The completion rate for the primary endpoint is defined as the number of patients who complete a sufficient number of items to score the FACT-BRM TOI according to the missing data rules for the instrument, divided by the number of eligible randomized patients at each time point. The completion rate is expected to decrease over time because some patients will not complete all protocol therapy and some patients will have disease recurrence or die.

The compliance rate for the primary endpoint is defined as the number of patients who complete a sufficient number of items to score the FACT BRM TOI according to the missing data rules for the instrument, divided by the number of patients who were expected to complete the PRO instrument. The denominator of the compliance rate will not include patients who have died, recurred, or went off protocol therapy prior to that time point, or could not complete an instrument due to language translation not being available.

The completion and compliance rates of the other subscales and total scores will be defined in a similar fashion. Completion and compliance rates by instrument, visit, and treatment arm will be described.

For any subscales, trial outcome indexes, or total scores, we also define the minimum completion rate as the number of patients who complete at least one item included in the subscale, TOI, or total score, respectively, in order to assess the extent to which sites successfully administer a form to patients, even if only minimal information on the form is collected and the form cannot be scored according to the missing data rules for the instrument.

The primary reason for not completing any of the PRO assessments for any assessment time point will be collected on the PRO Coversheet, to be filled out by the personnel administering PROs at each site. The reasons will be summarized in table format.

g. **PRO analyses:** Consistent with the design and to aid in clinical interpretation, the analysis of the primary endpoint of the Cycle 3 FACT BRM TOI will be conducted using multivariable linear regression analysis, adjusting for randomization stratification factors and the baseline FACT BRM TOI score as covariates. A window of +/- 2 weeks around the completion of cycle 3 will be allowed for inclusion of the FACT-BRM TOI in the final analysis. We will also conduct longitudinal modeling of the outcome measures over time, to assess whether the longitudinal results are consistent with the primary analysis. Power for the longitudinal analysis will be greater since the addition of all available FACT BRM TOI scores over time will provide more information. For longitudinal modeling, linear mixed models will be used, with random effects for intercepts and slopes and using both compound symmetric and unstructured correlation models. Covariates for longitudinal modeling will include treatment arm, assessment time, their interaction, the baseline score, as well as the randomization stratification variables and the baseline FACT BRM TOI score. Additionally, a treatment by time-squared interaction will be evaluated. These models are nested and so log-likelihood values will be compared using a Chi-squared tests with appropriate degrees of freedom to assess which model provides a best fit to the data. When summarizing results from models with the best fit, coefficients for the intercept, treatment arm, time point, and baseline score will be tabulated, along with 95% confidence intervals and nominal p-values. We will also plot scale and subscale means for groups of patients based on the number of time points that instruments were completed.

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. The linear mixed models described above assume that data is missing at random (MAR). The MAR assumption implies that the probability of missingness depends only on the observed data, which can be accounted for through covariate adjustment in the models. However the potential exists that missing data are a function of other, unobserved variables. For instance, in this study missingness may also depend on ill health, death, and disease recurrence, in a fashion that cannot be predicted by baseline factors. If the alternative hypothesis is correct and patients on the standard treatment arm are more likely to have worse PRO outcomes, they are also more likely not to report PRO outcomes due to worsening health or death. In this setting, differential dropout by arm will bias the results towards the null hypothesis of no difference between arms, in which case the observed result by arm is likely to be conservative, such that difference between the arms in favor of the experimental arm would, in truth, be even more favorable that what is observed. However such a pattern cannot be assumed.

Additional analyses will be performed to assess the MAR assumption. To evaluate potential cohort biases, baseline characteristics will be compared between evaluable (that is, those who complete both their baseline and cycle 3 FACT BRM TOI) and inevaluable patients. Also, 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. *(28,29,30)* Pattern mixture models estimate PRO trajectories for different patterns of attrition. The pattern groups are defined by the last PRO assessment time points for patients. In this study a total of six patterns will be identified: 1) complete all PRO assessments; 2) die before end of PRO assessments; 3) disease recurrence before end of PRO assessments; 4) alive without disease recurrence before end of PRO assessments but do not complete 9 cycles of protocol therapy; 5) alive, recurrence-free, and complete 9 cycles of protocol therapy but stopped completing PRO assessments before Cycle 3; 6) alive, recurrence-free, and complete 9 cycles of protocol therapy but stopped completing PRO assessments after Cycle 3. If some patterns have small numbers of patients, patterns may be collapsed for analysis.

The pattern mixture models will be fit by estimating a linear mixed model within the six pattern groups defined above, estimating the proportion of patients in each pattern group, and then averaging out the pattern-specific PRO endpoint trajectories using weights equal to the proportions. The variance will be calculated using the delta-method.

Observed mean scores for the quantitative endpoints will be plotted across assessment time points with fitted results from the linear mixed model analysis overlaid.

Descriptive statistics, multivariable linear regression analyses, and longitudinal modeling analyses will also be conducted for the FACIT-D and EQ-5D instruments and all subscale scores as secondary analyses. As additional secondary analyses, the same analyses will be done in the subgroups of patients identified by choice of control arm before randomization (used a randomization stratification factor, choice between high-dose interferon alfa-2b or ipilimumab).

Interpretation of Longitudinal Model Results: For models in which the simple linear model (no interaction) provides the best fit, the fitted models will have parallel trajectories for the treatment arms, representing a treatment effect that is constant over time. Significant non-zero treatment arm coefficients will indicate that one arm having higher endpoint values over time compared to the other arm.

Significant non-zero time coefficients will indicate upward or downward endpoint changes over time (depending on the sign of the coefficient).

Models with an interaction will indicate a differential treatment effect on PRO endpoints over time, so the trajectories will not be parallel. If a square interaction is significant, the differential treatment effect will be modeled as quadratic (i.e., non-linear or curved). With significant interactions, the main effect coefficients for treatment arm and time cannot be interpreted independently but must be considered in combination with the coefficients for the interaction terms.

h. **Power and sample size calculations:** The primary hypothesis for sample size calculation is that pembrolizumab is superior to IFN with respect to the cycle 3 TOI score. PRO will be collected and data analyzed on all patients on the trial, not a subset of patients.

We do not have preliminary PRO data on the FACT-BRM TOI with pembrolizumab or IFN in this particular patient population (the trial has wider eligibility than prior trials). The follow-up standard deviation for the FACT-BRM TOI was 20 in a set of nearly 200 patients receiving IFN for renal cell carcinoma. *(31)* This is consistent with data from Trask et al. (2004) in a small series of patients receiving IFN for high risk melanoma. *(32)* Thus we assume a cycle 3 standard deviation of the FACT BRM TOI of 20, common between both arms. Using Yost (2005), the estimated minimally important difference for the FACT BRM TOI is 5-8 points. If the standard deviation is 20 points, this difference is consistent with clinically meaningful effect sizes of 0.25-0.33, using distribution-based methods and anchor-based methods, respectively, identified by Yost et al. *(33)* Given the sample size is large, power is based on identifying a small effect size of 0.25. It is assumed, conservatively, that with a median OS for non-long term survivors of 3.96 and a median RFS for non-long term survivors of 1.44 years, then by cycle 3, 5% of patients will drop out due to death, 12% due to worsening disease, and 3% for other reasons, producing an overall dropout rate of 20% at cycle 3. Further, an additional 10% patients are assumed to be non-adherent. Patients who drop out or are non-adherent are considered inevaluable. Note that in power calculations, the 10% non-adherence rate reduces the nominal effect size by 10% (to 0.225), while the 20% dropout rate inflates the estimated sample size by a factor of 1/(1-0.2) or 25%. Using a 2-sided alpha=0.05 test and a two-arm normal design, and accounting for dropout and non-adherence as specified, there will be 94% power to detect the effect size difference of 0.25 between the two arms.

Power will be worse with a smaller sample size. For instance, a sample size of 260 patients (130 per arm) will provide 83% power for a notably higher standardized difference (difference between means / standard deviation) of 0.4, using the same parameters as specified above. This effect size corresponds to a minimally important difference of 8 points in the FACT BRM TOI at cycle 3 if the standard deviation is 20%, the upper limit of the range of the minimally important difference as indicated in Yost et al.

11.9 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of this study. The Committee consists of four members from outside of the SWOG, 3 SWOG 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.

In addition to the above DSMC review, toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician, and the Disease Committee Chair. Endpoint

monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

a. STEP 1 Registration - Screening

Patients must meet the eligibility criteria in the Step 1 Registration criteria in Section 5.0. Patients must be registered within 7 business days prior to submission of specimens for PD-L1 testing. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

b. STEP 2 Registration – Randomization

Patients who meet the eligibility criteria as stated in the Step 2 Registration criteria in Section 5.0 will be registered to STEP 2 – Randomization. Patients must register within 7 working days after receiving the e-mail notification confirming that their tissue sample was adequate for PD-L1 testing.

Patients must be randomized prior to the initiation of treatment (no more than 5 working days prior to the planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five-person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	X	X			
Financial Disclosure Form	X	X	X		
NCI Biosketch (education, training, employment, license, and certification)	X	X	X		
GCP training	X	X	X		
Agent Shipment Form (if applicable)	X				
CV (optional)	X	X	X		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both

Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm
For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov

c. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.
Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).
Include the following (highlighted) paragraph for trials that will include sites using their local IRB or REB as well as for trials with non U.S.-based NCTN and NCORP sites.
Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:
•Local IRB documentation;
•IRB-signed CTSU IRB Certification Form; and/or
•Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:
•Have an active CTEP status;
•Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
•If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
•Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
•List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
•Have the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional site requirements to obtain an approved site registration status include:
•An active Federal Wide Assurance (FWA) number;
•An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
•An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
•Compliance with all applicable protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol number *S1404.*
- Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Requirements for S1404 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted

to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Text for Patient Enrollment
Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at

https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

d. **Text for Data Submission / Data Reporting**

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.3 OPEN Registration Requirements

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org . For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com .

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Country of Residence

i. ZIP Code

j. Gender (select one):
- Female Gender
- Male Gender

k. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

l. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

m. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. Patient Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

• Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

• To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;

• If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and

• Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

b. Additional Required

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

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.

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org).

14.3 Data Submission Procedures

a. Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the Trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

• Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
and
• Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;

- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and

- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com .

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (https://swog.org)).

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.

d. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION TO STEP 1:

Submit the following:

S1404 Eligibility Checklist, confirmed a patient's eligibility (NOTE: This must be uploaded into Rave® via Source Documentation Baseline Form)

S1404 Onstudy Form

S1404 Medical History Form

Submit slides for PD-L1 evaluation as specified in Section 15.2.

*__S1404__ Local Pathology Review Form (Section 18.4)

*Radiology reports from all scans performed to assess disease at baseline

*Pathology reports documenting histologic confirmation and complete resection of all disease.

*NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.

b. IF PATIENT WILL NOT BE REGISTERED TO STEP 2 (RANDOMIZATION), SUBMIT WITHIN 7 DAYS OF DECISION NOT TO RANDOMIZE PATIENT:

S1404 Pre-Randomization Off Study Form

NOTE: For patients who do not register to Step 2 (Randomization), no additional follow-up is required other than the items listed in Sections 14.4a and 14.4b.

c. WITHIN 28 DAYS OF REGISTRATION TO STEP 2 (RANDOMIZATION):

If patient consents to banking, submit specimens as specified in Section 15.3.

d. WITHIN 14 DAYS OF REGISTRATION TO STEP 2 (RANDOMIZATION):

Submit **S1404** Baseline Laboratory Values Form

Submit to IROC via TRIAD for Image Banking. Images from scans performed to assess disease as specified in Section 15.6.

e. PATIENTS RANDOMIZED TO ARM 2, MK-3475 (PEMBROLIZUMAB), THEREBY PARTICPATING IN PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) TESTING:

Submit specimens as specified in Section 15.4.

f. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT (CYCLE 1 AND CYCLE 2 = 6 WEEKS EACH; ALL SUBSEQUENT CYCLES = 12 WEEKS):

Submit the following:

S1404 Treatment Form

S1404 Adverse Event Form

S1404 Laboratory Values Form

S1404 Concomitant Medications Form

g. AFTER RANDOMIZATION, WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT, INCLUDING ANNUAL BRAIN IMAGING (SEE STUDY CALENDAR FOR SCHEDULE) UNTIL RECURRENCE (AS DEFINED IN SECTION 10.0) OR 5 YEARS AFTER RANDOMIZATION (WHICHEVER OCCURS FIRST):

Submit the following:

S1404 Disease Assessment Form

Radiology reports from all scans performed to assess disease (uploaded via the Source Documentation: Follow-Up Form in Rave®)

Submit to IROC via TRIAD for image banking. Images from scans performed to assess disease as specified in Section 15.6.

If patient is no longer on protocol treatment, also submit the Adjuvant Melanoma Follow-up Form

h. AFTER RANDOMIZATION, WITHIN 14 DAYS AFTER EVERY QOL ASSESSMENT (SEE STUDY CALENDAR FOR SCHEDULE):

Submit the following:

S1404 Cover Sheet for Patient-Completed Questionnaires

S1404 FACT-BRM - FACIT-D

S1404 EQ-5D-3L

For the first two patients enrolled at each site, in addition, upload copies of the patient completed paper forms via Source Documentation: Other form in Rave®. NOTE: Some sites, identified by Risk-Based Monitoring, may be required to submit for additional patients.

i. WITHIN 7 DAYS OF DISCONTINUATION OF PROTOCOL TREATMENT:

Submit the following:

Off Treatment Notice documenting reasons for off treatment

S1404 Treatment Form

S1404 Adverse Event Form

S1404 Laboratory Values Form

S1404 Concomitant Medications Form

j. ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS, THEN YEARLY THROUGH YEAR 10:

Adjuvant Melanoma 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).

k. WITHIN 14 DAYS OF PROGRESSION OR RELAPSE:

Submit the following:

S1404 Disease assessment form

S1404 Cover Sheet for Patient-Completed Questionnaires

S1404 FACT-BRM-FACIT-D

S1404 EQ-5D-3L

Site(s) of progression/relapse Form

Radiology reports from all scans performed to assess disease (uploaded via the Source Documentation: Follow-Up Form in Rave®).

Submit to IROC via TRIAD for image banking. Images from scans performed to assess disease as specified in Section 15.6.

If patient is no longer on protocol treatment, also submit the Adjuvant Melanoma Follow-Up Form.

l. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Notice of Death and **all of the items listed in** Section 14.4e **or** 14.4f (if the patient was still on protocol treatment) or the Adjuvant Melanoma Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

a. All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (https://swog.org) and logon using your CTEP ID and password. After you have logged on, click on the "Member Resources" tab, and then from this page click on "CRA Workbench". . Non- SWOG users may log into SpecTrack using their CTSU User ID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack. For non-SWOG members, please visit https://crawb.crab.org/TXWB/Logon.aspx.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples for SWOG Biospecimen Bank Submission is identified as follows:

Lab #201:	SWOG Specimen Biospecimen Bank Solid Tissue, Myeloma, and Lymphoma Division
Phone:	614-722-2865
FAX:	614-722-2897
E-mail:	bpcbank@nationwidechildrens.org

b. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. Mark the box "Biohazard".

15.2 Submission of slides for PD-L1 Evaluation

At time of tissue selection, quality control measures of tumor tissue should be performed to ensure sufficient viable tumor tissue, which should contain ≥ 100 viable tumor cells. Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. This must be documented by having the pathologist sign the **S1404** Local Pathology Review form (see Section 18.4). If slides do not contain a sufficient number of cells for analysis the site will be asked to resubmit and/or the patient may be deemed ineligible.

Specimens for PD-L1 evaluation (submitted to the designated central laboratory, Lab #218) (**required** for patient):

a. Five unstained slides from the primary, lymph node, or metastatic site, and the Pathology Report must be submitted at the following times:

- Within 7 days after Registration to Step 1.

b. Specimen submissions must be entered and tracked using the SWOG **Online Specimen Tracking System (SpecTrack). See Section 15.1 for instructions.**

The following will be provided to sites by the Central Laboratory:

- Plastic slide holders (each can hold up to 5 slides)
- Positively charged microscope slides
  - Please use only positively charged slides provided by CENTRAL LAB which are standard sized positively charged microscope slides (75 mm x 25 mm x 1 mm).
- Bubble wrap pouch
- CENTRAL LAB Labels (NOTE: Labels may use an alternate study ID number: "MK3475-053". This is how the lab is identifying **S1404**).
- Amber Bag
- Biohazard Bag (also labeled as Specimen Transport Bag)
- Shipping container
- Gel packs

NOTE: Expiry dates will be clearly marked on the label that is placed on the outside of the collection kit box. The expiry date is always reflective of the tube that expires the earliest. The expiry date displayed on the label is good to the last day of the month displayed unless otherwise noted.

c. Kit Ordering

1. To order initial specimen kits log onto the SWOG Specimen Tracking System (https://crawb.crab.org/SpecTrack/Logon.aspx) and click on the link "Specimen kits for S1404" at the bottom of the page. When placing this initial order, sites must provide laboratory contact information. For SWOG institutions the fields will be pre-populated based on the current data in the SWOG roster. Please note, the initial order will contain four PD-L1 kits and three PK/ADA kits and may take up to 15 days to be filled by PPD. Once PPD CL receives site information, a site username will be assigned and faxed to the site on the fax verification form. This username will be used for sites to access http://preclaruslabdata.ppdi.com to reorder supplies.

   If your site does not receive the fax verification form within 3 days of registration, please call SWOG Data Operations at 206/652-2267.

2. For subsequent orders only, sites may reorder supplies at http://preclaruslabdata.ppdi.com. After reordering, a confirmation email will be sent automatically to the site email address.

d. Sample Preparation and Collection Procedures

1. A fine needle aspirate, frozen sample, plastic embedded sample, cell block, bone, bone marrow, clot, or cytologic specimen will **not** be acceptable for IHC analysis.

2. Obtain a plastic slide holder container from kit. Each slide holder can hold a maximum of 5 slides (placing additional slides in the holder above 5 will result in slide breakage during shipping).

3. Prepare freshly cut serial sections at 4 micron thickness onto the provided positively charged microscope slides (4-5 micron thickness is acceptable) as close to the day of shipping as possible (no more than 20 days). Other non-standard sized slides cannot be accepted for testing.

4. Standard sized positively charged slides are required for samples; slide measurements are 75 mm x 25 mm x 1 mm. Other sized slides cannot be accommodated.

5. DO NOT BAKE SLIDES – only air dry at room temperature12-24 hours prior to shipment.

6. Five slides are required to be submitted.

7. **Label each slide with SWOG Patient ID Number and serially in the order they were sectioned with indelible ink**.

8. Place slides in slots of the plastic slide holder in order of sectioning, with a maximum of 5 slides per plastic slide holder. Place the provided label on one side of the plastic slide holder to allow the barcode to be scanned. Do not wrap the label.

9. Once plastic slide holder is closed, tape shut with some standard masking or general purpose tape prior to shipment.

10. Place sample within amber bag to ensure sample will be in the dark.

11. Store in the dark at 2-8 ºC until ready to ship.

12. Bubble wrap the slide holders to help prevent breakage.

13. Place bubble wrapped slide holders in the biohazard bag (Specimen Transport Bag).

14. If needed, secure the slide box in the shipping container with packing paper.

15. **Using the appropriate provided shipper from kits, ship cold (2-8ºC) by using the frozen gel packs/wraps.**

16. In the shipping container along with the Specimen Transport Bag and frozen gel packs/wraps, place copies of 1) the Pathology Report, and 2) the SWOG Specimen Tracking System Packing List.

17. **A minimum of 5 slides need to be shipped for PD-L1 testing and slides need to be shipped within 20 days of cutting the slides**.

18. PD-L1 testing may need to be repeated if first set of slides were not adequate for testing. A minimum of 5 slides would need to be shipped for PD-L1 re-testing.

e. Shipping instructions

When submitting tissue to LabCorp for PD-L1 testing, be prepared to provide answers to the following questions in the SWOG specimen Tracking System:

- Tissue collection method (surgical resection, biopsy)
- Anatomic location of tumor tissue collection (Liver, Lung, Lymph node, Oral, Skin/subcutaneous tissue, Other)
- Month and year of patient's birth
- Date unstained slides were cut
- Method used to prepare paraffin embedded tissue (unknown, 10% neutral buffered formalin, Other)
- Time from tissue excision to immersion in fixative (unknown, >= 60 min, >30 - < 60 min, <= 30 min)

Shipping:

- Airway bills will be provided by PPD for shipping directly to **LabCorp**
- Shipments to LabCorp should be on **Mondays through Thursdays.**
- Forms to be included in shipping:
  - A copy of SWOG Specimen Tracking System Packing List
  - A copy of the pathology report
- FFPE sectioned slides should be shipped refrigerated (2ºC-8ºC) and in the dark (amber bag to be used). GEL packs used must be FROZEN.

- Ship the container overnight Monday through Thursday, along with a copy of SWOG Specimen Tracking System Packing List, the same day to the address below:

  Lab #218: LabCorp Clinical Trials

  Note: LabCorp identifies **S1404** using an alternate study ID number: "MK3475-053".

- Refer to PPD Laboratory Manual for additional shipping instructions.

f. Within 10 business days after specimen submission, institutions will be notified via e-mail whether or not the tissue specimen was adequate for PD-L1 testing. If the result comes back as "adequate", register the patient to Step 2 "Randomization" with 7 working days of receiving the email. If the result comes back as "inadequate", a second tissue specimen may be submitted if sufficient tissue remains. NOTE: The email will not include the patient's PD-L1 status.

If there are any questions, please contact the SWOG Data Operations Center at 206/652-2267.

15.3 Specimens for Banking

Specimens for banking (submitted to the SWOG Specimen Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (**optional** for patient):

a. Specimen collection kits are not being provided for this submission; sites will use institutional supplies. Please do not use tubes provided by PPD. **Do NOT submit specimens for banking to LabCorp.**

b. With patient's consent, the following specimens must be submitted at the following times:

1. Entire block of paraffin embedded tissue (from primary, lymph node, and metastasis if present) or 10 unstained slides may be submitted if the institution cannot release a pathology paraffin embedded block, **and one H&E (Hematoxylin and Eosin) stained slide** at the following times:
   - Baseline
   - Relapse

   Submit tissue according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect three tubes of whole blood in 10 mL red/black marble top (SST) vacutainer tubes with no anticoagulant. Process whole blood to **serum** according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect at the following times:
   - Baseline (prior to the start of study treatment)
   - Start of Cycle 3 (Week 13, if there are no dose delays)
   - Start of Cycle 4 (Week 25 if there are no dose delays)
   - When patient is removed from protocol therapy for any reason
   - Relapse

   Collect three tubes of whole blood in 10 mL pink/lavender top vacutainer tubes with EDTA. Process whole blood to **plasma and buffy coat** according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect at the following times:
   - Baseline (prior to the start of study treatment)
   - Start of Cycle 3 (Week 13 if there are no dose delays)
   - Start of Cycle 4 (Week 25 if there are no dose delays)
   - When patient is removed from protocol therapy for any reason
   - Relapse

c. If a patient has a treatment delay or interruption due to an adverse event, the blood sample for banking should be drawn even if the patient did not receive study treatment. The goal is to collect the sample as close to the week designated by the protocol.

d. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

15.4 Pharmacokinetic (PK) and Anti Drug Antibody (ADA) testing

NOTE: AS OF 12/11/2017 PK/ADA SAMPLING HAS BEEN DISCONTINUED.

a. Requirements

All patients randomized to the MK-3475 (pembrolizumab arm) will have blood draws for PK and ADA analysis.

b. PK/ADA Sampling for the trial

PK/ADA sampling may be discontinued upon confirmation that results are consistent with the current PK/ADA profile of MK-3475 (pembrolizumab) as determined by the Merck Pharmacokinetics and Pharmacodynamics Drug Metabolism Quantitative Pharmacology and Pharmacometrics group.

c. Specimen Tracking

Specimen submissions must be entered and tracked using the SWOG Online Specimen Tracking System (SpecTrack). See Section 15.1 for instructions.

d. Kit ordering

1. To order initial specimen kits log onto the SWOG Specimen Tracking System (https://crawb.crab.org/SpecTrack/Logon.aspx) and click on the link "Specimen kits for **S1404**" at the bottom of the page. When placing this initial order, sites must provide laboratory contact information. For SWOG institutions the fields will be pre-populated based on the current data in the SWOG roster. Please note, the initial order will contain three (3) PK/ADA kits and four (4) PD-L1 kits and may take up to 15 days to be filled by PPD. Once PPD receives site information, a site username will be assigned and faxed to the site on the fax verification form. This username will be used for sites to access the PPD portal to reorder supplies: http://preclaruslabdata.ppdi.com.

   If your site does not receive the fax verification form within 3 days or registration, please call SWOG Data Operations at 206/652-2267.

2. For subsequent orders only, sites may reorder supplies at http://preclaruslabdata.ppdi.com. After placing the order, a confirmation email will be sent automatically to the site email address.

e. Frequency

PK and ADA samples will be collected before first infusion Cycle 1 (Week 1), before second infusion Cycle 1 (Week 4), before second infusion Cycle 2 (Week 10), before third infusion Cycle 3 (Week 19), before first infusion Cycle 4 (Week 25), before infusion Cycle 6 (Week 49) and 30 days after discontinuation of study drug (as long as patient has not started new anti-cancer therapy). Samples should be drawn within 24 hours before infusion of MK-3475 (pembrolizumab).

f. Sample collection and preparation procedures

1. SST and corning tubes will be pre-labeled with study/protocol number. Note that the study number on the pre-printed labels appear as MK3475-053 instead of **S1404**. That is how the lab is identifying the study. Site should write the 6-digit SWOG Patient ID and collection date/time on the label and the PPD Requisition Form. Please ensure to mark the corresponding visit name on the PPD Requisition Form.

   Each pre-labeled tube is linked to a pre-labeled Requisition Form in each kit.

2. At each time point, collect 3 mL whole blood PK sample in one properly labeled 3.5 mL SST tube and collect 6 mL whole blood ADA sample into one properly labeled 8.5 mL SST tube.

   Record the time and cycle number (or week since off protocol therapy) each sample is collected as you will need to enter these data into the SWOG Specimen Tracking System. Record the date and time of administration of MK-3475 (pembrolizumab) as you will need to enter these data on the **S1404** Treatment Form (see Section 14.4d) and on audit the times will need to confirm that the PK/ADA samples were drawn before infusion of MK-3475 (pembrolizumab). NOTE: If a sample needs to be drawn post-dose in error, the sample collection must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the sample collection should be from a different site.

3. Invert each tube 5 times and let stand for 30 minutes (but no longer than 60 minutes). The blood samples should remain at room temperature prior to centrifugation.

4. Centrifuge each sample 1100-1300 g for 15 minutes (speed/time may vary according to make and model of centrifuge).

5. Immediately transfer the PK serum evenly to two labeled 2mL Corning cryovials (PK Aliquot 1 and 2). Transfer the ADA serum evenly to three labeled 2 mL Corning cryovials (ADA Aliquot 1, 2, and 3) (each containing approximately 1 mL of serum). Serum samples must be frozen within 30 min of separation after the centrifuge at -20ºC for storage up to 1 month) and maintained in the frozen state until assayed.

g. Shipping instructions

1. Batch ship monthly to PPD Central Lab
   - Place PK Aliquot 1 and ADA Aliquot 1 in one box.
   - Place PK Aliquot 2 and ADA Aliquot 2, 3 in a separate box.

   NOTE: Samples from multiple patients may be sent in the same box.

2. Complete the PPD Requisition Form (2-part form) that is included in each kit. Include the original form (white form) in the sample shipment box and keep the copy (yellow form) on site for your records. The visit and patient information on the Requisition form is critical to accession of samples. Incomplete or missing requisition forms will delay testing and put the site lab report on hold. Refer to PPD Laboratory Manual for additional shipping instructions and PPD requisition forms. Instructions for filling out the PPD Requisition Form are also provided in Appendix 18.7.

3. All shipments should be made in freezer boxes containing at least 20 kg DRY ICE, and labeled as HUMAN SAMPLES: NONINFECTIOUS. Samples should not be shipped on a holiday. It is recommended to send batched dry ice shipments monthly on Monday through Wednesday to ensure arrival before the weekend. PK and ADA samples should be shipped frozen on dry ice (-20°C):

   Lab #219: PPD Central Lab for PK and Anti-pembrolizumab Antibodies

15.5 Quality of life assessments: Instructions for administration

a. Administration of questionnaires

1. All questionnaires should be completed prior to the visit with the physician. The time the questionnaire is completed and the time of the physician visit should be documented.

2. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each patient questionnaire. 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.

3. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note on the **S1404** Cover Sheet for Patient-Completed Questionnaires what assistance was required and indicate reason (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.

4. It is very important to review the questionnaires after the patient has completed them 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 she is feeling. If the patient has skipped a question, tell the patient that a question was not answered and ask if 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.

5. If a patient refuses or cannot complete the questionnaire for some reason, this must be documented on the **S1404** Cover Sheet for Patient Completed Questionnaires and submitted (see Section 14.4h).

6. Questionnaires must be completed by the patient at disease recurrence. On-treatment questionnaires may be submitted in place of recurrence questionnaires if:
   - The patient has already completed the on-treatment questionnaires, AND
   - The patient was aware of recurrence prior to completing the on-treatment questionnaires, AND
   - The patient did not receive any treatment after completing the on-treatment questionnaires.

   Otherwise, separate recurrence questionnaires must be completed by the patient and submitted by the study site.

b. Additional quality control procedures:

When a patient is registered on **S1404**, 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. 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.

If a patient refuses or cannot complete the patient questionnaires at one time **point, he or she should be asked to do so at the next scheduled assessment** time. Submit the **S1404** Cover Sheet for Patient-Completed Questionnaires documenting the reason why the questionnaires were not done.

Anyone involved in the collection of quality of life data in SWOG trials should review the training program available on the SWOG website accessible from three

locations. On the SWOG Home Page (prior to member login), in the QUICKLINKS section on the bottom right corner of the page, there is a link to the Patient Reported Outcomes Training. The other two locations that the training is available are after SWOG member login on the CRA Workbench. The Training section and the New CRAs! section both contain access to the Patient Reported Outcomes (PROs) training module. The training program is a narrated set of slides designed to standardize the way quality of life data is collected from patients. Questions regarding the quality of life assessments can be addressed to the SWOG Data Operations Office (206/652-2267).

c. **S1404** Cover Sheet for Patient-Completed Questionnaires

For each time point that the FACT-BRM, EQ-5D-3L, and FACIT-D are administered, the nurse or CRA completes the **S1404** Cover Sheet for Patient-Completed Questionnaires. The Cover Sheet is submitted with the set of patient-completed forms at each scheduled assessment. The Cover Sheet is very important for tracking how and when the patient forms were completed. When a patient-completed form is not administered at a scheduled time point, it is important to know why the assessment did not occur; the form includes potential reasons for a patient not completing a form. See Section 14.4g for data submission guidelines.

d. QOL Questionnaire Administration Schedule

The FACT-BRM, EQ-5D-3L, and FACIT-D are scheduled to be administered at the following time points:

- Prior to Cycle 1
- Week 4 of the first cycle of treatment
- Prior to Cycles 3, 4, 5 and 6
- Week 24 after the date of last treatment
- Week 48 after the date of last treatment
- Relapse

Patients who relapse before 48 weeks after date of last treatment will complete a questionnaire at relapse. Patients do not need to complete any further questionnaires after relapse. Patients who go off protocol therapy before Week 49 (Cycle 6) without recurrence will complete the two post-treatment questionnaires (at 24 and 48 weeks from the date of last treatment).

15.6 Submission of Images for Banking (Required)

All participants will undergo PET-CT, CT or MRI imaging at baseline/pre-treatment and every 12 weeks until 2 years from randomization, then every 6 months until 5 years from randomization. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for quality control and image banking. Any imaging that is used for relapse detection must be submitted; this would include ultrasound imaging if that is used by your institution for nodal basin surveillance. In addition, if imaging done for other reasons detects a relapse (i.e., chest-x-ray done for pulmonary symptoms that subsequently detects a metastasis) it must also be submitted.

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

•Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

•Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and

•TRIAD Site User role on an NCTN, ETCTN, or other relevant roster. All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:
To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

15.7 Mandatory Site Training

Prior to registering patients, at least one person involved with the study at each institution is required to view the **S1404** training module. To obtain credit for completing the training, after viewing the presentation sites must complete the short form at the bottom of the training page. The form is automatically forwarded to CTSU Regulatory Support System for processing and may take up to 3 days to be included in the system.

The training is available at:
https://www.swog.org/member-resources/training-forms/required-s1404-training

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Merck (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator"
(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

a. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

    1. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    2. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    3. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other

Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

4. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

b. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

c. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

d. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

e. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This study will have abbreviated CDUS monitoring.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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 more timely 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 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.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301/897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

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 agents as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is MK-3475 (pembrolizumab). 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 CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] MK-3475 (Pembrolizumab).

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

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 30 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 CTEP IND**:

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced 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. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used this study are interferon alfa 2b and ipilimumab. 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 Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on interferon alfa-2b or ipilimumab who have received the commercial drug(s) listed in Section 16.1g within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. *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.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an 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/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - 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.

i. ***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.

2. *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.*

3. **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.

4. **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.

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18.0 APPENDIX

18.1 Surgical Management Guidelines

18.2 Guidelines for Self Administration of Interferon Alfa-2b Template

18.3 **S1404** Patient Interferon Diary (for patients who self-administer Interferon)

18.4 **S1404** Local Pathology Review Form

18.5 TNM Definitions for Pathologic Staging

18.6 QA Auditing and Monitoring

18.7 Instructions for PPD Requisition Form

18.8 Translational Medicine: Retrospective T-Cell Receptor Beta Chain (TCRβ) Sequencing of Banked Samples from **S1404**

18.9 Instructions for the SWOG Biospecimen Bank - Lab #201, Solid Tissue, Myeloma and Lymphoma Division

18.10 Translational Medicine: Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients

18.1 Surgical Management Guidelines

All patients must be free of disease at the time of registration. All surgery is to be completed prior to registration and meet the criteria outlined in Section 5.0, Eligibility Criteria. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

a. Excision of the Primary Site

These guidelines apply to patients presenting with an intact primary and undergoing sentinel lymph node biopsy or regional lymph node dissection to establish eligibility. All such patients must undergo adequate wide excision of the primary tumor meeting the suggested criteria outlined below. In most cases, this must be a wide excision with 1 cm minimum margins. In all cases, the margins of excision must be histologically free of melanoma (including melanoma in-situ or atypical junctional melanocytic hyperplasia). For all sites except head & neck and extremities distal to the wrist or ankle, the primary melanoma must be excised with at least 1 cm margins of normal skin in all directions, measured either from the edge of the primary tumor or from the edge of the biopsy scar if prior excisional biopsy has been done. The excision should go down to the fascia; including the fascia in the resection is optional. Measurements of margins should ideally be done by the surgeon at the time of wide excision using a ruler; if the measurement is done by the pathologist, allowance of 33% for shrinkage will be made. In addition to the gross margin, a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained.

For primary melanomas on the head & neck or extremities distal to the wrist or ankle, the primary melanoma must be excised and a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained. Measured margins of at least 1 cm are desirable, but not mandatory. Acral-lentiginous melanomas (including subungual primaries) may be resected by any procedure that yields a histologically negative margin, including amputation and digit-conserving surgery.

b. Excision of Recurrent Disease

All patients enrolled with regional disease, including recurrence after initial presentation, must have no evidence of active disease at the primary site or have undergone a re-excision of the primary site that meets the criteria outlined in Section 18.1a above (including histologically negative margins of excision) prior to registration. Patients presenting with satellite metastases (within 2 cm of the primary) or in transit metastases (beyond 2 cm from the primary but proximal to the regional lymph nodes) are eligible provided that all tumor has been excised with negative margins, they have undergone complete lymph node dissection meeting the criteria outlined below (if any histologic or clinical evidence of lymph node involvement), and they have NOT undergone prohibited systemic therapy for their satellite/in transit metastases (see Section 5.1b).

c. Regional Lymph Nodes

Regional lymph node dissection is mandatory for all patients with histologic or clinical evidence of regional lymph node involvement enrolled on this trial. (Patients with satellite/in transit disease and no evidence of nodal involvement may be enrolled without having undergone lymph node dissection.) The node dissection must be done in accord with the following guidelines; lymph node sampling is not acceptable. Sentinel lymph node biopsy alone, without completion lymph node dissection, is not acceptable.

The number of tumor-involved nodes must be documented for all cases. Either H&E or immunohistochemical evidence of involvement is acceptable for determining the number of involved nodes, but RT-PCR or other molecular techniques are not. Patients with confluent nodal involvement that makes determination of the exact number of involved nodes difficult are eligible, and are considered to have "matted nodes" and classified as N3.

Micrometastasis versus macrometastasis - As outlined in Section 4.0 Staging Criteria, the status of regional lymph node involvement will be determined by histopathologic assessment and by the clinical presentation of those nodes. By definition, micrometastases are diagnosed by sentinel node biopsy or elective lymph node dissection. Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically. Note: Patients with extranodal extension are eligible for the trial, and for the purposes of this protocol are considered to have macrometastatic involvement (i.e., eligible even if only one tumor-involved node).

1. Cervical Lymph Node Dissection

   A classic radical neck dissection is not required and is discouraged. In cases with clinically negative nodes, less than a full neck dissection is permissible, including modified dissections such as supraomohyoid or posterior triangle dissections. In such cases, the entire triangle should be dissected. Preservation of the internal jugular vein, sternocleidomastoid muscle, and eleventh cranial nerve ("functional neck dissection") should be performed whenever possible. Radionuclide lymphatic drainage scans may be helpful in delineating lymph node groups at risk for tumor involvement. Consideration should be given to the parotid gland nodes, particularly for melanomas of the face, anterior ear and temporal region, which should be removed by superficial or if necessary total parotidectomy if there is evidence of involvement by tumor. The facial nerve (seventh cranial nerve) should be spared unless invaded by tumor.

2. Axillary Lymph Node Dissection

   Removal of at least the level I and II axillary lymph nodes is the minimum acceptable operation. Level III nodes must be removed if clinically suspicious. The minimum borders of the dissection are the latissimus dorsi muscle laterally, the axillary vein superiorly, and the medial border of the pectoralis minor muscle medially. The nerves to the serratus anterior (long thoracic nerve) and latissimus dorsi (thoracodorsal nerve) should be identified and preserved if possible. If the primary tumor is on the trunk, consideration should be given to remove the low axillary nodes (at or below the level of the nipple) by following the latissimus dorsi muscle down to its origin on the chest wall and dissecting the node-bearing tissue between it and the serratus anterior muscle.

3. Inguinal or Ilioinguinal Lymph Node Dissection

   The minimum operation for groin node dissections is a superficial inguinal lymph node dissection (inguinal or inguinofemoral lymphadenectomy). A pelvic (iliac and obturator) node dissection is also necessary (ilioinguinal lymphadenectomy) if these nodes are felt to be involved by imaging studies or intraoperative palpation. The borders of a superficial inguinal lymph node dissection are the adductor muscles medially, the sartorius laterally, the junction of these two muscles caudally, the femoral vessels posteriorly, and a line connecting the pubic tubercle and the anterior

superior iliac spine superiorly. The node-bearing tissue superficial to the external oblique fascia and superior to the inguinal ligament should be included with the specimen, up to the level of this line. Removal of the pelvic nodes, if required, may be accomplished through the same or a separate incision; "sampling" of the deep nodes rather than a radical dissection is adequate. Minimally invasive surgical approaches, such as robotic-assisted pelvic lymphadenectomy, are acceptable provided the operation otherwise conforms to the standards described.

d. Other Sites of Nodal Involvement

Lymph node dissections at sites other than those mentioned (e.g., popliteal or epitrochlear) should be carried out only if involvement of the nodes with melanoma is documented or if the primary site lies directly over the node group and node dissection is necessary to allow adequate wide excision. Patients with nodal involvement in these sites, as well as those with recurrent disease in the regional nodal basin after a previous complete lymphadenectomy, are eligible for this trial provided that all evidence of disease has been resected with histologically negative margins. Failure to document the margin status may lead to the patient being declared ineligible.

e. Resection of Distant Metastatic Disease

Patients with Stage IV melanoma metastatic to skin, subcutaneous sites, distant lymph nodes or lung or other visceral sites are allowed provided all sites are resected with histologically negative margins, they have NOT undergone prohibited systemic therapy for their metastatic disease (see Section 7.2) and the patient otherwise meets the eligibility criteria outlined in Section 5.0. Patients with resected brain metastases are not eligible. Minimally invasive surgical approaches, such as video-assisted thoracotomy, are acceptable. Failure to document the margin status may lead to the patient being declared ineligible. Stereotactic radiosurgery or ablative techniques that do not involve resection of the tumor to negative margins are not acceptable.

18.2 Guidelines for Self-Administration of Interferon Alfa-2b Template

For emergency contact:

Insert Site Contact Information.

Instructions for Self-Administering Medication

1. Preparation

   a. Wash hands well. Take acetaminophen (Tylenol®) as premedication if directed by your doctor.

2. Assemble necessary supplies. The Interferon should be kept refrigerated until several minutes before each treatment. You also need a syringe with a needle, at least 3 alcohol prep pads, and a container* for used materials.

   _____

   *An unbreakable, leak-proof, reclosable container - milk carton, coffee can.

3. Reconstituting the Interferon Powder

   a. If this is the first dose that will be coming from a vial, the Interferon powder must be dissolved, using the diluent provided. Snap the plastic cap off both vials, and cleanse both rubber stoppers with an alcohol pad and allow to air dry.

   b. There may be a different syringe/needle provided that you will use to reconstitute the Interferon. Open the package containing one of these syringes and attach (or tighten) the appropriate needle to it. Pull back the plunger of the syringe so that the top of it rests right on the line representing the volume of diluent that you are to add to the Interferon powder.

   c. Insert the needle through the stopper of the diluent vial, and invert the vial/syringe in front of you at eye level, holding the syringe in your dominant hand and the vial in the other.

   d. Inject the air from the syringe into the vial slowly. If you feel like you are forcing it, pull back the plunger to allow some solution into the syringe, then push the remaining air into the vial. Ultimately, your syringe should be filled with diluent solution up to the correct line and no air will be left in the syringe. If you have bubbles, tap the syringe with your finger until they rise to the top, push them up into the vial and recheck the plunger to insure that it is still at the correct volume mark.

   e. Withdraw the needle from the diluent vial and insert it into the vial containing the Interferon powder. This time keep the vial on the surface and push the plunger down to inject the diluent into the powder vial. If you meet resistance, allow some air to rise into the syringe before pushing down and expelling the remaining solution into the vial.

      Eventually, all the solution will be in the vial. Pull back the plunger to return it to the line that is the same as the volume of solution that you injected. This will prevent pressure build-up in the Interferon vial. Remove the needle and discard it appropriately.

f. To help dissolve the Interferon powder, you may need to roll the vial between your palms or swirl the solution around. DO NOT shake the vial. Be sure that all the powder is dissolved before proceeding to #3.

4. Withdrawing Your Dose From the Vial

a. Cleanse the rubber stopper of the vial containing the Interferon solution with an alcohol pad and allow to air dry.

b. Open syringe package and needle package (if separate) and attach or tighten needle by twisting until tight. Pull back the plunger to the mark that represents your dose (i.e., 3 MU/0.5 ml, top of plunger should rest at the 0.5 ml mark). This fills the syringe with air in a volume equal to the volume of your dose.

c. Uncap the needle and push it through the stopper, at least half-way into the vial. Now pick up the vial (with syringe/needle in it) with your left hand and turn it upside down, holding it at eye-level, about 12 inches from your face. You should now have the vial in one hand and your other hand free to manipulate the syringe. (Note: Left-handed persons should have the vial in their right hand, so that they can manipulate the syringe with their left hand.)

d. Inject air from the syringe into the vial slowly, and then withdraw the plunger. The syringe will gradually fill with drug solution. Repeat this procedure until only solution is in the syringe, solidly, to the mark that indicates your dose. Withdraw needle and recap it.

5. Administration

a. Thoroughly clean the area to be injected with an alcohol pad. Areas appropriate for this type of injection have been shown to you. A new site should be used for each injection whenever possible.

b. As demonstrated, pinch 1 1/2 to 2 inches of loose skin from the site to be injected.

c. Uncap the needle, and insert the needle approximately 1/4 inch into the skin and push the syringe plunger in all the way, thereby giving the dose of Interferon.

d. Remove needle and wipe injection site with a new alcohol pad, but do not massage the area to any great extent.

e. Carefully recap needle and return needle and syringe to the clinic pharmacy for disposal.

If the interferon vial is a multidose vial (eg., solution for injection vial) and contains more than one dose, write the date on the label. It is usable for 30 days. Unused doses in a multidose vial must be discarded after one month.

Reconstituted vials (eg., powder for injection vials) must be discarded after one dose has been withdrawn from the vial. Do not re-use reconstituted vials, as bacterial contamination may occur.

f. If a drug administration diary has been provided, remember to complete it after each dose. Enter the date and time of day given, along with any

notable side effects that you may have experienced since the previous dose was given.

18.3 **S1404** Patient Interferon Diary (for patients who self-administer Interferon)

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of injections you self-administer. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from interferon alfa-2b, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____
Your next appointment is: _____

Special instructions: The dose of interferon alfa-2b for maintenance is 10 MU/$m^{2/}$d.

Month: _____ **Year:** _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____

18.4 **S1404** Local Pathology Review Form

SWOG
S1404 LOCAL PATHOLOGY REVIEW FORM

Patient Identifier | | | | | | | **Study Identifier** | S | 1 | 4 | 0 | 4 | **Registration Step** | 1 |

Patient Initials _____ (L, F M)

Instructions: This form must be completed and signed by a local pathologist prior to registration for confirmation of eligibility per S1404 protocol Section 5.1e. Upload the completed form via Medidata Rave™ in the Source Documentation-Baseline form, include a copy with the tissue submission, and retain the original in the patient's research record. Please see protocol Section 15 for complete information regarding tissue submission.

Pathologic Diagnosis: _____

Preliminary Data Specimen Submission (select all that apply):

☐ Primary ☐ Lymph Nodes ☐ Satellite/In-Transit Metastases ☐ Distant Metastases

Specimen Type Submitted:

☐ Unstained Slides – Local Surgical Pathology Number(s) _____

Specimen Review

Tumor Cells Available (PLEASE CHECK ONLY ONE):

☐ Adequate: ≥ 100 viable tumor cells (ELIGIBLE) ☐ Inadequate: < 100 viable tumor cells (INELIGIBLE)

_____ _____
Signature of Interpreting Pathologist **Date**

_____
Printed Name of Interpreting Pathologist

Comments:

18.5 TNM Definitions for Pathologic Staging

Table 1 TNM Definitions for Stage III Melanoma: Pathologic Staging[b]

Stage	TNM	Description
IIIA	T1–4a	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
	N1a	1 regional lymph node metastasis with micrometastasis[c]
	N2a	2–3 regional lymph node metastases with micrometastasis[c]
	M0	No detectable evidence of distant metastases
IIIB	T1–4b	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N1a	1 regional lymph node metastasis with micrometastasis[c]
	N2a	2–3 regional lymph node metastases with micrometastasis[c]
	M0	No detectable evidence of distant metastases
IIIB	T1–4a	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration

Stage	TNM	Description
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
	N1b	N1b = 1 regional lymph node metastasis with macrometastasis[d]
	N2b	N2b = 2–3 regional lymph node metastases with macrometastasis[d]
	N2c	N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
	M0	No detectable evidence of distant metastases
IIIC	T1–4b	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N1b	N1b = 1 regional lymph node metastasis with macrometastasis[d]
	N2b	N2b = 2–3 regional lymph node metastases with macrometastasis[d]
	N2c	N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
	M0	No detectable evidence of distant metastases
IIIC	Any T	TX = Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
		T0 = No evidence of primary tumor
		Tis = Melanoma *in situ*
		T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration.
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration

Stage	TNM	Description
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N3	≥4 regional lymph node metastases; or matted nodes; or in transit met(s)/satellite(s) with metastatic lymph node(s)
	M0	No detectable evidence of distant metastases
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
Adapted with permission from AJCC: Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 325-44.		
The explanations for superscripts b–d are at the end of Table 2.		

Table 2 TNM Definitions for Stage IV Melanoma

Stage		TNM	Description
Clinical[a]	**Pathological[b]**		
IV	IV	Any T	TX = Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
			T0 = No evidence of primary tumor
			Tis = Melanoma *in situ*
			T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
			T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
			T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
			T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
			T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
			T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
			T4a = Melanomas >4.0 mm in thickness without ulceration
			T4b = Melanomas >4.0 mm in thickness with ulceration
		Any N	NX = Regional lymph nodes cannot be assessed (e.g., previously removed for another reason)
			N1a = 1 regional lymph node metastasis with micrometastasis[c]
			N1b = 1 regional lymph node metastasis with macrometastasis[d]
			N2a = 2–3 regional lymph node metastases with micrometastasis[c]
			N2b = 2–3 regional lymph node metastases with macrometastasis[d]
			N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
			N3 = ≥4 regional lymph node metastases; or matted nodes; or in transit met(s)/satellite(s) with metastatic lymph node(s)
		M1	M1a = Metastases to skin, subcutaneous, or distant lymph nodes and normal serum LDH
			M1b = Metastases to lung and normal serum LDH
			M1c = Metastases to all other visceral sites and normal serum LDH; or distant metastases to any site and elevated serum LDH

Stage		TNM	Description
Stage		**TNM**	**Description**
Clinical[a]	**Pathological[b]**		
LDH = Lactate dehydrogenase; T = primary tumor; N = regional lymph nodes; M = distant metastasis.			
Adapted with permission from AJCC: Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 325-44.			
[a]Clinical staging includes microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.			
[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.			
[c]Micrometastases are diagnosed after sentinel lymph node biopsy and complete lymphadenectomy (if performed).			
[d]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.			

18.6 QA Auditing and Monitoring

The Quality Assurance Program of the Groups participating in the NCTN was developed to enhance the reliability and validity of clinical trials data through the use of routine monitoring procedures which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Data Operations Center and to verify compliance with protocol and regulatory requirements. The program also surveys data management practices at each institution in order to provide educational support to the sites regarding issues related to data quality, data management, and other aspects of quality assurance.

Audits are conducted according to FDA regulations and NCI guidelines for Auditing Clinical Trials for the National Clinical Trials Network (NCTN) Program, NCI Community Oncology Research Program (NCORP) and Research Bases:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmbauditguidelines.pdf.

Each institution is audited at least once every three years, but remains at annual risk of an audit. Routine monitoring of Institutional Performance Review reports and timeliness of reporting of Serious Adverse Events (SAEs) is conducted to identify institutions that may require more frequent audits.

The audit team consists of qualified individuals capable of providing a medical assessment of the patient cases (Quality Assurance, physician, nurse or experienced clinical research associate [CRA]). A number of patients equal to 10% of the accrual since the last audit with a minimum of three are randomly selected for review at each institution. In addition, a limited review of eligibility and consent only is conducted for at least one unannounced case at each on site audit.

The major objective of the audit process is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data against the source documents. Primary source documentation reviewed during an audit includes the following: research records, hospital charts, clinic charts, lab reports, x-rays, scans, radiotherapy reports, operative reports, pathology reports and other special studies required by protocol.

By comparing the data collection forms submitted to the Data Operations Center with the primary records and referring to the protocol, the audit team reviews the records to determine compliance with protocol requirements for eligibility, treatment administration, response assessment, toxicity reporting and general data quality. Auditors verify that the current IRB-approved version of the consent form was signed prior to registration and that subjects were informed of new findings that could affect their willingness to participate in the study. NCTN investigators and institutions are expected to follow the protocol and lead Group policies in treating patients registered on Group protocols. Among other requirements, investigators/institutions must follow SWOG's policies for dosing principles, reporting of SAEs, and follow-up of all patients.

The audit team also verifies that the protocol and its amendments received initial and continuing IRB review and approval and that safety reports and serious adverse events were submitted to the IRB. Investigational drug accountability record forms (DARFs) are reviewed and random patients are cross referenced against the medical record. A tour of the pharmacy is conducted to verify security and storage conditions as well as the physical inventory.

The audit report is comprised of three components: 1) conformance to IRB and informed consent requirements, 2) the pharmacy and use of NCI DARFs, and 3) patient case review. An acceptable rating requires no deficiencies, few lesser deficiencies, or major deficiencies that were addressed prior to the audit. Institutions found to be “unacceptable” or “acceptable, needs follow-up” on any component are required to submit a written

response and/or corrective and preventative (CAPA) action plan. Failure to submit a written response including a corrective and preventative action plan within the required timeframe will result in suspension of registration privileges. A re-audit of any component rated as unacceptable will be conducted within one year after the unacceptable audit. An unacceptable rating for the same audit component on two consecutive audits will result in probation. Accrual will be suspended pending submission of a site improvement plan that addresses key infrastructural issues contributing to poor performance. An unacceptable rating at the second re-audit may result in termination from the group. If systematic misrepresentation of data is identified, an immediate repeat audit is scheduled by the representatives from the Group with the NCI and/or the FDA present.

In some cases, non-compliance for issues such as timeliness of data submission, SAE reporting and submission of specimens is monitored off site rather than scheduling a re-audit. Failure to show improvement may result in scheduling of a re-audit or other disciplinary action.

Results of all Quality Assurance Audits are reported to the NCI, the Principal Investigator of the institution that was audited, and representatives of the Group. Protocol specific audit results are also sent to the Statistical Center to inform the statisticians, data chairs and study chairs of any significant discrepancies involving eligibility, treatment, toxicity or response assessment.

The Quality Assurance Program performs their educational role through several mechanisms including presentations during the Group Meetings, online Clinical Trials Training Courses, collaboration with others such as the Pharmacy Committee and Statistical Center to develop training tools, and memos and newsletter articles that are distributed to all Group institutions to educate research staff about changes in regulatory and quality assurance issues and audit procedures.

Additional Monitoring

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- Routine monitoring by Data Coordinators at the Statistics and Data Management Center**.**
- Risk-based monitoring by Monitors at the Statistics and Data Management Center**.**
- Additional on-site monitoring visits by Quality Assurance Auditors at the Operations Office.

Routine Monitoring at the SWOG Statistics and Data Management Center

Data Coordinators at the SWOG Statistics and Data Management Center (SDMC) will perform routine monitoring with the following actions:

- Monitor data quality through routine review of submitted data such as on-study, baseline and follow up tumor assessment, lab, treatment, off treatment, and follow up case report forms to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site.

- Analyze site characteristics, performance metrics and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance through the SWOG Institutional Performance Reporting mechanism and other available reports.

- Verify critical source data remotely via the collection and review of pathology, radiology and applicable lab reports. This includes the review and confirmation of appropriate disease classification as determined by the pathology report, and assessment of response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the

Electronic Data Capture (EDC) system and submitted follow-up tumor assessment forms.

- To assure data are as consistent, complete and accurate as possible, all subject data must undergo careful review by Data Coordinators (DCs). After verifying that all data forms required to determine eligibility have been received or at a time point designated when all the required forms should have been received, the DC reviews the data and completes an initial evaluation.

The initial review includes the following:
- Determine that all required data fields on each form were completed and are consistent with other data.
- Determine if all prestudy tests and exams were performed within protocol specified time limits.
- Determine if each eligibility criterion was met and properly documented.
- Review and confirm pathology based on the pathology report uploaded to the EDC system.
- Verify that stratification and/or descriptive factors (if applicable) were correctly identified at registration.
- Verify that the subject received the assigned study treatment and correct dose(s).
- Verify that the treatment was started within the time limit indicated in the protocol (if applicable).
- Determine if adverse events reported are consistent with other data and entered as required by study specifications.
- Post internal notes to add additional information which may be useful to the study sponsor, monitors, or statisticians, but which do not require action by site personnel.
- Use the query tool to request additional data classifications and corrections of the CRA.

The DC will perform subsequent review of data when new data become available or queries are answered. Regular review will also occur while patients are still on-study, at the time of progression, once they are removed from study and at the time of death.
Subsequent reviews include the following:
- Determine if all required data fields on each newly submitted form were completed and consistent with other data.
- Evaluate all new treatment documentation for correct treatment and dose.
- Conduct assessment of response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the EDC and submitted follow-up tumor assessment forms.
- Review and code any new concomitant medications as required by study specifications.
- Evaluate if the subject is or should be off protocol treatment per protocol criteria.
- Review and evaluate death if death of subject is reported.
- Use the query tool to request additional data classifications and corrections.
- Post internal query notes to add additional information that may be useful to the study sponsor, monitor, or statisticians but which do not require action by site personnel.
- Review site responses to the queries and the corrected or amended eCRF pages. When corrections and responses are considered satisfactory, queries are closed by the data coordinators. Unsatisfactory responses are re-queried and tracked.
- Perform re-evaluations promptly after responses to queries are received

<u>Centralized Risk-based Monitoring at the Statistics and Data Management Center (SDMC)</u>
Monitors at the Statistics and Data Management Center (SDMC) will support the risk based monitoring approach for this trial through off-site monitoring to include auditable elements through administration of eight weeks of treatment for the first two patients randomized at each site. Within 10 weeks of randomization, the Head CRA (or Data Manager) at the study site will be contacted by a SDMC monitor via email with instructions for uploading the auditable elements including:

- Copy of the signature page of the patient informed consent signed prior to registration.

- Documentation to support all eligibility criteria including:
  - Copy of the signed and dated eligibility checklist (unless previously uploaded into RAVE)
  - Operative and pathology reports to support histology and stage of disease
  - An H & P including vital signs, height and weight, review of symptoms, performance status and past medical history. The medical history should include details of the malignancy, prior surgical procedures, prior chemotherapy and/or radiotherapy, history of relevant medical disorders and concomitant medications
  - Lab reports to support all required prestudy tests. Lab reports must include institutional normal limits.
  - Reports of baseline scans, brain CT/MRI, and EKG
  - Documentation of baseline toxicities

- Documentation for the first eight weeks of treatment including:
  - An H & P including weight, BP, performance status, concomitant medications and toxicity notation
  - Lab reports prior to each cycle
  - Drug orders and documentation of drug administration through chemo flowsheets, progress notes, etc.
  - Documentation to support dose modifications or treatment delays

Onsite Monitoring by the Quality Assurance Program

- Additional on-site monitoring visits will be conducted with the first site visit within 6 months of first patient randomization.
- Monitoring visits will be combined with other routine audits whenever possible. The initial monitoring visit may be postponed up to 3 months to coincide with a routine audit or to coincide with a routine audit of another institution in the same geographic area. Monitoring visits may also be postponed if no accrual or activity has occurred beyond the timeframe covered by the off-site central monitoring.
- Subsequent monitoring visits will be conducted according the following criteria:
  - If > 10 patients per year (~ 10% of sites) – annually
  - 5 – 10 patients per year (~ 20% of sites) – every 2 years
  - < 5 patients per year – every 3 years or as part of routine audit cycle
- More frequent monitoring visits to a site may be scheduled in response to several factors – high rate of accrual, unacceptable monitoring visit results, centralized electronic monitoring outcome, turnover in staff, etc.
- All sites that receive and dispense investigational agents must be monitored on site to allow at least one visit to the pharmacy with the following exceptions:
  - Sites that use a centralized pharmacy may be monitored at this central location.
  - After an initial onsite visit, NCORP sites and LAPS/Main Member Affiliates may be monitored at a central location.
  - Pharmacies monitored during SWOG site visits for other studies will suffice for the on site monitoring requirement.
  - The need for subsequent onsite visits will be determined on a case by case basis including past audit results, number of patients on the investigational agent, etc.

Communication of Monitoring Results

The monitoring team will meet routinely to share all aspects of monitoring (on site, centralized, safety, for-cause). When needed, the SWOG Executive Officer for Quality Assurance will be consulted.

All monitoring visits results will be reported according to NCI-CTMB requirements via the CTMB-AIS data base and regularly reviewed by SWOG monitoring staff.

Summarized results of all monitoring visits will be provided semi-annually to the SWOG Board of Governors and the study team. Any problems or issues of concern will be reported to the Data and Safety Monitoring Committee on an as-needed basis.

Safety Specific Centralized Monitoring
Each Serious Adverse Event (SAE) report submitted (via CTEP-AERS) will be reviewed by the SWOG SAE Coordinator at the Operations Office. Supporting documentation for any deaths on study will be requested and compiled with the report and sent to the Physician Reviewer. As mentioned below all sites will undergo mandatory training and this will include training regarding SAE reporting. SWOG regularly monitors timeliness of SAE reporting and addresses any issues of poor performance with individual sites.

The study will be monitored for under reporting/missed Serious Adverse Events: The SWOG SAE Coordinator receives a weekly report from the data base that includes all adverse events that are submitted through routine submission that potentially also meet expedited reporting criteria but for which no CTEP-AERS report is found. The Coordinator is responsible for following up with the responsible site to ensure that SAEs are not missed/under-reported.

The study will be monitored for trends in Serious Adverse Events: A “new SAE on study” report is generated each time a new Serious Adverse Event is entered into the SWOG data base. It is a cumulative report that lists all SAEs reported for the protocol. This allows those who review the report to identify concerning trends in reported events; events that may be occurring at greater intensity (higher toxicity grade) or frequency than expected. The SAE Coordinator, Physician Reviewer, Study Chair, and assigned Statisticians are responsible for regularly monitoring this report.

Additional Approaches to be Used
- Mandatory training of key site personnel prior to first patient registration.
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.
- Mentoring visits and additional communication between monitor and site staff to assess potential problem areas, provide feedback on data submission quality and timeliness, identify staff turnover, etc.
- Additional mandatory centralized training to be provided to all sites if major changes to the protocol occur or common problem areas are identified.

Management of Noncompliance

Issues of particular concern related to patient safety and questions of site fraud will be managed according to SWOG standard policies and the policies of the NCI CTMB for auditing of clinical trials under the NCI National Clinical Trials Network (NCTN) Program. Where important deviations are discovered, additional site training components will be developed and implemented.

As with standard NCTN procedures, sites will be required to develop and implement corrective action plans in response to any major deficiencies identified at a monitoring visit

Ensuring Quality Monitoring

All staff involved in monitoring are required to undergo training in the principles of clinical investigations and human subjects protection. They are also required to complete the same protocol specific training required of the site staff.
All monitoring and auditing processes for the study will be reviewed by study leadership twice per year to ensure conformance to the monitoring plan.

Monitoring Plan Amendments

At each formal review of the monitoring plan and conformance to it, the study leadership will make a recommendation regarding the need for amendments to the monitoring plan. These amendments will be reviewed and approved by the NCI and provided in this protocol section and will be submitted to the FDA.

18.7 Instructions for PPD Requisition Form

Instructions for filling out the PPD Requisition Form.
Every PPD/ADA specimen submission must include a copy of the PPD Requisition Form. This form is supplied along with the kit. In addition, PPD will send you a copy of their Laboratory Manual.

Subject Information Section	
Site Number:	Fill in the NCI code for your institution. In addition, PPD requires that you add leading zeros so that all 10 spaces are filled. Do not leave any blank spaces or it will delay processing of your specimen. For example, if your NCI code is CA006, then you would enter “00000CA006” in this field.
Patient ID:	Enter the 6-digit SWOG patient identification number assigned at registration.
Year of Birth:	Enter all 4 digits of the patient’s year of birth. For example, “1976”.
Gender:	Place a mark in the appropriate box.

Below is an example of how this would look:

Visit Information Section

PK and ADA sampling should be done based on the treatment cycles for pembrolizumab, not on calendar weeks. However, PPD has created visit labels assuming that there will be no treatment delays or variation in schedule. The following table is intended to help you pick the most appropriate visit label for your PK/ADA specimen submission:

Visit Label	Specimen to be submitted
Week 1	Sample collected prior to the first infusion on Cycle 1
Week 4	Sample collected prior to the second infusion during Cycle 1.
Week 10	Sample collected prior to the second infusion during Cycle 2
Week 19	Sample collected prior to the third infusion on Cycle 3
Week 25	Sample collected prior to the first infusion on Cycle 4
Week 49	Sample collected prior to the infusion on Cycle 6
Post Treatment FU 30 Days	Sample collected 30 days after discontinuation of pembrolizumab (provided patient has not started a new anti-cancer therapy prior to this time)
Unscheduled	PPD has provided 10 “unscheduled visit” labels. These should be used sparingly if at all. Using the guide provided above, you should be able to identify the correct visit label for your submission.

18.8 Translational Medicine: Retrospective T-Cell Receptor Beta Chain (TCRβ) Sequencing of Banked Samples from S1404

a. Objectives

1. Primary: To evaluate the association between TCRβ variable gene (TRBV) haplotype and Grade 3-4 immune-related adverse events (irAEs) among Stage III melanoma patients treated with adjuvant Ipilimumab or Pembrolizumab.

2. Secondary: To describe the TRBV haplotype distribution among this cohort of patients studied.

3. Secondary: To assess associations between baseline patient demographics and TRB haplotype.

b. Background

Checkpoint blockade immunotherapy (CPI) can elicit anti-cancer T cell responses mediating durable progression free survival but may also promote T cell destruction of healthy tissue to elicit irAEs. Efforts to identify germline variants associated with irAEs using whole genome sequencing (WGS) or microarrays have yet to reveal markers predictive of adverse events following immunotherapy. Identifying such biomarkers could allow for personalized drug selection and dosing to ultimately enable safer and more effective immunotherapy, particularly in light of the increasing use of combination CPI regimens having a significant incidence of severe adverse events. *([1])*

Despite previous efforts, three lines of reasoning support the notion that germline encoded TRBV polymorphism could be a key determinant of adverse events during CPI. First, the TCR locus is repetitive and structurally complex, impeding the measurement of variation by traditional short read WGS or microarray-based methods. *(2)* Second, single amino acid substitutions within the framework or complementarity-determining region (CDR) 1 and 2 regions of the rearranged TCRβ chain are known to significantly alter TCR affinity for human leukocyte antigen (HLA). *(3)* Third, adverse events during immunotherapy may manifest as acute versions of chronic autoimmune diseases (i.e. fulminant type 1 diabetes) that have been separately linked to TRBV polymorphism. *(4)* To circumvent the challenge in measuring TRBV polymorphism by WGS, Thermo Fisher has developed a cost-efficient and rapid method for detection of TRBV polymorphism by next-generation sequencing (NGS) of rearranged TCRβ chains from peripheral blood leukocytes. *([5])* Based on current knowledge, this represents the first NGS-based method to permit haplotype-level resolution of the TRB locus.

A pilot study involving haplotype analysis of the TRB locus by TCRβ sequencing was previously conducted at the University of Texas MD Anderson Cancer Center (MDACC) under the PI, Aung Naing, MD, using the peripheral blood of 81 Caucasians who had graded adverse events following immunotherapy. The results of this analysis revealed the presence of 6 major haplotype groups within the study cohort. Strikingly, members of one haplotype group, accounting for 33% of patients, appear to be protected against severe (Grade 3-5) adverse events (0% frequency) while 14% to 44% of patients in other haplotype groups had severe adverse events (p=7.1E-4, Fisher's 2x2 exact test). Should this finding be confirmed in the larger SWOG cohort, this would indicate that TRBV allele profiling may serve as a predictive biomarker for adverse events to enable personalized checkpoint blockade drug selection and dosing.

c. Experimental Research Technique

Baseline banked blood samples from Caucasian patients on **S1404**
Preferred source of sample: buffy coat

Total RNA extracted from PBL or whole blood will be used as input for TCRβ sequencing using the Thermo Fisher Scientific product Oncomine TCRB-LR (SKU A35386). This assay utilizes a long-amplicon approach (up to 400 bp) to capture the sequences of all 3 CDR regions of the TCR Beta chain. Sequencing assays for up to 240 patients (details of patient selection provided in the statistical section) will be performed at Thermo Fisher. Results from the haplotype analyses will be provided to the PI, Aung Naing, MD and the SWOG Statistical Center. This protocol will allow for extraction of both DNA and RNA from the cryopreserved cell pellets. Total RNA will then be used for TCRB-LR library preparation at Thermo Fisher.

d. Statistical Plan

Sample selection: the pilot haplotype work has been in Caucasian patients, so we will use baseline blood samples from Caucasian patients enrolled on S1404. We note that melanoma incidence is higher among Caucasian patients than other races, and 95% of patients enrolled on **S1404** were Caucasian. In addition, we will restrict analyses to the subset of patients who planned to receive Ipilimumab as their control arm regimen prior to randomization. First, we will analyze 120 patients who were randomized to the control arm and treated with Ipilimumab on **S1404**; we will select 60 patients with Grade 0-2 irAEs and 60 patients with Grade 3-4 irAEs (selection will be random among all patients with appropriate consent who have baseline samples meeting these criteria [>150 patients available for each irAE cohort]). We note that the Grade 3-4 irAE rate is 35% among patients treated with Ipilimumab on the control arm. We chose to over-sample Grade 3-4 irAE because the incidence of haplotype 2 among this subset is expected to be small, and we want adequate power to evaluate the incidence (further details of expected incidence below in the primary analysis section). If the pilot data results are validated among these Ipilimumab patients (details of primary analysis below), we will select 120 patients randomized and treated with pembrolizumab; we will select 60 patients with Grade 0-2 irAEs and 60 patients with Grade 3-4 irAEs (selection will be random among all patients with appropriate consent who have baseline samples meeting these criteria [>150 patients available for each irAE cohort]). We note that the Grade 3-4 irAE rate is 15% on the pembro arm.

Primary analysis: TRBV haplotype analysis will be performed as described in Looney et al. (at Thermo Fisher) and the results of the analysis will be provided to Dr. Naing and the SWOG statistical center. The association between haplotype Group 2 and the incidence of severe Grade 3-4) adverse events will be assessed using Fisher's exact test; haplotypes 1, 3, 4, 5, 6 will be grouped together for this analysis (i.e., we will compare haplotype 2 versus all other haplotypes). *(6)* In the pilot data, the haplotype 2 incidence was 33%. We assume the Grade 3-4 irAE to be 12% among haplotype 2 patients (was 0% in the pilot data) and to be 46% among other haplotype patients. Given these incidence assumptions, we expect that 11% (0.33*0.12/ (0.33*0.12+0.67*0.46)) of patients with a Grade 3-4 irAE in the Ipilimumab cohort of **S1404** will be haplotype 2, and that 89% will have another haplotype. Similarly, we expect that 43% (0.33*0.88/ (0.33*0.88+0.67*0.54)) of patients with a Grade 0-2 irAE in the Ipilimumab cohort of **S1404** will be haplotype 2, and that 92% will have another haplotype. With 60 patients with Grade 3-4 irAE and 60 patients with Grade 0-2 irAE, under these assumptions Fisher's exact test has 92% power with a two-sided alpha of 5%.

If a significant association between haplotype 2 and Grade 3-4 irAE is observed in the Ipilimumab cohort, we will process samples on the 120 Pembro patients and perform the same analysis (Fisher's exact test with two-sided alpha = 5%). If we assume the same incidence of haplotype 2 (33%), and that 2% of of the Grade 3-4 AE cohort will be haplotype 2, this test has 86% power.

Secondary analysis: Associations between haplotype and baseline patient characteristics (age, performance status, stage, primary tumor characteristics, LDH) will be evaluated using Fisher's exact test and Wilcoxon-rank sum tests.

Analyses and interpretation of data output will be completed within 1 year of the receipt of specimens.

e. Data Analysis

The data will be analyzed by the SWOG Statistics and Data Management Center (Megan Othus, Ph.D.). The Haplotype Analysis will be performed by Thermo Fisher (Tim Looney).

f. Specimen Information

Laboratory Performing Analysis:

The University of Texas MD Anderson Cancer Center
Aung Naing, MD (c/o Mohamed Derbala)
The University of Texas MD Anderson Cancer Center
Investigational Cancer Therapeutics
1515 Holcombe Blvd., Room Y3.5623, Box 387
Houston, Texas 77030
713-745-9805

Thermo Fisher Scientific:
Loni Pickle
Thermo Fisher Scientific
5781 Van Allen Way | Carlsbad, CA 92008 U.S.A.
Phone +1 (760) 268-8334
Loni.Pickle@thermofisher.com | thermofisher.com

Specimens used:
Preserved frozen pelleted peripheral blood leukocytes (PBL), peripheral blood mononuclear cells (PBM) are highly preferred, though whole peripheral blood is also acceptable.

2 ml of whole peripheral blood, from which peripheral blood leukocyte (PBL) total RNA will be extracted in the laboratory of Thermo Fisher. 50 ng of PBL RNA will be used for library preparation and sequencing via the Oncomine TCRB-LR assay.
Baseline (pretreatment) samples are highly preferred, though any timepoint is acceptable.

g. References

1 Larkin, J et al. Combined Nivolumab and Ipilimumab or monotherapy in untreated melanoma. NEJM 373:23-34, 2015.

2 Watson, C et al. Comment on ‘A database of human immune receptor alleles recovered from population sequencing data’. J Immunol 198:3371-3373, 2017.

3 Robbins, P et al. Single and dual amino acid substitutions in TCR CDRs can enhance antigen-specific T cell functions. J Immunol 180:6116-6131, 2008.

4 Pierce, B et al. The missing heritability in T1D and potential new targets for prevention. J Diabetes Res 737485, 2013.

5 Looney, T et al. Haplotype analysis of the TRB locus by TCRB repertoire sequencing. bioRxiv 406157, 2018.

6 Looney, T et al. Haplotype analysis of the TRB locus by TCRB repertoire sequencing. bioRxiv 406157, 2018.

18.9 Instructions for the SWOG Biospecimen Bank - Lab #201, Solid Tissue, Myeloma and Lymphoma Division

a. **General Banking Instructions**

The SWOG Biospecimen Bank will store formalin-fixed paraffin-embedded (FFPE) tissue blocks or slides at room temperature.

Aliquots of frozen, processed plasma, buffy coat, and serum are banked in -80°C freezers for long-term storage.

b. **Instructions Related to RNA Extraction and T-Cell Receptor Beta Chain (TCRβ) Sequencing (Appendix 18.8)**

The SWOG SDMC will provide a list of patients and time points to the Bank for distribution to Thermo Fisher. For each patient, the Bank will ship 1 vial of frozen buffy coat (from Baseline time point, if possible) on dry ice for RNA extraction and T-Cell Receptor Beta Chain (TCRβ) Sequencing.

c. **Instructions Related to circulating tumor DNA (ctDNA) (Appendix 18.10)**

The SWOG SDMC will provide a list of patients and time points to the Bank for distribution to the Natera laboratory. For each patient, an H&E slide from the primary tumor or lymph node metastasis will be scanned to a 40X digital image for digital pathology review by Dr. Allie Grossmann, who will provide specimen quality data (e.g., %tumor vs. necrosis, %tumor vs. normal, confirmation of concordance with institutional diagnosis, and comments when applicable) and will digitally annotate slides, as needed, for specimens that will require macrodissection to enrich tumor content. Following pathology QA review, the Bank will either scrape unstained slides (macrodissected as needed), or section FFPE blocks. All tissue will undergo co-extraction for DNA and RNA.

DNA will be extracted from buffy coat from one time point for each patient.

All nucleic acids will undergo quantitation and QC before storage in a -80°C freezer.

For each patient, the Bank will ship the following specimens to Natera on dry ice for overnight delivery:

- At least 500 ng DNA from primary tumor or lymph node metastasis and DNA from buffy coat
- A minimum of 4 ml of frozen plasma from Baseline
- A minimum of 4 ml of frozen plasma at start of cycle 3
- A minimum of 4 ml of frozen plasma at start of cycle 4
- A minimum of 4 ml of frozen plasma at removal from protocol therapy or relapse

18.10 Translational Medicine: Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients

a. Objectives

1. Primary (integrated): To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms
2. Secondary (integrated): To evaluate associations between pretreatment ctDNA and relapse within 2 years of randomization in a case-control

analysis within each treatment arm (after treatment arm data are unblinded to investigators).

3. Secondary (integrated): To evaluate associations between "early-on treatment" ctDNA levels and relapse within 2 years of randomization
4. Secondary (integrated): To describe ctDNA levels at end of therapy and time of relapse

b. Background

From a double-blind, randomized, placebo-controlled trial, Eggermont, AMM et al. reported improved relapse free survival with adjuvant pembrolizumab in high risk, resected, Stage III melanoma patients compared to placebo. Specifically, pembrolizumab therapy was associated with a one-year rate of recurrence-free survival of 75.4% [95% confidence interval CI, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1] in the placebo cohort. Thus, while anti-PD-1 therapy reduces the risk of disease progression of Stage III melanoma, 25% of patients are predicted to relapse within 1-year. For those untreated, up to 39% will relapse. At present, there are no biomarkers available to predict which of these patients are most likely to relapse. Improving outcomes for these patients in the future will require significant advancements in risk stratification tools.

The Signatera test, offered by Natera, is an emerging biomarker that has shown promising clinical utility for the detection of minimal residual disease and early detection of relapse. *(1, 2, 3, 4)* The assay quantifies cell free, circulating tumor DNA (ctDNA) present in plasma, down to a 0.1% mutant allele fraction. In patients with non-small cell lung cancer, colorectal cancer, muscle-invasive bladder cancer and breast cancer, studies with Signatera have shown an unprecedented positive predictive value (PPV) for relapse ranging from 93%-100%with an average lead time of 2.8-9.5 months compared to radiographic detection. *(5, 6,. 7*, 8)

The **S1404** Stage III melanoma cohort includes post-operative plasma samples collected prior to the initiation of immunotherapy. With these samples, we may be able to discern if baseline ctDNA levels can risk stratify patients. The overall goal is to determine if highly sensitive, tumor-guided ctDNA testing can distinguish **S1404** patients who remain disease free from those who have relapsed. We hypothesize that the Signatera test results will be associated with relapse outcomes in the trial (and within each treatment arm) and that nondetectable ctDNA levels will be associated with lack of relapse within 2 years. For patients who have detectable ctDNA at time zero, we hypothesize that reduction in ctDNA levels will be associated with a lack of relapse within 2 years.

c. Experimental Research Technique

The Natera Signatera assay is a personalized medicine approach for cancer patients that allows for serial testing of peripheral blood for monitoring of minimal residual disease and molecular relapse. Sixteen patient tumor-specific, somatic, non-driver mutations are selected based on exome sequencing comparisons of germline (buffy coat) to tumor (FFPE tissue). Through a proprietary algorithm, Natera chooses truncal, founder mutations that persist throughout the clonal phylogeny of the heterogeneous tumor population. Each patient plasma sample is then tested with a custom-designed assay that quantifies the 16 unique somatic mutations. For this study, germline and tumor exome data files will be provided to SWOG for future studies.

Dr. Allie Grossmann (PI) is board certified in both Anatomic Pathology and Molecular Genetic Pathology. She is a Medical Director of Molecular Oncology at ARUP Laboratories, a national reference laboratory owned by the University of Utah, where she oversees the design, validation and routine clinical testing of a

variety of molecular, genomic and immunohistochemical clinical assays, including ctDNA assays. She is an independent investigator at the Huntsman Cancer Institute (Department of Pathology, University of Utah), with an NCI and American Cancer Society-funded melanoma research laboratory. She is Co-Director of the Biospecimen Pathology Core for the HCI Melanoma SPORE initiative. She is a quality control anatomic pathologist for HCI Biorepository – providing histomorphologic review of melanoma and sarcoma tumor banking. Dr. Grossmann is ideally suited to lead this study.

d. Statistical Plan

The case-control pairs will be selected randomly among eligible patients with all required samples. Cases will be patients who relapsed within 2 years of randomization. Controls will be patients who were alive without relapse for at least 2 years after randomization. To the degree possible with the sample sizes available, case-control patients will be matched based on the randomization stratification factors stratification factors stage (stage IIIA and IIIB versus IIIC and IV) and PD-L1 status (positive versus negative versus indeterminate). Also, to the degree possible with the sample sizes available, we will restrict to patients who received ipilimumab on the control arm, and restrict to patients on the pembrolizumab arm who declared before randomization that they would have received ipilimumab if randomized to the control arm.

With 100 total patients, 50 cases and 50 controls, and assuming 24% of control patients (no relapse or death within first two years) have detectable baseline ctDNA levels, we will have 90% power with a two-sided alpha of 5% to detect an odds ratio (OR) of 5.3 or more extreme if the correlation between cases and controls is 0.5. If the correlation is lower than 0.5, we have additional power. For example, if the correlation is 0.2, we have 90% power to detect an OR of 4.26 or more extreme.

For secondary analyses we will:

- evaluate baseline ctDNA as a quantitative covariate in a conditional logistic regression model,
- evaluate associations between presence/absence of ctDNA and quantitative ctDNA levels at the third and fifth cycles and relapse within 2 years using conditional logistic regression and landmark analyses,
- descriptively summarize changes in ctDNA levels over time using descriptive statistics including means, medians, and inter-quartile ranges and spaghetti plots
- perform all the above analyses within each treatment arm, and fit regression models with a treatment arm interaction covariate (to be performed after results by treatment arm from the trial are released by the DSMC).

No information on arm label will be provided during the processing, labeling, or analyses of this project until the DSMC releases results of the trial.

Analyses and interpretation of data are planned to be completed within 1 year of the receipt of specimens.

e. Data Analysis

Natera will report ctDNA levels to SWOG Statisticians. SWOG statisticians will perform all analyses linking ctDNA results with patient-level data.

f. Specimen Information

Exome sequencing and ctDNA detection will be performed by Natera and statistical testing will be performed by SWOG statisticians ctDNA and outcome correlation data will be reported to Dr. Allie Grossmann (PI).

The SWOG Biospecimen Bank - Lab #201 will ship the following specimens to Natera on dry ice for overnight delivery as outlined in Section 18.9.c:

1) DNA from FFPE tumor
2) DNA from germline (buffy coat)
3) frozen plasma aliquots

Natera
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Specimens used:

Eligible patients who received ipilimumbab or pembolizumab on **S1404**. This proposal requires:

- primary tumor or lymph node metastasis AND plasma AND buffy coat from baseline,
- plasma at start of cycle 3 (if relapsed after start of cycle 3),
- plasma at start of cycle 4 (if relapsed after start of cycle 4),
- plasma at removal from protocol therapy or relapse.

50 patients from each arm will be selected with a 1:1 case control design as follows:

- control arm (patients who received IFN)
  n=25 patients who relapsed within 2 years
  n=25 patients who were alive without relapse at 2 years
- pembrolizumab arm
  n=25 patients who relapsed within 2 years
  n=25 patients who were alive without relapse at 2 years

We note that treatment arm information will not be released until the DSMC releases the treatment arm results of the trial.

g. Reference

1 Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.05282.

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3 Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.

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5 Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.05282.

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7 Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.

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