SWOG CANCER RESEARCH NETWORK

Version Date: February 15, 2023

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

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

RE: **S1801**, "A Phase II Randomized Study of Adjuvant Versus Neoadjuvant Pembrolizumab (MK-3475) for Clinically Detectable Stage III-IV High Risk Melanoma". Study Chairs: Dr. S. Patel

REVISION #11

Study Chair: Sapna Patel, M.D.
Phone number: 713/792-2921
E-mail: S1801SCquestion@swog.org

Action Codes
(✓) Patients Must be Informed*
(✓) Consent Must Be Amended*
* See "Patient Notification and Use of Consent Addendum" and "Regulatory Considerations" instructions below.

Key Updates
(✓) Dose modification updates
(✓) Informed Consent changes
(✓) Other: Other: Pembrolizumab (MK-3475, NSC 776864) CAEPR update

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 distribution of this notice through the CTSU Bi-Monthly Broadcast email.

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 through the CTSU Bi-Monthly Broadcast email.

REVISION #11

S1801 has been revised with the following changes in response to the Request for Rapid Amendment (RRA) received on February 3, 2023 from Dr. Elad Sharon (sharone@mail.nih.gov). The associated Action Letter is attached.

Protocol Changes

1. The version date has been updated.

2. The Table of Contents has been updated.

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

4. Section 3.1.c: Instances of "MK-3475 (pembrolizumab)" have been updated to "pembrolizumab (MK-3475)". The Pembrolizumab (MK-3475) CAEPR has been updated to Version 2.7, December 13, 2022 as follows:

   a. Added New Risk:
   - Rare but Serious: Endocrine disorders - Other (hypoparathyroidism); Nervous system disorders -Other (optic neuritis)

b. Decrease in Risk Attribution:
   - Changed to Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution from Less Likely: CPK increased; Joint effusion; Pleuritic pain

c. Deleted:
   - Less Likely: Immune system disorders - Other (pseudoprogression/tumor inflammation); Infection; Musculoskeletal and connective tissue disorder – Avascular Necrosis; Musculoskeletal and connective tissue disorder - Other (tenosynovitis)
   - Footnote #4 “Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.” is deleted.

5. Section 7.1: A section regarding supportive care for pembrolizumab has been added. Subsequent sections have been renumbered.

6. Section 8.2: A new section for “General Considerations” has been added. Information regarding missed doses and dose delays has been moved to this section. A statement regarding supportive care information has been added to cross reference Sections 7.1 and 8.3a. Subsequent sections have been renumbered.

7. Section 8.3: The Dose Modification Guidelines for Pembrolizumab have been updated in this section to reflect the Jan.10, 2023 NCI modifications to pembrolizumab dose modification guidelines. The changes are as follows:

   a. Section 8.3a: The section title has been updated to “Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab”. Additional information has been added regarding identification and management of immune-related AEs (irAEs), infusion-reactions, and non-irAEs.

   b. Section 8.3a, Table 1 has been updated as follows:

      General instructions
      - Instruction 1 has been changed to include non-endocrine-related severe and life-threatening irAEs. A statement has been added to highlight that some non-endocrine irAEs do not require steroids.
      - Instruction 2 has been revised to specifically mention non-endocrine-related toxicities.
      - Instruction 3 has been reworded for clarity.
      - Instruction 4 has been revised to clarify instructions for non-endocrine irAE.

      irAEs Toxicity Management Guidelines
      - Diarrhea / Colitis:
        - In the "Corticosteroid and/or other therapy" section, a sentence has been added to clarify that a gastroenterologist should examine patients who do not respond to corticosteroids in order to confirm the diagnosis and assess secondary immune suppression.
        - The section "Monitoring and Follow-up" has been updated to include a statement that participants should specifically be evaluated for celiac disease serologically and rule out Clostridium difficile infections. Additionally, wording has been added for assessing mucosal severity for participants with ≥Grade 2.

      - Type 1 diabetes mellitus (T1DM) or Hyperglycemia:
        - New guidelines for “Grade 1 or 2” have been added.
        - “New Onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of B-cell failure” has been updated to “New onset T1DM (evidence of B-cell failure) or Grade 3 or 4 hyperglycemia” and the following have been added: a clarification for resuming pembrolizumab and updates to management, monitoring, and follow-up.

- Hypophysitis:
  - Under the column "Monitoring and follow-up," a statement has been added to instruct patients are to be provided with adrenal insufficiency precautions, including indications for stress dosage steroids and medical alert jewelry, and that they should consider referral to an endocrinologist.

- Hyperthyroidism:
  - For Grade 2, in the column "Action with pembrolizumab", “continue" have been updated to "Consider withholding. Resume pembrolizumab once symptoms have subsided and thyroid function has improved".
  - A sentence has been added under the column "Corticosteroid and/or other medications" to initiate treatment with an anti-thyroid medicine such as methimazole or carbimazole as needed.
  - A sentence has been inserted under the column "Monitoring and follow-up" stating that patients should strongly consider referral to an endocrinologist.

- Nephritis:
  - In the "Monitoring and Follow-up" section, a statement has been added advising patients to strongly consider referral to a nephrologist.

- The “Myocarditis” section have been updated to “Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)”
  - Grade 1 has been clarified as “Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1” and now has separate guidelines for management, monitoring, and follow-up. Additional guidelines have been added for Grade 1.
  - The guidelines for Grade 2 have been combined with Grades 3-4. Additional guidelines for management, monitoring, and follow-up have been added.

- Guidelines for “Exfoliative Dermatologic Conditions” have been added.

- The footnotes have been updated as follows:
  - Added definitions for acronyms used within the table.
  - Added a note about managing non-irAEs following clinical practice recommendations.
  - The sentence referring to resuscitation equipment and physician availability has also been included here.

c. Section 8.3b, Table 2: The table title was revised to “Pembrolizumab (MK-3475) Infusion Reaction Treatment Guidelines”. The table has been updated as follows:
   - An additional column has been added for “Infusion Reactions” description as it applies to each NCI CTCAE Grade.
   - Under grade 3 treatment, corticosteroids was clarified to include the following additional information “ (e.g. methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours)”
   - "Grade 4" guidelines have been separated from “Grade 3”. Instructions have been added to admit participants to the intensive care unit (ICU) with monitoring and additional treatment and, as appropriate, follow Grade 3 recommendations.

d. Section 8.3, Table 3: A section has been added for Management of Neurological toxicities and The Neurological Toxcities table has been added to this section. Subsequent sections have been renumbered.

Model Consent Form Changes

1. The version date has been updated.

2. The Pembrolizumab (MK-3475) risk profile date has been updated to CAEPR Version 2.7, December 13, 2022.

3. Possible Side effects of Pembrolizumab (MK-3475) updates:

   Deleted Risk Attribution:
   - Occasional: Infection

   Decreased in Risk Attribution:
   - Changed to Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Fluid in the joints; Pain in chest
   - Provided Further Clarification: Rare: Changed from "Swelling and redness of the eye" to "Swelling and redness of the eye which may cause blurred vision with a chance of blindness"

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

Patient Notification and use of Consent Addendum:

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?
- All patients currently on study treatment with Pembrolizumab (MK-3475).

How must patients be notified?
- For patients currently receiving Pembrolizumab (MK-3475): Notification must take place either via the attached Consent Addendum or via amended consent form by next study visit. After the change has been discussed with the patient, the patient must sign and date either the Consent Addendum or the 2/15/2023 version of the consent form.

What is the notification deadline and process?
- For patients currently receiving treatment with Pembrolizumab (MK-3475): Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved. Important: Any changes to eligibility criterion are effective 30 days after distribution of this notice. If local IRB approval is not granted within 30 days, new registrations must meet any revised eligibility criteria included in the revision or accrual must be suspended until approval is obtained.

Regulatory Considerations:

Do local consent forms need to be updated?

- It depends. If your site will utilize the updated consent form for notification and formal reconsent then local consent forms must be updated. If your site will not utilize updated consent form for notification and formal reconsent then local consent forms need not be updated.

Can accrual continue until local implementation of the 2/15/2023 version of the consent form?

- Unless otherwise noted in the Action Letter, accrual may continue; however:
  - Patients enrolled after the notification deadline must be enrolled under the 2/15/2023 version of the consent form.
  - Sites using the NCI CIRB as their IRB of record: Patients enrolled prior to the notification deadline but before the 1/30/2023 version is implemented locally may be consented by signing the previous version of the consent form 3/21/2022 together with signing the attached Consent Addendum.
  - Sites not using the NCI CIRB as their IRB of record: Patients enrolled prior to the notification deadline but before the 1/30/2023 version is implemented locally may be consented by signing the previous version of the consent form 3/21/2022 together with being notified of the updated information verbally at the time of consent. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved. Important: Any changes to eligibility criterion are effective 30 days after distribution of this notice. If local IRB approval is not granted within 30 days, new registrations must meet any revised eligibility criteria included in the revision or accrual must be suspended until approval is obtained.
  - Patients enrolled prior to the notification deadline but before the 2/15/2023 version is implemented locally may be consented by signing the previous version of the consent form 3/21/2022 together with signing the attached Consent Addendum.

PLEASE NOTE: If the Action Letter requires suspension of accrual until the updated consent is implemented locally, the Action Letter instructions supersede this memo.

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.

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

Informed Consent Addendum Model for S1801

S1801, "S1801 A Phase II Randomized Study of Adjuvant vs. Neoadjuvant Pembrolizumab (MK-3475) for Clinically Detectable Stage III-IV High-Risk Melanoma"

The following information should be read as an update to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated below, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The following risk has been identified with the to Pembrolizumab (MK-3475) updates:

- **Rare:** Changed from "Swelling and redness of the eye" to **"Swelling and redness of the eye which may cause blurred vision with a chance of blindness"**

Patient Signature and Date

By signing this form, I acknowledge that I have read the information above or had it read to me. I have discussed it with a member of the study team and my questions have been answered. I understand that I will be given a copy of this form.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG

A PHASE II RANDOMIZED STUDY OF ADJUVANT VERSUS NEOADJUVANT PEMBROLIZUMAB (MK-3475) FOR CLINICALLY DETECTABLE STAGE III-IV HIGH RISK MELANOMA

NCT# 03698019

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AGENTS:

NCI Supplied Investigational Agents

(DCTD-sponsored):
Pembrolizumab (MK-3475) (NSC 776864)

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TABLE OF CONTENTS

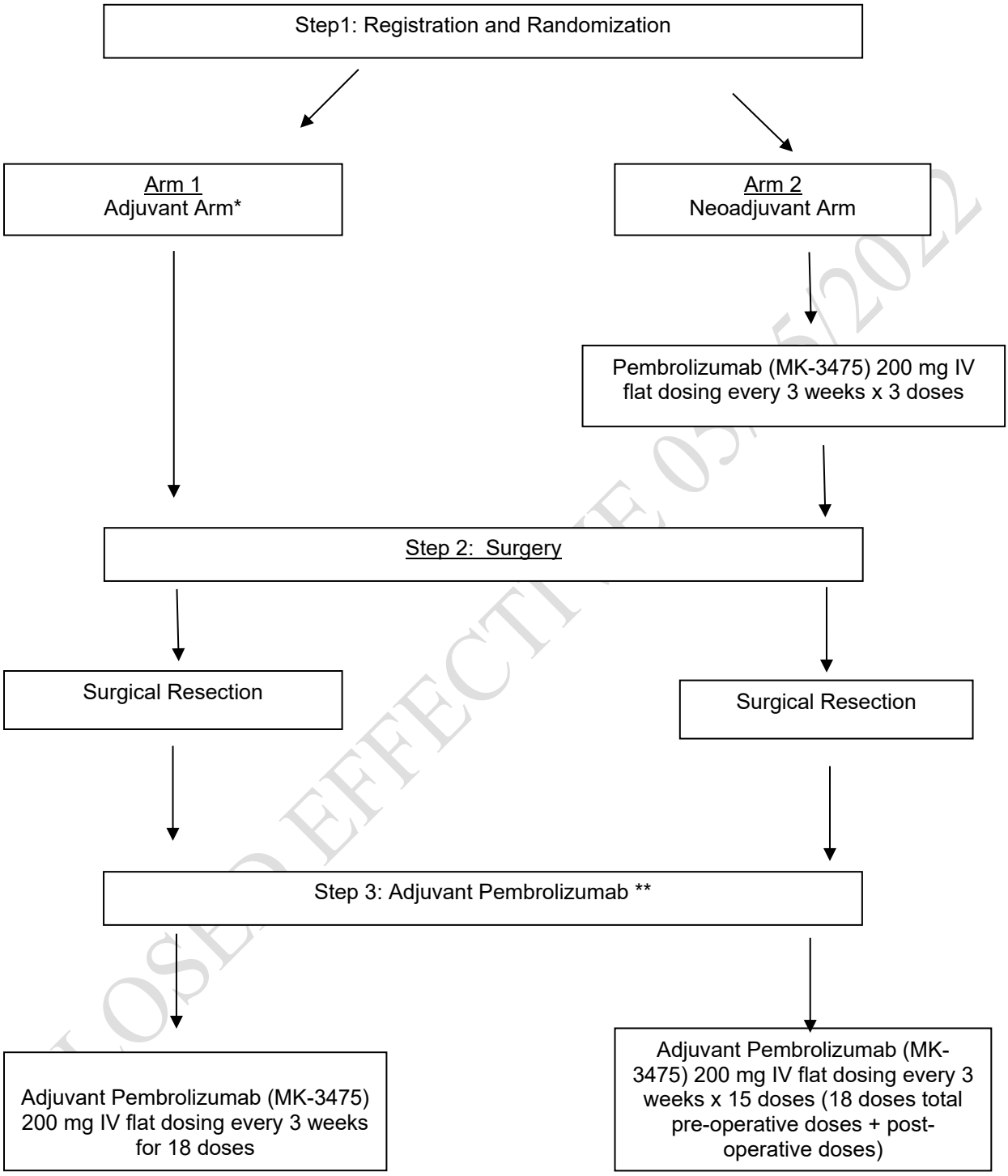
PROTOCOL CONTACT INFORMATION

Eligibility, RAVE, Data Submission:	SWOG Statistics and Data Management Center E-mail: melanomaquestion@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent:	SWOG Operations Office E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions):	Email: S1801SCquestion@swog.org or call: Dr. Sapna P. Patel, M.D. at Phone: 713/792-2921
Investigational Drug questions: Requests for Investigator's Brochures: Access issues for the PMB Online Agent Ordering Processing (OAOP) application:	See Protocol Section 3.0 or PMBAfterHours@mail.nih.gov See Protocol Section 3.0 or http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm IBCoordinator@mail.nih.gov
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL)	See Protocol Section 14.2 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
TRIAD installations:	https://triadinstall.acr.org/triadclient/ Questions: TRIAD-Support@acr.org
Participant Transfers:	patienttransfer@crab.org
Serious Adverse Event Reporting questions:	See Protocol Section 8.5 Email: adr@swog.org
Source Documentation Portal – Central Monitoring	centralmonitorquestion@crab.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For participant enrollments:**	**For study data submission:**
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 participants waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the participant enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For participant eligibility or data submission questions contact the SWOG Data Operations Center by phone or email: 206/652-2267 melanomaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: Sapna P. Patel, M.D. Phone: 713/792-2921 E-mail: S1801SCquestion@swog.org		
For non-clinical questions (i.e. unrelated to participant eligibility, treatment, or clinical data submission) 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.		
The CTSU Website is located at https://www.ctsu.org		

SCHEMA



*** Participants on Adjuvant arm must be registered to Step 2 (Surgery) within 17 days (preferably within 14 days) after randomization and must undergo surgical resection within 17 days (preferably within 14 days) after Step 2 registration.**

**** See Section 7.1 for dosage and timing. Participants must start adjuvant therapy within 84 days of surgery.**

1.0 OBJECTIVES

1.1 Primary Objective(s)

a. To compare event-free survival (EFS) in participants with high-risk resectable melanoma randomized to neoadjuvant pembrolizumab (MK-3475) with participants randomized to adjuvant pembrolizumab (MK-3475).

1.2 Secondary Objective(s)

a. To assess the frequency and severity of toxicities on each of the arms.

b. To compare between arms overall survival (OS), disease control at 24 weeks, locoregional control in the surgical site(s), and total number of pembrolizumab (MK-3475) doses received.

c. On the neoadjuvant arm, to estimate the pathologic response rate, the RECIST 1.1 response rate (confirmed and unconfirmed CR and PR), and the iRECIST response rate (confirmed and unconfirmed CR and PR), before surgical resection; to compare definitions of pathologic partial response; and to evaluate the association between pathologic response and EFS and OS.

d. To describe the proportion of participants on each arm who received the surgery planned at randomization.

1.3 Additional Objective(s)

a. To bank tumor tissue and whole blood in anticipation of future correlative studies in this participant population. Such proposed analysis includes deep immune profiling, with evaluation of CD3, CD8, PD-L1, CD20, whole exome sequencing studies, and RNA analysis.

2.0 BACKGROUND

Although the long-term relapse-free survival (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 in Stage III patients of approximately 50%. *(1)* Modern therapy has significantly improved outcomes for patients with Stage IV melanoma such that 20% of patients are alive beyond 4 years or longer after diagnosis, but 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.

Treatment with anti-programmed death-1 (PD-1) antibody induces significant response rates and durable survival in patients with metastatic melanoma. *(4,5,6)* Historically, adjuvant therapy for melanoma typically involves treatment with either high-dose interferon or high-dose ipilimumab. *(7,8)* But the role of PD-1 has moved to the forefront of adjuvant therapy with the results of CheckMate-238. *(9)* At this time, we are not able to predict which patients will derive benefit from adjuvant therapy and be long-term survivors (or cured). However, there is a need to identify patient or tumor characteristics that can distinguish those who will benefit from the cost, side effects, and time commitment of adjuvant treatment from those who will not.

While adequate and effective surgery is the goal of early treatment of primary melanoma, some cases with bulky nodal involvement are at high risk of local or distant recurrence despite upfront surgical resection. Neoadjuvant treatment offers the benefit of an early on-treatment pathological sample that can be profiled for additional biomarkers and correlated with survival. Additionally, treating with anti-PD1 antibody while tumor transiently remains in the body may generate a stronger

immune response against *in vivo* tumor antigens compared to the traditional adjuvant setting where tumor antigen is presented by microscopic residual tumor burden.

Patients with bulky resectable disease have been treated in pilot studies using a neoadjuvant approach with chemotherapy, targeted therapy, and more recently, checkpoint blockade. Multidisciplinary coordination in these cases is paramount as is timing of surgical resection. In these pilot studies investigating neoadjuvant targeted therapy for melanoma, an improvement in relapse-free survival and overall survival has been observed; additionally, pathologic response rates to neoadjuvant therapy have been estimated in small studies. An unpublished Phase II clinical trial of adjuvant versus neoadjuvant targeted therapy in melanoma patients at MD Anderson had a RECIST 1.1 response rate after neoadjuvant targeted therapy of 85% and a pathologic complete response rate of 58%. Compared to patients randomized to surgery followed by adjuvant targeted therapy, there was a statistically significant difference in 12-month EFS favoring the neoadjuvant arm.

Among **S1404** enrollment, 43% of patients had clinically detectable and resectable nodal disease, the ideal population for a neoadjuvant cohort. This study, **S1801**, will answer two pressing questions in the field of melanoma: 1) Is there evidence that neoadjuvant treatment with a PD-1 inhibitor can improve relapse-free and overall survival in patients with clinically detectable resectable node-positive melanoma compared to adjuvant PD-1 inhibitor treatment; and 2) Can a multi-center multidisciplinary high-quality neoadjuvant melanoma trial be executed within the cooperative group system.

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

The current standard of care has been set by the recently reported CheckMate-238 study, and the FDA has approved the use of nivolumab for completely resected node-positive or metastatic melanoma. *(10)* Nivolumab and pembrolizumab (MK-3475) have never been tested head-to-head but results from clinical trials in metastatic melanoma demonstrate equitable outcomes with these two agents. Ongoing adjuvant clinical trials in patients with melanoma include **S1404** (pembrolizumab (MK-3475) versus choice of standard of care), KEYNOTE-054 (pembrolizumab (MK-3475) versus placebo), and CheckMate-915, a randomized, Phase III, double-blind study of nivolumab versus the combination of nivolumab plus ipilimumab in patients with resected, Stage III melanoma). As of May 2018, KEYNOTE-054 data demonstrated that adjuvant pembrolizumab is associated with an improved 1-year and 18-month recurrence-free survival (RFS) compared to placebo. *(11)* The data have not yet matured to produce distant metastasis-free survival and overall survival results.

Biological rationale for the study population based on the anticipated mechanism of action of pembrolizumab (MK-3475):

Patients with bulky resectable melanoma have been treated using a neoadjuvant approach with chemotherapy, targeted therapy, and more recently, checkpoint blockade at multidisciplinary academic medical centers. Studying systemic treatment in this resectable population offers insight into biologic and pathologic response to treatment. It also provides an intact tumor-infiltrating lymphocyte population upon which checkpoint blockade often has its greatest effects in antigen presentation and generation of an anti-tumor immune response. While adequate and effective surgery is the goal of early treatment of primary melanoma, some cases with bulky nodal involvement are at high risk of local or distant recurrence despite upfront surgical resection. Neoadjuvant treatment further offers the benefit of an early on-treatment pathological sample that can be profiled for additional biomarkers and correlated with survival.

Inclusion of Women and Minorities

2.1 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. To date, studies of pembrolizumab (MK-3475) 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	2	0	0	2
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	4	4	0	0	8
White	145	337	2	4	488
More Than One Race	0	0	0	0	0
Total	149	345	2	4	500

3.0 DRUG INFORMATION

Investigator's Brochures

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

For this study, pembrolizumab (MK-3475) 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).

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

a. PHARMACOLOGY

Pembrolizumab (MK-3475) 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. PEMBROLIZUMAB (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 pembrolizumab (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, pembrolizumab (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) 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 participants.* Below is the CAEPR for pembrolizumab (MK-3475).

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.

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (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]		
		Blood and lymphatic syster disorders - Other (immune thrombocytopenic purpura)	
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency		
		Endocrine disorders - Othe (hypoparathyroidism)	
	Endocrine disorders Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vog Koyanagi-Harada syndrom	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	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]		
		Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin 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]		
	Back pain		
	Joint range of motion decreased		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (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 (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (optic neuritis)	
		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		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2***
	Rash acneiform[2]		
	Rash maculo-papula		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrom	
		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 pembrolizumab (MK-3475). Adverse events potentially related to pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

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

Adverse events reported on pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pembrolizumab (MK-3475) 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 – CPK increased; 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; Joint effusion2; 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; Pleuritic pain2; 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: Pembrolizumab (MK-3475) 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: pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm. Participants 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. Participants 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).

   Participants 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 participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

   Pregnancy: If a participant inadvertently becomes pregnant while on treatment with pembrolizumab (MK-3475), the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant'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 pembrolizumab (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, participants 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 participant medication list, including pembrolizumab (MK-3475), should be screened prior to initiation of and during treatment with pembrolizumab (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

Pembrolizumab (MK-3475) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vile contains 100 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for injection, USP.

f. PREPARATION

Pembrolizumab (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 pembrolizumab (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 pembrolizumab (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

Refer to the package label for expiration.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 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. PARTICIPANT CARE IMPLICATIONS

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

l. DRUG ORDERING AND ACCOUNTABILITY

1. Drug Ordering

Sites may order initial agent supplies when a subject has been randomized. Starter supplies will not be provided. NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). 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 participating investigator at that institution.

Submit agent requests 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, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

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, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

3. Drug return and/or disposition instruction

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).

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

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

4.0 STAGING CRITERIA

All participants will be staged using the AJCC 8th edition, 2017. Below are the study specific staging criteria for eligibility purposes. For a full list of staging criteria, see Section 18.2

Clinically detectable Stage III or Stage IV

	T Stage	Nodal Disease	Satellite / In-Transit Metastases	M stage
IIIB	T0,T1,T2,T3a	One clinically detected node	No	M0
	T0,T1,T2,T3a	none	Yes	M0
IIIC	T3b, T4	One clinically detected node	No	M0
	T3b, T4	0-1 clinically detected nodes	Yes	M0
	T0,T1,T2,T3,T4a	2+ clinically detected nodes or matted nodes	No	M0
	T0,T1,T2,T3,T4a	2+ clinically detected nodes or matted nodes	Yes	M0
IIID	T4b	2+ clinically detected nodes or matted nodes	No	M0
	T4b	2+ clinically detected nodes or matted nodes	Yes	M0
IV	any T	any N	yes/no	M1

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 randomization. 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 randomization. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

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 28, 30, 42 or 84 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1 REGISTRATION (Randomization)

a. Disease Related Criteria

1. Patients must have **clinically detectable** Stage III (clinically detectable N1b, N1c, N2b, N2c, N3b and N3c) or Stage IV **resectable** melanoma. Patients with melanoma of mucosal or acral origin are eligible. Patients with melanoma of uveal origin are not eligible. Patients with a history of brain metastases are not eligible.

   Clinically detectable is defined as disease that is apparent and measurable via physical examination or radiographic imaging (Section 10.1).

Note: Planned surgery must be documented on the **S1801** Planned Surgery Form.

2. 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.

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

4. Patients must have histologically proven Stage IIIB or higher. This would entail pathologic confirmation beyond the primary or initial diagnosis of melanoma involving fine needle aspiration cytology or biopsy confirmation of any N-category or M-category resectable site.

b. Prior/Concurrent Therapy Criteria

1. Patients must not have received previous neoadjuvant treatment for their melanoma. Patients may have received prior non-immunotherapy adjuvant therapy. 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 treatment phases on the study.

2. Patients must not be planning to receive concomitant other biologic therapy, hormonal therapy, other chemotherapy, surgery, while on protocol therapy.

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

c. Clinical/Laboratory Criteria

1. Patients must be ≥ 18 years of age.

2. All patients must have disease status documented by a complete physical examination and imaging studies within 42 days prior to randomization. Imaging studies must include a CT of the chest, abdomen, and pelvis with intravenous contrast (unless contraindicated). For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with intravenous contrast) is required. If the patient has unknown primary with disease in the axilla, neck imaging is required. CT imaging must be done with intravenous contrast if there are no contraindications for it. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium.

   Note: PET-CT scans are NOT acceptable to establish eligibility. Non-iodinated CT scans that are part of common PET-CT imaging protocols do not provide contrast for difficult to ascertain areas such as the neck and liver, and do not provide enough CT detail to perform appropriate RECIST 1.1 measurements. As such, a PET-CT with non-contrast CT or non-diagnostic quality CT images is considered insufficient for the detection of melanoma.

3. All patients must have a CT or MRI of the brain within 42 days prior to randomization. The brain CT or MRI should be performed with intravenous contrast (unless contraindicated).

4. 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 randomization.

5. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except patients with 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 randomization.

6. Patients must have LDH performed within 42 days prior to randomization.

7. Patients must have adequate renal function as evidenced by calculated creatine clearance > 30 mL/min. The creatinine level (mg/dL) used in the calculation must be obtained within 42 days prior to randomization.

   Calculate creatinine clearance = $\frac{(140\text{-age}) \times \text{wt (Kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dL}}$

8. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.14).

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

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

11. 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.

12. Patients must not have received live vaccines within 42 days prior to randomization. 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. NOTE: The COVID-19 vaccines (currently available and those in the pipeline for FDA emergency use authorization or FDA approval) do not contain live virus, and therefore, COVID-19 vaccination does not affect or preclude eligibility for the **S1801** trial. For patients who have undergone lymphadenectomy, vaccines should be delivered to a limb with an intact lymph node basin (Sentinel lymph node biopsy in a limb is acceptable). The vaccine should not be administered in a limb that has undergone lymphadenectomy.

13. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to randomization: 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.

14. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to randomization. Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

15. Prior malignancy is allowed providing it does not require concurrent therapy.

16. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to randomization. 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.

17. Patients must be deemed medically fit to undergo surgery by the treating medical/surgical team.

d. Specimen Submission Criteria

1. Patients must be willing to submit the following surgical specimens: either all tissue blocks from the surgical specimen or two slides per block [(1) H&E slide and (1) unstained slide OR (2) unstained slides if H&E stained slides cannot be provided)

2. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.2.

e. Regulatory Criteria

1. 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.

2. As a part of the OPEN randomization 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 (Surgery)

a. Patients randomized to Arm 2 (Neoadjuvant arm) must be willing to submit tissue to determine pathologic response as described in Section 15.1 regardless of number of pre-operative doses of pembrolizumab (MK-3475) received. Determination of pathologic response cannot be done on less than the full surgical specimen.

b. Patients must have disease assessments by CT chest/abdomen/pelvis with IV contrast, and neck CT with IV contrast if primary head and neck melanoma, performed within 42 days (and no more than 49 days) before the planned date of surgery. MRI combined with non-contrast CT is an acceptable alternative for patients with CT contrast allergy, but imaging must encompass total body.

c. Patients must register to Step 2 within 17 days prior to planned date of surgery.

5.3 STEP 3 REGISTRATION (Adjuvant Therapy)

a. Patients must have undergone surgery prior to Step 3 registration. The Step 2 surgery must have completely resected their melanoma.

- Patients with gross positive residual disease following surgery do not qualify as having disease-free status, and, therefore, such patients are not eligible to register for adjuvant therapy.
- Patients with microscopic residual disease (i.e., positive margins) can be treated with re-excision or radiation, per site discretion, to render the patient disease-free prior to registration of adjuvant therapy.
- Disease-free status must be documented by a complete physical examination and radiographic imaging studies within 42 days prior to Step 3 registration. Imaging studies must include a CT of the chest, abdomen, and pelvis (unless contraindicated). Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium. CT imaging must be done with intravenous contrast if there are no contraindications for it.
- For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with IV contrast, unless contraindicated) is required.

- If the patient has had unknown primary with disease in the axilla, neck imaging is required to assure the region is clear of cancer.
- Any other clinically indicated imaging studies if performed (e.g., bone scan) must show no evidence of disease.

b. Patients must be registered to Step 3 no more than 84 days after date of Surgery.

c. Patients with R0 or R1 resections must have disease-free status documented by a complete physical examination and imaging studies within 42 days prior to Step 3 Registration. These patients must have disease assessment by CT chest/abdomen/pelvis with IV contrast, and neck CT with IV contrast if primary head and neck melanoma. MRI combined with non-contrast CT is an acceptable alternative for patients with CT contrast allergy.

d. Patients with R2 resections are not eligible for Step 3 and must be removed from study treatment per Section 7.4.

6.0 STRATIFICATION FACTORS

Participants will be randomized between the Adjuvant arm and the Neoadjuvant arm in a 1:1 fashion, using dynamic balancing. Stratification will be based on:

1. Baseline LDH: Low/Normal (≤ institutional upper limit of normal) versus High (> institutional upper limit of normal) and

2. Stage of disease at randomization: IIIB* versus IIIC* versus IIID*/IV

*Note: **Based on clinical staging as outlined in Section 4.0.** Participants who have only clinically occult lymph nodes, i.e. N1a-N3a, are not eligible.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Sapna Patel at 713/792-2921 or Dr. Kenneth Grossmann at 801/213-8435 (or S1801SCquestion@swog.org). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/about/policies-procedures.

7.1 Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 8.2b. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

NOTE: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

7.2 Treatment

a. Pre- pembrolizumab (MK-3475) Labs

Blood collected for pretreatment laboratory tests must be collected and analyzed no more than 3 days prior to dosing.

b. Surgery

Participants must undergo surgical resection (lymphadenectomy or resection of in-transit or distant metastasis +/- wide local excision, if applicable) of clinically detectable melanoma. **Timing of surgery is dependent on treatment arm.**

For all participants, the **S1801 Planned Surgery Form** must be filled out prior to randomization and the **S1801 Post-Surgery Form** filled out post-surgery. Submit forms as indicated in Section 14.0.

Pembrolizumab (MK-3475) timing after surgery is up to the discretion of the local investigator. Interval between surgery and start of adjuvant therapy should not exceed 84 days.

c. **Arm 1: Pembrolizumab (MK-3475) Adjuvant Arm**

Step 1: RANDOMIZATION

Participants will be randomized.

Step 2: SURGERY

Participants on Adjuvant arm must be registered to Step 2 (Surgery) within 17 days (preferably within 14 days) after randomization and must undergo surgical resection within 17 days (preferably within 14 days) after Step 2 registration. Radiation is allowed after surgery. **However, interval between Surgery and the start of Adjuvant therapy must not exceed 84 days.**

Step 3: ADJUVANT THERAPY

It is recommended that participants be registered to and initiate treatment on Step 3 (Adjuvant therapy) within 17 days (preferably within 14 days) after surgery. Radiation is allowed after surgery. However, interval between Surgery and start of Adjuvant therapy must not exceed 84 days.

Agent	Dose	Schedule	Route
MK-3475 (pembrolizumab)	200 mg	IV over 30 minutes	Day 1, Q 3 weeks for 18 doses

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

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

Pembrolizumab (MK-3475) 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, participant vacation, and/or holidays). Participants 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 participant's study record.

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

d. **Arm 2: Pembrolizumab (MK-3475) Neoadjuvant Arm**

Step 1: RANDOMIZATION AND NEOADJUVANT THERAPY

Agent	Dose	Route	Schedule
MK-3475 (pembrolizumab)	200 mg over 30	IV for 3 doses minutes	Day 1, Q 3 weeks followed by surgical resection.

Participants will receive 3 doses of pre-operative (MK-3475) pembrolizumab Administration of less than 3 doses of pre-operative pembrolizumab (MK-3475) may be allowed in cases of progressive disease requiring surgery or due to toxicity. This must be discussed with the Study Chair for approval. No additional doses of pre-operative pembrolizumab (MK-3475) treatment beyond 3 doses may be given.

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

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

Pembrolizumab (MK-3475) 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, participant vacation, and/or holidays). Participants 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 participant's study record.

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

Step 2: SURGERY:

Surgery should be arranged prior to Step 2 registration. It is recommended that participants undergo Surgery within 3 weeks after the last dose of pembrolizumab (MK-3475).

Note: participants must be registered to Step 2 (Surgery) before surgery is performed.

If participants are unable to undergo Surgery by Week 12 due to development of irAE or an unrelated event such as intercurrent medical illness or life event, additional doses of pre-operative pembrolizumab (MK-3475) must be discussed with the Study Chair for approval with a plan to reschedule Surgery at the safest and earliest time point. **Inability to coordinate Surgery by Week 12 with the local surgeon is not an acceptable reason to administer additional doses of pembrolizumab (MK-3475).**

Step 3: ADJUVANT THERAPY

It is recommended that participants be registered to and initiate treatment on Step 3 (Adjuvant therapy) within 17 days (preferably within 14 days) after surgery. Radiation is allowed after surgery. However, interval between Surgery and start of Adjuvant therapy must not exceed 84 days.

Agent	Dose	Route	Schedule
MK-3475 (pembrolizumab)	200 mg	IV over 30 minutes	Q 3 weeks for 18 doses total (pre-operative doses + post-operative doses)

Pembrolizumab (MK-3475) is to be resumed after surgery and continued every 3 weeks x 15 doses for a total of 18 doses (neoadjuvant + adjuvant).

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

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

Pembrolizumab (MK-3475) 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, participant vacation, and/or holidays). Participants 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 participant's study record.

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

7.3 Prohibited and Cautionary Medications

- 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 pembrolizumab (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.

Participants 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. Participants may receive other medications that the investigator deems to be medically necessary.

7.4 Follow-Up Disease Assessment Schedule

The same imaging modality as used at prestudy for disease assessment (see Section 5.1.c) must be used throughout the study.

For 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. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium.

Neoadjuvant participants must undergo disease assessments after the 3rd pre-operative dose/before surgery (Weeks 7-12, timing per site discretion). Disease assessments then occur every 12 weeks thereafter until participant receives surgery or has progression of disease before surgery such that the participant cannot receive the planned surgery.

Following surgery, disease-free status must be documented within 42 days prior to step 3 registration, using the same modalities as prestudy. If the interval between scans and Adjuvant therapy exceeds 42 days, repeat imaging must be obtained.

Disease assessments will then continue every 12 weeks (+/- 2 weeks) until relapse or 2 years from randomization and timed from prior imaging. Participants who are still relapse-free will then have disease assessments performed every 6 months (± 4 weeks) until relapse or 5 years from randomization.

In the case of a variation in scan schedule due to early or missed or delayed scans, the subsequent scan is to be scheduled at the appropriate interval from the date of prior total body scan.

During treatment and follow-up (through year 5), brain MRI/CT must be **repeated annually (± 4 weeks)**; for years 6 through 10, brain MRI/CT to be performed annually as clinically indicated. If there is a gadolinium allergy, or MRI brain intolerable for the participant, CT with iodinated IV contrast is adequate brain imaging. Brain imaging is required for participants with progressive disease.

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease per RECIST 1.1 or requires additional surgery (as defined in Section 10.0). Progression of disease that maintains the ability to undergo the planned surgery is not a criterion for removal from treatment.

b. Relapse of disease after surgery (as defined in Section 10.0).

c. Unacceptable toxicity.

d. The investigator may discontinue treatment if they determine that the participant'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. Participant's surgical margins note R2 resection.

f. Positive pregnancy test in a female participant

g. Completion of protocol treatment.

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

i. The participant may withdraw from the study at any time for any reason.

7.6 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4, the **S1801** Treatment Form, and the **S1801** Adverse Event Form). A cycle is defined as 21 days.

7.7 Discontinuation of Treatment

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

7.8 Follow-Up Period, End of Study

Randomized participants 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 General Considerations

a. Missed doses of MK-3475 should be made up.

b. Refer to Section 7.1 and 8.3a for supportive care information for pembrolizumab.

c. 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.

8.3 Dose Modification Considerations for Participants Receiving pembrolizumab (MK-3475)

Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in the tables below.

Adverse events (both nonserious and serious) 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 study 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.

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 for irAEs and infusion reactions associated with pembrolizumab are provided in the table below.

NOTE that non-irAEs will be managed as appropriate, following clinical practice recommendations.

a. Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

Table 1 Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, 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. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a 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 to 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 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool with or

	Recurrent Grade 3 or Grade 4	Permanently discontinue	Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity Participants with diarrhea/colitis 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 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value

	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	returned to baseline or is stable)
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines.

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc.*) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
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) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist

	Grade 3 or 4	Withhold or permanently discontinue [d]	methimazole or carbimazole as needed	
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, 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 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	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		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.
a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal
b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 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: encephalitis and other clinically important irAEs (e.g. vasculitis and sclerosing cholangitis).

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.

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 patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475)

Table 2 Pembrolizumab (MK-3475) Infusion Reaction Treatment Guidelines

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	**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.* 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**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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 3	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) 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.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	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.			

c. Management of Neurological Toxicities

Table 3 Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  ○ If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  ○ If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  ○ If event resolves fully, resume pembrolizumab. [b]
	  ○ If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.
[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

8.4 Anti-infectives

Participants 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.

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Sapna Patel at 713/792-2921 or S1801SCquestion@swog.org or if Dr. Patel is not available, please contact Dr. Grossmann at 813/745-3437. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/about/policies-procedures

8.6 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 CALENDAR

9.1 Pembrolizumab (MK-3475) Adjuvant Arm

REQUIRED STUDIES	Pre-Study	STEP 1: Random-ization	STEP 2: Surgery *	STEP 3: ADJUVANT PEMBROLIZUMAB (MK-3475) ON TREATMENT Infusions to be given q 3 weeks (+/- 3 days) for 18 total infusions						End of Treatment Assessment	Off treatment F/U prior to progression/ relapse[c]	F/U post relapse[d]
PHYSICAL				C1	C2	C3	C4	C5	C6[g]	C18		
History, PS & Physical [a] (w/BP, Height & Weight) [t]	X			X	X	X	X	X	X	X	X	
Toxicity Notation [h]	X			X	X	X	X	X	X	X	X	X
LABORATORY [e]												
CBC with Diff, Comprehensive Metabolic Panel [a]	X			X	X	X	X	X	X	X		
LDH	X											X
TSH, Free T_4 [o]	X											
Pregnancy Test[i]	X			X	X	X	X	X	X			
Cardiac Function[v]												
X-RAYS AND SCANS	Please refer to footnotes j and k for details on the timing of scans.											
CT neck [j], chest, abdomen & pelvis [k]	X											
Brain MRI or CT with contrast [l]	X											

Study Calendar 9.1 continued on next page. Click here for footnotes.

REQUIRED STUDIES	Pre-Study	STEP 1: Randomi-zation	STEP 2: Surgery *	STEP 3: ADJUVANT PEMBROLIZUMAB (MK-3475) ON TREATMENT Infusions to be given q 3 weeks (+/- 3 days) for 18 total infusions						End of Treatment Assessment	Off treatment F/U prior to progression / relapse[c]	F/U post relapse[d]
				C1	C2	C3	C4	C5	C6[g]	C18		
SPECIMEN SUBMISSION												
Tissue [m,n] for banking				X								X
Whole Blood for banking [m,n]				X				X		X		X
TREATMENT												
Surgical Resection			X									
pembrolizumab (MK-3475)				X	X	X	X	X	X	X		

Click here for footnotes**.**

NOTE: Forms are found on www.ctsu.gov. 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/2019-06/Best%20Practices_6.19.pdf.

9.2 Pembrolizumab (MK-3475) Neoadjuvant Arm

REQUIRED STUDIES	Pre-Study	ON TREATMENT [a] Infusions to be given q 3 weeks (+/- 3 days) for 18 total infusions								End of treatment assessment	Off treatment F/U prior to progression/ relapse[c]	F/U post progression/ relapse[d]
		STEP 1: NEOADJUVANT pembrolizumab (MK-3475)			STEP 2: SURGERY **	STEP 3: ADJUVANT MK-3475 (PEMBROLIZUMAB						
PHYSICAL		C1	C2	C3	Surgery	C 4	C 5	C 6	C 7	C8	C18		
History, PS, & Physical [a] (w/BP, Height & Weight) [t]	X	X	X	X		X	X	X	X	X	X	X	
Toxicity Notation [h]	X	X	X	X		X	X	X	X	X	X	X	X
LABORATORY [e]													
CBC with Diff, Comprehensive Metabolic Panel [a]	X	X	X	X		X	X	X	X	X	X		
LDH	X												X
TSH, Free T_4 [o]	X												
Pregnancy Test[j]	X	X	X	X		X	X	X	X	X			
Cardiac Function[v]													
X-RAYS AND SCANS	Please refer to footnotes j and k for details on the timing of scans.												
CT neck [j], chest, abdomen & pelvis [q]	X				X[q]								
Brain MRI or CT with contrast [q, l]	X												

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

9.2 Pembrolizumab (MK-3475) Neoadjuvant Arm (contd.)

REQUIRED STUDIES	Pre-Study	ON TREATMENT Infusions to be given q 3 weeks (+/- 3 days) for 18 total infusions [w]									End of treatment assessment	Off treatment F/U prior to progression/ relapse[c]	F/U post progression/ relapse[d]
		STEP 1: NEOADJUVANT pembrolizumab (MK-3475)			STEP 2: SURGERY **	STEP 3: ADJUVANT PEMBROLIZUMAB (MK-3475)							
		C1	C2	C3	Surgery	C4	C5	C6[g]	C7	C8	C18		
SPECIMEN SUBMISSION													
Tissue for assessing Pathologic Response					X								
Tissue [m,n] for banking		X											X
Whole Blood for banking [m,n]		X					X				X		X
TREATMENT													
MK-3475 [w] (pembrolizumab)		X	X	X		X	X	X	X	X	X		
Surgical Resection					X								

Click here for footnotes.

NOTE: : Forms are found on www.ctsu.gov. 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/2019-06/Best%20Practices_6.19.pdf.

Footnotes for Study Calendars

* Participants on Adjuvant arm must be registered to Step 2 (Surgery) within 17 days (preferably within 14 days) after randomization and must undergo surgical resection within 17 days (preferably within 14 days) after Step 2 registration. Interval between surgery and start of adjuvant therapy must not exceed 84 days.

** Participants on Neoadjuvant arm should: receive 3 doses of neoadjuvant (pre-operative) pembrolizumab (MK-3475) prior to registration to Step 2; arrange surgery before registration to Step 2; and register to Step 2 within 4 weeks after the last neoadjuvant dose of pembrolizumab (MK-3475). Administration of less than 3 doses of pre-operative pembrolizumab (MK-3475) must be discussed with the Study Chair for approval.

a. Following exams & labs are performed prior to receiving first dose and prior to every cycle until end of protocol treatment: physical (including BP & WT), PS, toxicity notation, CBC with differential (including ANC) and Comprehensive Metabolic Panel (Na, K, $HC0_3$ or CO_2, Serum creatinine or CrCl, non-fasting glucose, albumin, total bilirubin, AST, ALT, alkaline phosphatase).

c. Post-treatment follow-up (prior to relapse): Participants should be seen at 3 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if participant is < 2 years from study entry, every 6 months (+/- 4 weeks) if participant is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if participant 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 (including BP & wt), and PS. For post-treatment follow-up regarding scans, see footnote k.

d. Follow-up post progression/relapse: Participants who develop recurrent melanoma or who have progression of disease such that the participant cannot receive their planned surgery or require additional surgery will be followed for survival (vital status). Participants should be followed every 6 months for up to 2 years from the date of progression/relapse, then annually thereafter until 10 years from treatment randomization.

e. While on study, blood collected for pretreatment laboratory tests must be collected and analyzed no more than 3 days prior to dosing. NOTE: if pembrolizumab (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.

g. Treatment and visits should continue at these intervals through Cycle 18.

h Adverse Event Assessments on the study will continue for all participants until 30 days after the last study drug administration. However, participants with ongoing toxicities should be seen more often as clinically indicated.

i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to randomization. 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. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.

j. Participants 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 CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed within 42 days (+/- 1 week) before surgery, and every 12 weeks (+/- 2 weeks) from the start of Adjuvant therapy until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. In the case of a variation in scan schedule due to early or missed or delayed scans, the following scan is to be scheduled at the appropriate interval from the date of prior scan. If the interval between scans and Adjuvant therapy exceeds 42 days, repeat imaging must be obtained. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium.
Note: PET-CT scans are NOT acceptable to establish eligibility.

(k. continued)
NOTE: If the disease assessment was completed within the last 42 days between the post-cycle 3 scan and registration for Step 3 (Adjuvant therapy), scans do not need to be repeated. If more than 42 days have elapsed between the post-cycle 3 scan and registration for Step 3 (Adjuvant therapy), scans must be repeated.

l During treatment and follow-up (through year 5), brain MRI/CT must be repeated annually (± 4 weeks); for years 6 through 10, brain MRI/CT to be performed annually as clinically indicated. If there is a gadolinium allergy, or MRI brain intolerable for the participant, CT with iodinated IV contrast is adequate brain imaging. Brain imaging is required for participants with progressive disease.

m If participant consents, submit specimens for banking as specified in Section 15.2.

n. Blood needs to be drawn prior to treatment.

o. TSH (with a reflex to free T4) to be done at baseline on the same day of treatment (but prior to administration) and then as clinically indicated while on protocol treatment.

q. Neoadjuvant participants must undergo disease assessments and tumor measurements via RECIST 1.1 at baseline and after the 3rd pre-operative dose/before Surgery (Weeks 7-12, timing per site discretion). Disease assessments then occur every 12 weeks thereafter until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. In the case of a variation in scan schedule due to early or missed or delayed scans, the following scan is to be scheduled at the appropriate interval from the date of prior total body scan. If the interval between scans and the start of Adjuvant therapy exceeds 42 days, repeat imaging must be obtained. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium.

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.

v. Participants 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. Participants 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.

w. Neoadjuvant Arm: pembrolizumab (MK-3475) 200 mg flat dosing IV every 3 weeks for 3 doses followed by surgical resection. Post-operative dosing every 3 weeks x 15 doses (18 doses total).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. Therefore, PET-CT is not allowed as an imaging modality for S1801. Extremity melanomas must be imaged using CT with intravenous contrast or MRI with and without gadolinium.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 **RECIST Objective status at each disease evaluation**:

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to participants with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

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.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. **Objective status notes**

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a participant who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. 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.

6. 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 participant could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 **RECIST Best Response**. This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Progression before surgery

a. Progression of disease per RECIST 1.1 before surgery such that the participant cannot receive the planned surgery or requires additional surgery.

Note: Progression of disease that maintains the ability to undergo the planned surgery is not criteria for removal from treatment.

10.5 Relapse after surgery

Appearance of any new metastatic lesion/site.

a. 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.

b. Any enlargement in lymph nodes >1 cm in short axis and >50% from baseline must be biopsied to rule out relapse of disease.

c. 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 participant 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.

10.6 Pathologic Response

In prior studies using neoadjuvant targeted (BRAF/MEK inhibitor) and neoadjuvant immune checkpoint blockade therapy, previously agreed upon standard definitions of pathologic response are:

- Complete pathologic response (path CR): the complete absence of viable tumor cells in the surgically resected post-treatment specimen.
- Partial pathologic response (path PR): admixture of viable tumor cells but these comprise less than 50% of the treated tumor bed surface area together with evidence of treatment effect, including necrosis, fibrosis, and a lymphohistiocytic inflammatory infiltrate including aggregates of pigmented macrophages (tumoral melanosis).
- Pathologic non-response (path NR): admixture of viable tumor cells and these comprise greater than 50% of the treated tumor bed surface area together with evidence of treatment effect, including necrosis, fibrosis, and a lymphohistiocytic inflammatory infiltrate including aggregates of pigmented macrophages (tumoral melanosis).

10.7 **iRECIST Objective status at each disease evaluation:**

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

New lesions: All measurable lesions not present at baseline up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as new target lesions (NTL). All other new lesions (not present at baseline) including any measurable new lesions over and above the 5 new target lesions should be identified as new lesions, non-target (NLNT). Measurements must be provided for NTL, while presence or absence must be noted for NLNT.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to participants with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Immune-related Unconfirmed Progression (iUPD)**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target lesions over smallest sum observed (over baseline or nadir) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Do not include the sum of diameters of NTL. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration.

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

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

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.

e. **Immune-related Confirmed Progression (iCPD)**: Can only be reported in the assessment immediately following iUPD. One or more of the following must occur:

- An absolute increase of at least 0.5 cm in the sum of target lesions over the sum observed at iUPD. Do not include the sum of diameters of NTL
- An absolute increase of at least 0.5 cm in the sum of NTL over the sum observed at iUPD. Do not include the sum of diameters of target lesions.
- Clear worsening of unequivocal progression of non-measurable disease in the opinion of the treating physician as documented at iUPD (an explanation must be provided).
- Unequivocal progression, in the opinion of the treating investigator, of new non-target lesions (NNTL) initially documented at iUPD
- Any additional cause of progression, as defined in 10.7a, that was not present at iUPD.

f. **Immune-related Complete Response (iCR):** Can only occur after an assessment of iUPD, but not necessarily in the assessment immediately following iUPD. Cannot occur after iCPD**.** Complete disappearance of all lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target, non-target, NTL, or NLNT) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

g. **Immune-related Partial Response (iPR):** Can only occur after an assessment of iUPD, but not necessarily in the assessment immediately following iUPD. Cannot occur after iCPD. Applies only to participants with at least one measurable lesion at baseline. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target lesions present at baseline. Do not include the sum of diameters of NTL. No unequivocal progression of non-measurable disease. No new lesions other than those documented at iUPD. No increase in the sum of diameters of NTL, or an increase of less than 0.5 cm. All target lesions must be assessed using the same techniques as baseline.

h. **Immune-related Stable Disease (iSD):** Can only occur after an assessment of iUPD, but not necessarily in the assessment immediately following iUPD. Cannot occur after iCPD. Does not qualify for iCR, iPR, iUPD or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

i. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

j. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

10.8 Objective status notes

Non-measurable disease does not affect objective Status in determination of iCR (must be absent--a participant who otherwise has a iCR, but who has non-measurable disease present or not assessed, will be classified as having an iPR). However, non-measurable lesions are included in determination of iPD (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

a. An objective status of iPR or irD cannot follow one of iCR. iSD can follow iPR only in the rare case that tumor increases too little to qualify as iPD, but enough that a previously documented 30% decrease no longer holds.

b. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not iPD unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

c. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

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

e. Appearance of new pleural effusions does not constitute unequivocal iPD 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 iPD, since the fluid status of the participant could alter the size of the effusion.

f. If iCR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.9 iRECIST Best Response

This is calculated from the sequence of iRECIST objective statuses. *(12)*

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before iUPD or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before iUPD or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before iUPD or symptomatic deterioration, but not qualifying as anything else above.

f. iCR: Two or more objective statuses of iCR a minimum of four weeks apart documented before iCPD or symptomatic deterioration, but not qualifying as CR.

g. iPR: Two or more objective statuses of iPR or better a minimum of four weeks apart documented before iCPD or symptomatic deterioration, but not qualifying as iCR, CR or PR.

h. Unconfirmed iCR: One objective status of iCR documented before iCPD or symptomatic deterioration but not qualifying as CR, PR, unconfirmed CR, iCR or iPR.

i. Unconfirmed iPR: One objective status of iPR documented before iCPD or symptomatic deterioration but not qualifying as CR, PR, unconfirmed CR, unconfirmed PR, iCR, iPR or unconfirmed iCR.

j. iSD: At least one objective status of iSD before iCPD or symptomatic deterioration, but not qualifying as anything else above.

k. iUPD: Objective status of iUPD within 12 weeks of registration, before symptomatic deterioration or iCPD and not qualifying anything else above. There can be multiple IUPD assessments with no iCPD when the original cause of iUPD persists and no new causes of progression appear.

l. iCPD: An objective status of iCPD, which must be documented a minimum of four weeks apart from and immediately follow an objective status of iUPD and must be documented before symptomatic deterioration.

m. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

n. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies

10.10 Event-Free Survival

Measured from date of randomization to date of first: documentation of progression that renders participant unable to receive planned protocol surgery, off protocol therapy for any reason without subsequent protocol surgery (with one exception noted below), failure to begin adjuvant therapy within 84 days after surgery, relapse after surgery or death due to any cause. Participants last known to be alive and event-free are censored at date of last contact. On both arms, all participants who do not register for adjuvant therapy (for whatever reason) will be assigned the event time of 84 days.

Patients treated on the neo-adjuvant arm who achieve an unconfirmed PR or CR (per RECIST 1.1) at the first protocol disease assessment and choose not to undergo protocol surgery will not be counted as an event if the PR or CR is confirmed prior to starting any non-protocol therapy other than pembrolizumab. Such patients will not have an event when not receiving protocol surgery, and their EFS will be measured from the date of randomization to the first of relapse or death due to any causes with patients last known to be alive without relapse censored at the date of last contact. All other patients who do not receive protocol surgery will be assigned the EFS event time of 84 days.

10.11 Length of disease control

Measured from date of randomization to date of the first of the following events: progression such that the participant cannot receive protocol surgery, protocol surgery that does not render the participant disease-free, relapse after surgery that did render a participant disease-free, death due to any cause; participants last known to be alive without any of these events will be censored at the date of last contact.

10.12 Length of loco-regional control

Measured from date of randomization to date of the first of the following events: progression such that the participant cannot receive protocol surgery, protocol surgery that does not render the participant disease-free, relapse at the primary site and pre-randomization defined regional nodal basins after surgery that did render a participant disease-free; participants last known to be without any of these events will be censored at the date of death or date of recurrence outside of the primary site or pre-randomization defined nodal basin, whichever comes first.

10.13 Overall Survival

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

10.14 Performance Status

Participants 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 **S1404** accrual, 43% of **S1404** participants would have been eligible for this neoadjuvant protocol. **S1404** has enrolled an average 80 participants/month. Not all sites participating in **S1404** will necessarily participate in this trial, so we anticipate that approximately 24 participants/month would enroll in this trial.

11.2 Analysis plan and sample size justification for primary objective

Based on EFS trends in this participant population, we will use exponential-mixture cure models to describe EFS patterns in the arms. Based on Weber 2017, we assume that on the adjuvant pembrolizumab (MK-3475) arm (null hypothesis) 60% participants will be long-term survivors (or cured or not observed to have an event during the finite follow-up of the trial) and that median EFS for participants who are not long-term survivors will be 2 years. We power this study to detect an alternative EFS in the neoadjuvant arm with 70% of participants being long-term survivors and median EFS among those who are not long-term survivors of 2.5 years. We note that these survival patterns do not follow a proportional hazards assumption and that average hazard ratios from Cox models are expected to become more null with additional follow-up.

We assume 1:1 randomization, accrual over 2 years, and up to10 years of follow-up after randomization. Under these assumptions the average hazard ratio under the alternative is 0.64. Under the alternative, with a sample size of 500 eligible participants (250/arm), 100% of expected events is 104 events across both arms. At 50% of expected events (51 events, expected approximately when accrual completes), we will perform a futility test testing the alternative hazard ratio from a Cox regression model at the one-sided 2.5% level. No formal interim test of efficacy will be performed. Under the null hypothesis the probability of stopping early for futility is 45% and under the alternative is 2%. The final analysis will consist of a log-rank test of the null hypothesis at the two-sided 15% level (expected 1.5 years after accrual completes). The power of this design is 81%.

11.3 Sample size re-design

Because accrual to the study has been slower than anticipated, it is expected that 100% of events may be reached before accrual to the study completes, and so the total sample size of the study will be adjusted as follows.

To account for the slower than anticipated accrual rate, a total of 336 eligible, randomized patients will be accrued. If up to 1.5% of patients are not eligible, up to 342 patients will be registered. With the same assumptions for EFS as in the original design, this design should have the same power as the original design using the same alpha. We expect to reach full events within 6 months of completing accrual.

11.4 Secondary endpoints and analyses

OS, local/regional control, and disease control will be estimated using the Kaplan-Meier method and compared between arms using log-rank tests and Cox regression models. Fisher's exact test will be used to compare the number of pembrolizumab (MK-3475) doses received by participants on each treatment arm. Pathologic response, RECIST 1.1

response rates, iRECIST response rates will be tabulated for the neoadjuvant arm and exact 95% confidence intervals will be constructed. For each arm, 250 participants will be sufficient to estimate toxicity to within $\pm$ 6%. Any toxicity occurring with at least 1% probability is likely to be seen at least once (99% probability).

Primary analyses will all be intent-to-treat. We will perform additional analyses per protocol, to understand how variation in treatment in the neoadjuvant arm can impact the analyses.

11.5 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the 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.

After 20, 40, and 60 eligible participants are randomized to the neoadjuvant arm, the following proportions will be tabulated and provided to the DSMC: 1) proportion of participants who develop a higher disease stage (i.e., are upstaged) between randomization and surgery, 2) proportion of participants who become unresectable prior to surgery, and 3) proportion of participants who become ineligible for surgery due to toxicity. At each analysis, we will evaluate whether any of the proportions crosses one of the following thresholds: 1) proportion of participants who develop a higher disease stage (i.e., are upstaged) between randomization and surgery is greater than 25%, 2) proportion of participants who become unresectable prior to surgery is greater than 16%, or 3) proportion of participants who become ineligible for surgery due to toxicity is greater than 5%. If any proportion crosses the corresponding threshold, accrual to the study will be suspended while the study team reviews and evaluates the data from the neoadjuvant arm. Accrual will only re-open after the DSMC reviews the study team evaluation and approves any protocol modifications if proposed.

12.0 DISCIPLINE REVIEW

12.1 Surgical Review and Quality Assurance

All surgeries performed as part of this study will undergo a pathologic response assessment. Refer to Section 15 for specimen submission and labeling instructions. The goal of this review is to verify that the resection was done according to the criteria specified in the protocol (Section 18.1). The central surgery review will evaluate whether the planned surgical intervention does not change in response to systemic therapy or randomization. This minimizes variables influencing relapse or disease progression by avoiding incomplete or lesser surgery in participants receiving upfront systemic treatment (Neoadjuvant Arm).

Surgical management should follow principles outlined in Section 18.1.

The surgical note originating before study entry describing the planned surgical intervention and the operative report performed on study as part of **S1801** should be submitted to **S1801** Surgical Chair for review. The surgical quality monitoring will be completed by the Surgical Study Chair (Dr. Vernon Sondak). Surgical data including operative notes and pathology reports will be reviewed. Any deviations in surgical quality that are identified will be addressed by the study chairs, Drs. Patel and Grossmann.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Participants must be registered prior to initiation of treatment (no more than 14 calendar days prior to planned start of treatment.

13.2 Investigator/Site Registration

Prior to the recruitment of a participant 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.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent.
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- 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	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (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:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principle (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role 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.

13.4 CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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

a. **IRB Approval:**

For 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 after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). 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 for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. 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).

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 in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;

- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

b. **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 based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- 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 **S1801.**
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

c. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU 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 participants waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

d. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling

investigator's status with NCI or their affiliated networks.

13.5 Oncology Patient Enrollment Network (OPEN) Registration Requirements

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 participant registration/randomization assignment. OPEN will populate the participant enrollment data in NCI's clinical data management system, Medidata Rave.
Requirements for OPEN access:

- A valid CTEP-IAM account;
- 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 participant 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 participant 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:

- Participant has met all eligibility criteria within the protocol stated timeframes; and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All participants 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. 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.

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

- Institution CTEP ID
- Protocol Number
- Registration Step
- Treating Investigator
- Credit Investigator
- Participant Initials
- Participant's Date of Birth
- Participant SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- Country of Residence
- ZIP Code
- Gender (select one):

  - Female Gender
  - Male Gender
- Ethnicity (select one):
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Unknown
- 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
- Race (select all that apply):
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or other Pacific Islander
  - White
  - Unknown

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Participants 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 Requirement

Data must be submitted according to the protocol requirements for **ALL** participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible. Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Data Submission Procedures

a. 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://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must

hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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 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 888/823-5923 or by e-mail at ctsucontact@westat.com

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.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.

14.3 Data Submission Overview and Timepoints

Please reference the ***ORP Manual*** on the CRA Workbench (www.swog.org) for detailed General Forms and Guidelines, as well as some disease-specific and study-specific forms. There are also many other chapters available in the manual to be used for regular reference of SWOG processes and procedures.

a. **STEP 1 REGISTRATION**

1. WITHIN 15 DAYS AFTER RANDOMIZATION:

Submit the following:

S1801 Onstudy Form

S1801 Baseline Tumor Assessment Form

S1801 Planned Surgery Form

S1801 Baseline Abnormalities Form

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

*Pathology reports documenting histologic confirmation (must include confirmation of any N-category or M-category resectable site).

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

2. NEOADJUVANT ARM: WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT (1 CYCLE = 3 WEEKS):

Submit the following:

S1801 Treatment Form

S1801 Adverse Event Form

3. NEOADJUVANT ARM: AFTER RANDOMIZATION, WITHIN 15 DAYS AFTER EACH DISEASE ASSESSMENT UNTIL SURGERY OR RECURRENCE (AS DEFINED IN SECTION 10.0) OR 5 YEARS AFTER RANDOMIZATION (WHICHEVER OCCURS FIRST):

Submit the following:

Follow Up Tumor Assessment Form (iRECIST)

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

4. WITHIN 15 DAYS OF DISCONTINUATION OF STEP 1 PROTOCOL TREATMENT (INCLUDES PARTICIPANTS RANDOMIZED TO THE ADJUVANT ARM WHO DO NOT REGISTER TO STEP 2):

Submit the following:

If participant will not receive surgery on protocol, submit the Notice that Participant Will Not Receive Protocol Surgery

NEOADJUVANT ARM:

Off Treatment Notice documenting reasons for off treatment

S1801 Treatment Form

S1801 Adverse Event Form

b. **STEP 2 REGISTRATION: SURGERY**

1. WITHIN 84 DAYS AFTER SURGERY:

Submit the following:

S1801 Post-Surgery Form

S1801 Adverse Event Form

*Operative and Pathology Reports

If participant received radiation therapy:

*Anonymized Radiation Treatment Record including the date, fraction #, daily dose for each treatment fraction, reason for any missed days of RT, and the Treatment Prescription page which has the Radiation Oncologist's treatment prescription for the case PRIOR to the start of RT

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

S1801 Post-Surgery Disease Assessment Form

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

Off Treatment Notice documenting reasons for off treatment

If participant will not receive surgery on protocol, submit the Notice that Participant Will Not Receive Protocol Surgery

c. **STEP 3 REGISTRATION: PEMBROLIZUMAB (MK-3475)**

1. WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT (1 CYCLE = 3 WEEKS):

Submit the following:

S1801 Treatment Form

S1801 Adverse Event Form

2. WITHIN 15 DAYS AFTER EACH DISEASE ASSESSMENT (SEE STUDY CALENDAR FOR SCHEDULE) UNTIL RECURRENCE (AS DEFINED IN SECTION 10.0) OR 5 YEARS AFTER RANDOMIZATION (WHICHEVER OCCURS FIRST):

Submit the following:

S1801 Post-Surgery Disease Assessment Form

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

3. WITHIN 15 DAYS OF DISCONTINUATION STEP 2 OF PROTOCOL TREATMENT:

Submit the following:

Off Treatment Notice documenting reasons for off treatment

S1801 Treatment Form

S1801 Adverse Event Form

d. **FOR ALL REGISTRATION STEPS:**

1. ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 6 MONTHS FOR 2 YEARS (SEE STUDY CALENDAR FOR SCHEDULE), THEN YEARLY THROUGH YEAR 10:

   S1801 Follow-Up Form

   S1801 Late Adverse Events Form

2. WITHIN 15 DAYS AFTER PROGRESSION OR RELAPSE:

   Submit the following:

   S1801 Follow-Up Form

   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®).

3. WITHIN 30 DAYS AFTER KNOWLEDGE OF DEATH:
   Submit the Notice of Death, and all of the items listed in Section 14.3d.1 (if the participant was still on protocol treatment) or the Follow-Up Form (if the participant was off protocol treatment) documenting death information.

14.4 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see above for details.

15.0 SPECIAL INSTRUCTIONS

15.1 Submission of surgical tissue for pathologic response assessment (Required for all participants on the Neoadjuvant arm).

Note: all specimens are to be shipped to Lab #201 (see Section 15.3).

a. The submission of surgical tissue for pathologic response assessment is required for all participants on the Neoadjuvant arm. Submit the following from the surgically resected specimen:

- all tissue blocks, OR
- two (2) representative unstained FFPE slides per block, OR
- one (1) representative H&E slide and one (1) representative unstained slide per block.

Note: A three-dimensional macroscopic measurement of the largest grossly positive identified lymph node should be provided in the gross description accompanying the specimen. Any grossly positive lymph node measuring < 5 cm in greatest dimension should be entirely submitted for histopathologic assessment at 2 mm serially sectioned intervals. For any grossly positive lymph node measuring > 5 cm in greatest dimension, representative sections of the largest lymph nodes may be utilized to avoid oversampling as follows: following serial sectioning of each lymph node, for those nodes > 5 cm, sections representing a ***complete cross section of the entire surface area*** should be submitted per 1 cm of each

grossly positive lymph node. Sections submitted should include grossly obvious tumor. All grossly positive lymph nodes < 5cm in specimens (in specimens where the largest node(s) exceeds 5 cm) should be submitted entirely as described above.

Note: For additional training guidance on the collection of this tissue, please visit ctsu.org or contact vprieto@mdanderson.org.

b. Ship within 3 months after surgery. Ship on cool packs.

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

Refer to the general labeling, packaging, and shipping instructions at https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures and ship to Lab #201 (SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division).

15.2 Specimens for Banking (Optional)

a. Participants must be offered the opportunity to participate in specimen banking. If participant consents, the following specimens must be submitted:

1. Entire block of formalin-fixed paraffin-embedded (FFPE) tissue (from primary, lymph node, and metastasis if present) submitted at the following times:
   - Baseline
   - Relapse

   Note: If the institution cannot release a pathology paraffin embedded block, then 10 unstained slides (5 um each), and one H&E (Hematoxylin and Eosin) stained slide may be instead.

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

2. Collect 30 mL whole blood in red/black marble top (SST) vacutainer tubes without anticoagulant or in red top tubes without anticoagulant. Collect at the following times:
   - Cycle 1
   - Cycle 5
   - Cycle 9
   - End of Treatment (Cycle 18)
   - When participant is removed from protocol therapy for any reason
   - Relapse, after starting adjuvant therapy.

3. **Process whole blood to serum** and ship with dry ice according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures

4. Collect 30 mL whole blood in pink/lavender top vacutainer tubes with EDTA. Collect at the following times:
   - Cycle 1
   - Cycle 5,

- Cycle 9,
- End of Treatment (Cycle 18)
- When participant is removed from protocol therapy for any reason
- Relapse, after starting adjuvant therapy.

5. Do not process. Ship at ambient temperature according to guidelines provided by SWOG Biospecimen Bank:
   - https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures

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

15.3 SHIPPING SAMPLES

a. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

b. Specimen Labeling

1. FFPE tissue specimens must be labeled with the following:
   - SWOG participant number
   - Redacted Pathology Report that includes pathology ID# or SWOG participant number
   - Participant initials
   - Collection date (date the specimen was collected from the participant)
   - Specify whether the tissue is from primary (P), metastatic (M), or normal/uninvolved (N)
   - For lymph nodes, indicate it positive (+) or negative (-) for tumor involvement
   - Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-1, B, etc.) must be on both the specimen label and the pathology report in order for the Bank to adequately match the specimen with any findings in the pathology report

2. Liquid specimens must be labeled with the following:
   - SWOG participant number
   - Participant initials
   - Collection date (date the specimen was collected from the participant)
   - Specimen type (e.g. blood, serum, etc.)

c. Whole blood specimens should be shipped on same day as collection and shipped overnight Monday - Friday, for Tuesday - Saturday delivery. If shipping for Saturday delivery, please mark for Saturday delivery and notify the Bank.

d. For additional information about labeling and shipping instructions for fresh blood or bone marrow, refer to the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

e. SWOG Specimen Tracking System (STS)

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 (http://swog.org) Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option “SWOG – SWOG – CTSU”). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

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. The Specimen Submission Form is NOT required when the online system is used.

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 (https://spectrack.crab.org/Instructions); 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 Biospecimen Bank
Solid Tissue, Myeloma, and Lymphoma Division
Phone: 614-722-2865
FAX: 614-722-2897
E-mail: bpcbank@nationwidechildrens.org

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 the Pharmaceutical Company(ies) (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:

1. 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 participant or participant'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.

2. 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"):

    a. 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.

    b. 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.

    c. 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.

3. 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.

4. 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.

5. 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.

6. 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.

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 participants 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 participant 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 should be submitted to CTEP per NCI guideline s for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

d. Other recipients of adverse event reports

The DCTD/NCI will forward reports and documentation to the FDA and drug companies as required

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the participant must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the participant 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 pembrolizumab (MK-3475). 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] pembrolizumab (MK-3475).

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 participant 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,

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 310-897-7404 and 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. 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 participant has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the Pregnancy, puerperium and perinatal conditions SOC**.

   Additionally, the pregnancy outcome for participants on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a participant death.

3. **Death Neonatal** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth" 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, "Death neonatal"** 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 participant 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 301-897-7404. 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 AJCC 8th Edition TNM Definitions for Pathologic Staging

18.3 Translational Medicine: Pathological Response

18.4 Specimen Banking Instructions for the SWOG Biospecimen Bank

18.1 Surgical Management Guidelines

a. Excision of the Primary Site

These guidelines apply to participants presenting with an intact primary and planning for a lymph node dissection as their surgical procedure.

Primary Tumor: All such participants must undergo adequate wide excision of the primary tumor meeting the suggested criteria outlined below, if not already completed. 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 participants enrolled with regional disease, including recurrence after initial presentation, must have clinically detectable, surgically resectable disease (regional or distant disease). Participants 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 they have been deemed surgically resectable by a surgeon, 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 participants with histologic or clinical evidence of regional lymph node involvement enrolled on this trial. (Participants with satellite/in transit disease and no evidence of nodal involvement may be enrolled without 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. Participants 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.

1. Cervical Lymph Node Dissection

   A classic radical neck dissection is not required and is discouraged. Preservation of the internal jugular vein, sternocleidomastoid muscle, and eleventh cranial nerve ("functional neck dissection") should be performed whenever possible. 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 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. 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. Participants 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.

e. Resection of Distant Metastatic Disease

Participants with Stage IV melanoma metastatic to skin, subcutaneous sites, distant lymph nodes or lung or other visceral sites are allowed provided sites are resectable per surgical note source document and they have NOT undergone prohibited systemic therapy for their metastatic disease (see Section 7.2) and the participant otherwise meets the eligibility criteria outlined in Section 5.0. Participants 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 participant being declared ineligible. Stereotactic radiosurgery or ablative techniques that do not involve resection of the tumor to negative margins are not acceptable.

18.2 AJCC 8th Edition TNM Definitions for Pathologic Staging

a. **Table 1 TNM Definitions for Stage III Melanoma: Pathologic Staging**

Stage	TNM	Description
IIIB	T0	No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma
	N1b	One clinically detected node without micrometastasis
	N1c	No regional lymph node disease with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIC	T0	No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma
	N2b	2-3 regional lymph nodes, at least one of which was clinically detected without in-transit, satellite, and/or microsatellite metastases
	N2c	One clinically occult or clinically detected regional lymph node with in-transit, satellite, and/or microsatellite metastases
	N3b	4 or more regional lymph nodes, at least one of which was clinically detected, or presence of any number of matted nodes without in-transit, satellite, and/or microsatellite metastases
	N3c	2 or more clinically occult or clinically detected regional lymph nodes and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIA	T1a/b-T2a	T1a= Melanomas < 0.8 mm in thickness without ulceration
		T1b = Melanomas <0.8 mm in thickness with ulceration; Melanomas 0.8-1.0 mm in thickness with or without ulceration
		T2a = Melanomas >1.0-2.0 mm in thickness without ulceration
	N1a	One clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
	N2a	2 or 3 clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIB	T1a/b-T2a	T1a= Melanomas < 0.8 mm in thickness without ulceration
		T1b = Melanomas <0.8 mm in thickness with ulceration; Melanomas 0.8-1.0 mm in thickness with or without ulceration
		T2a = Melanomas >1.0-2.0 mm in thickness without ulceration
	N1 b/c or N2b	N1b = One clinically detected regional lymph node without in-transit, satellite, and/or microsatellite metastases
		N1c = No regional lymph node disease with in-transit, satellite, and/or microsatellite metastases
		N2b = 2-3 regional lymph nodes, at least one of which was clinically detected without in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIB	T2b/T3a	T2b = Melanomas > 1.0-2.0 mm in thickness with ulceration
		T3a = Melanomas > 2.0-4.0 mm in thickness without ulceration
	N1a - N2b	N1a= One clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N1b= One clinically detected regional lymph node without in-transit, satellite, and/or microsatellite metastases
		N1c= No regional lymph node disease with in-transit, satellite, and/or microsatellite metastases

Stage	TNM	Description
		N2a= 2 or 3 clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIC	T1a-T3a	T1a = Melanomas < 0.8 mm in thickness without ulceration
		T1b= Melanomas <0.8 mm in thickness with ulceration; Melanomas 0.8-1.0 mm in thickness with or without ulceration
		T2a= Melanomas >1.0-2.0 mm in thickness without ulceration
		T2b= Melanomas > 1.0-2.0 mm in thickness with ulceration
		T3a= Melanomas > 2.0-4.0 mm in thickness without ulceration
	N2c or N3a/b/c	N2c= One clinically occult or clinically detected regional lymph node with in-transit, satellite, and/or microsatellite metastases
		N3a= 4 or more clinically occult regional lymph nodes (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N3c= 2 or more clinically occult or clinically detected regional lymph nodes and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIC	T3b/T4a	T3b= Melanomas > 2.0-4.0 mm in thickness with ulceration
		T4a= Melanomas > 4.0 mm in thickness without ulceration
	Any N ≥N1	N1a= One clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N1b = One clinically detected regional lymph node without in-transit, satellite, and/or microsatellite metastases
		N1c= No regional lymph node disease with in-transit, satellite, and/or microsatellite metastases
		N2a = 2 or 3 clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N2b = 2-3 regional lymph nodes, at least one of which was clinically detected without in-transit, satellite, and/or microsatellite metastases
		N2c = One clinically occult or clinically detected regional lymph node with in-transit, satellite, and/or microsatellite metastases
		N3a= 4 or more clinically occult regional lymph nodes (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N3b= 4 or more regional lymph nodes, at least one of which was clinically detected, or presence of any number of matted nodes without in-transit, satellite, and/or microsatellite metastases
		N3c = 2 or more clinically occult or clinically detected regional lymph nodes and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIIC	T4b	T4b= Melanomas > 4.0 mm in thickness with ulceration
	N1a-N2c	N1a= One clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N1b = One clinically detected regional lymph node without in-transit, satellite, and/or microsatellite metastases
		N1c= No regional lymph node disease with in-transit, satellite, and/or microsatellite metastases
		N2a = 2 or 3 clinically occult regional lymph node (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N2b = 2-3 regional lymph nodes, at least one of which was clinically detected without in-transit, satellite, and/or microsatellite metastases

Stage	TNM	Description
		N2c = One clinically occult or clinically detected regional lymph node with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease
IIID	T4b	T4b= Melanomas > 4.0 mm in thickness with ulceration
	N3a/b/c	N3a= 4 or more clinically occult regional lymph nodes (i.e., detected by SLN biopsy) without in-transit, satellite, and/or microsatellite metastases
		N3b= 4 or more regional lymph nodes, at least one of which was clinically detected, or presence of any number of matted nodes without in-transit, satellite, and/or microsatellite metastases
		N3c = 2 or more clinically occult or clinically detected regional lymph nodes and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastases
	M0	No evidence of distant disease

b. **Table 2 TNM Definitions for Stage IV Melanoma: Pathologic Staging**

IV		
	Any T, Tis	TX= Primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)
		T0= No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)
		Tis= Melanoma in situ
		T1a= Melanomas < 0.8 mm in thickness without ulceration
		T1b = Melanomas <0.8 mm in thickness with ulceration. Melanomas 0.8-1.0 mm in thickness with or without ulceration
		T2a = Melanomas >1.0-2.0 mm in thickness without ulceration
		T2b= Melanomas > 1.0-2.0 mm in thickness with ulceration
		T3a= Melanomas > 2.0-4.0 mm in thickness without ulceration
		T3b= Melanomas > 2.0-4.0 mm in thickness with ulceration
		T4a= Melanomas > 4.0 mm in thickness without ulceration
		T4b= Melanomas > 4.0 mm in thickness with ulceration
	M1	Evidence of distant metastasis with LDH elevated
T – primary tumor; N – regional lymph nodes; M – distant metastasis		
Adapted with permission from AJCC: Melanoma of the Skin. AJCC Cancer Staging Manual. 8th ed. Chicago, IL: Springer 2017, pp. 577-78.		

18.3 Translational Medicine: Pathological Response

Translational medicine study objective(s):

1) On the neoadjuvant arm, to estimate the complete pathologic response rate and compare different definitions of partial pathologic response.

2) To evaluate associations between pathologic responses and the endpoints of event-free survival and overall survival.

Background:

Pathologic response after neoadjuvant therapy as a surrogate for survival has been studied in breast cancer. However, the reliability of pathologic evaluation is controversial due to differing evaluation methods and definitions, as well as applicability to different subtypes of breast cancer. In melanoma, neoadjuvant therapy has been studied at only a few academic centers; however, collaborative efforts to standardize pathologic evaluation are underway. **S1801** affords an even greater opportunity for this effort and in addition, the opportunity to review a large cohort of neoadjuvant cases and establish guidelines and standardization for pathologic response evaluation.

1. Santa-Maria CA et al. Neoadjuvant Therapy for Early-Stage Breast Cancer: Current Practice, Controversies, and Future Directions *Oncology* 2015.

Statistical Plan:

The feasibility of specimen submission for this aim will be monitored as follows: the feasibility of obtaining full surgical specimens will first be evaluated after the first 10 participants are enrolled on the neoadjuvant arm. If difficulty exists at the site level releasing complete surgical specimens, SWOG will work with the local PIs to determine barriers and facilitate tissue release. The study team will continue to review and potentially modify the central path review specimen submission procedures until at least 85% of specimens are submitted. If this rate is not achieved in 20 consecutive participants (so 17/20 participants providing specimens) by the time 120 participants have undergone surgery on the neoadjuvant arm, the study team will re-visit the use a sub-study at a limited number of institutions for this objective.

The pathologic complete response (pCR) rate will be estimated on the neoadjuvant arm and exact 95% confidence intervals will be calculated. There is no current consensus definition of pathologic partial response (pPR). Some authors have proposed < 50% viable tumor, though others have argued that 40% necrosis should be considered a partial response. We will use the minimum p-value approach (Mazumdar and Glassman, Statistics in Medicine, 2000) to evaluate potential cut-points in percent viable tumor with respect to the outcome EFS for definitions of partial response. In addition, we will use Cox regression models to evaluate the association between the quantitative value of percent viable tumor and overall and event-free survival. We will use C-statistics to estimate the predictive ability of the quantitative and categorical versions of the data. In addition, associations between pCR and pPR (using the definition derived using EFS) and the outcome of overall survival will be assessed with log-rank tests and Cox regression models,

Laboratory conducting the testing:
The University of Texas MD Anderson
Department of Pathology, Immunohistochemistry Laboratory
Contact for this trial: Victor Prieto, M.D., Ph.D.
1515 Holcombe Blvd Unit 0085 – G1.3547
Houston, TX 77030
713/792-3187

Central review is essential to determine the extent of pathologic response in the post-treatment surgical excision specimens.

For this, the following are required from the surgical specimens for central review:

- all tissue blocks, OR
- two (2) unstained FFPE slides per block, OR
- one (1) H&E slide and one (1) unstained slide per block

To the extent that a consistent determination of pathologic response also correlates with pathologic response in other cancer types (notably breast), an accurate and consistent determination of pathologic response is critical.

A critical variable to a consistent pathologic review is consistent pathologic submission guidelines to ensure that the post-treatment surgically resected tumor bed has been adequately sampled when determining pathologic response.

Gross evaluation of the surgical specimen

For the most part, neoadjuvant trials in melanoma have been directed towards surgically resectable nodal disease. As such, the surgical specimen typically consists of regional lymphadenectomy specimens; however, for other specimen types, the same rules as below would apply. Gross examination of the excised regional lymph node basin should seek to identify all possible lymph nodes (including both grossly positive and negative nodes). Three dimensional measurements of all of the grossly positive nodes should be recorded, as the dimensions of the largest involved lymph node will direct subsequent tissue processing.

Histologic assessment by Dr. Victor Prieto:

(1) The largest contiguous viable deposit of metastatic melanoma (if there is viable tumor) will be recorded in two dimensions. This will be limited to contiguous viable tumor cells and will not include tumoral melanosis.

(2) The percentage of the entire apparent tumor bed surface area occupied by viable tumor will be designated as % Viable tumor.

(3) Viable extracapsular extension of melanoma tumor cells will be recorded as present or absent. If there is evidence of completely regressed extracapsular extension, then the extracapsular extension will be noted as “Present” (completely regressed)

(4) In addition, evidence of treatment effect will be recorded, including any of the following features and the relative percentages of each:
    (a) tumor necrosis (% of tumor bed)
    (b) tumoral melanosis and/or (% of tumor bed)
    (c) fibrosis (% of tumor bed)

Results of the testing will not be provided to the treating physicians or the participants.

18.4 Specimen Banking Instructions for the SWOG Biospecimen Bank

The SWOG Bank will receive formalin-fixed, paraffin-embedded (FFPE) tumor tissue as either blocks or unstained slides. Upon receipt, the Bank will accession, barcode, and bank all FFPE tissues at room temperature until distribution.

For each case, one H&E stained slide and one unstained slide will be sent to Dr. Victor Prieto for pathology review. These will be shipped with a redacted pathology report to Dr. Prieto in batches throughout the study.

The SWOG Bank will receive fresh whole blood in EDTA tubes at ambient temperature from up to 5 time points. Upon receipt, blood in EDTA tubes will be processed for plasma. After plasma processing, one tube (up to 10 mL blood) will be processed for buffy coat, and the remaining tubes (up to 20 mL) of blood will be processed for peripheral blood mononuclear cells (PBMCs) using a ficoll-hypaque gradient. Plasma will be divided into 1-mL aliquots, both buffy coat and plasma will be stored in a -80°C freezer for future studies.

The SWOG Bank will receive frozen serum aliquots from up to 5 time points. Upon receipt the Bank will accession, barcode and bank all serum aliquots in a -80°C freezer for future studies.