Official Title of Study:

A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma

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CLINICAL PROTOCOL CA045001/17-214-08

A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma

Protocol Amendment 03

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	19-May-2022	Key changes include: • Participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. • Nivolumab monotherapy dose for participants in Arm A and Arm B will be 480 mg IV (intravenous) Q4W (every four weeks) (participants < 40 kg: weight-based 6 mg/kg IV Q4W). • Maximum duration of the study is up to 2 years +100 days from the randomization of the last participant. • Tumor assessment evaluated by the Investigator only. • No further formal overall survival (OS) analyses will be performed. • Secondary and exploratory objectives except biomarker parameters will no longer be applicable. Biomarker sample collection will not be applicable. However, exploratory biomarker analysis on previously collected samples may be conducted.
Protocol Amendment 02	26-Aug-2021	Key changes include: • Clarified tumor tissue requirement. • Updated study treatment dose delay, resumption, and discontinuation, and adverse events management for NCI CTCAE version 5. Added permanent discontinuation criteria for bempegaldesleukin treatment related to CVA and TIA. Updated CVA management algorithm (Appendix 7). • Added cytokine release syndrome information and management/algorithm (Appendix 11). [redacted] • Updated projection of analysis times based on updated enrollment projection. • Added additional information on PFS assumptions and provided the estimated median PFS by arm. • Added provisional language for conducting OS final analysis at 60 months after last participant randomized if the planned OS event number is not reached by then. • Added additional sensitivity analyses for PFS and OS to account for potential non-proportional hazards in efficacy analyses. • Added information for SARS-C0V-2 infection and vaccine. • Updated Appendix 10 to include German-specific information (ca045001-revprot00a-de-specific and ca045001-revprot00b-de-specific). Incorporated Administrative Letter 03 and German-specific Administrative Letter 04.

Document	Date of Issue	Summary of Change
German-specific Administrative Letter 04	24-Aug-2020	Addresses 3 clarifications/inconsistencies of Revised Protocol 00b Germany Specific (dated 06-May-2020): [redacted] • In Section 7.4.1, removed the paragraph relating to Grade 3 or greater AEs that cause dose delay that was erroneously not removed. • In Section 9.8.3, removed the paragraph relating to a Grade 3 drug-related AE that results in a dose delay that was erroneously not removed.
Administrative Letter 03	09-Jul-2020	Addressed 4 clarifications/inconsistencies of Revised Protocol 01 in regard to: [redacted] • In Section 7.4.1, removed the paragraph relating to Grade 3 or greater AEs that cause dose delay that was erroneously not removed. • In Section 9.8.3, removed the paragraph relating to a Grade 3 drug-related AE that results in a dose delay that was erroneously not removed.
Revised Protocol 01	24-Feb-2020	• The sections on [redacted] Biomarker assessment were revised. • Nektar program updates were added. [redacted] • Study Design and Schema image were updated to include AJCC M stage change. • Internal inconsistencies were corrected. • Statistical analysis was updated to include one additional interim analysis of OS. • DoCR was removed as an Endpoint. • Appendices 2, 3, 4 and 6 were modified to include the latest updates. • Appendix 7 was added to include cerebrovascular accident management algorithm. As a result following Appendices were renumbered. • Appendix 8 was revised to include Mucosal Melanoma of the Head and Neck TNM definitions. • Appendix 10 was updated to include German-specific, Czech-specific and Ireland-specific amendments (ca045001-revprot00a). • Changes as per Admin Letter 01 and 02.
Administrative Letter 02	17-Sep-2018	Addresses four clarifications/inconsistencies of the protocol in regard to: [redacted] • Clarification on the brain imaging screening window in Table 2-1 and section 6.1 Exclusion Criteria

Document	Date of Issue	Summary of Change
Administrative Letter 01	08-Jun-2018	To correct study number to CA045001/17-214-08
Original Protocol	25-May-2018	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in progression free survival (PFS) (Hazard Ratio [HR] 1.09, 97% Confidence Interval [CI], 0.88-1.35) or objective response rate (ORR) compared to nivolumab monotherapy, and the significance threshold for overall survival (OS) was also not crossed at an interim analysis. Given there was no additional clinical benefit in the doublet therapy arm compared to the monotherapy arm for the primary endpoints of PFS and ORR, Bristol-Myers Squibb Company (BMS) and Nektar, in consultation with the Data Monitoring Committee (DMC), decided to unblind the trial and to perform no additional formal analyses for the OS endpoint. Furthermore, there was added toxicity with bempegaldesleukin plus nivolumab compared to nivolumab monotherapy, including a higher incidence of drug-related adverse events (AEs), drug-related serious adverse events (SAEs), and drug-related AEs leading to study treatment discontinuation.

Given that additional toxicities with no added efficacy were observed in the experimental arm, participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy.

On 14-Apr-2022, BMS and Nektar announced a joint decision to end the clinical development program for bempegaldesleukin in combination with nivolumab.

Minor formatting and typographical corrections have been made; therefore, they have not been summarized.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated title to remove PIVOT-IO-001.	This is a correction.
Summary	Updated text.	To align the Summary with updates made to the full protocol.
Table 2-2: On-Study Activities (CA045001)	Added that text related to bempegaldesleukin is not applicable.	No longer applicable as bempegaldesleukin will not be administered.
Table 2-2: On-Study Activities (CA045001)	Added new row for 'Administer Study Drug.'	To remove bempegaldesleukin and include updated nivolumab dose at 480 mg IV (intravenous) Q4W (every four weeks).
Table 2-2: On-Study Activities (CA045001)	Added that the following sections are not applicable per Protocol Amendment 03: Administer Study Drug,	Sections are no longer applicable as bempegaldesleukin will no longer be administered

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Administer Fluids, Review Hydration Guidelines with Participants, Oral Hydration Follow-up, Biomarker Assessments, Biomarker Sample Collection, Stool Sample Collection, Tumor Biopsy, [redacted]	
Table 2-2: On-Study Activities (CA045001)	• Updated body and brain imaging to include that Investigator assessment will be used instead of blinded independent central review (BICR). • Updated body and brain imaging assessment to include that imaging assessment will be performed per schedule of local standard of care (SOC).	Primary endpoints of PFS and ORR by BICR assessment were completed. Investigator tumor assessment will continue.
Table 2-3: Long-term Procedural Follow-Up (CA045001)	Added that the following sections were not applicable per Protocol Amendment 03: Subsequent Anti-Cancer Therapy, [redacted] Biomarker Assessments (Blood PD Sampling and Tumor Biopsy) [redacted].	Additional biomarker sample collection will not be applicable. However, exploratory biomarker analysis may be conducted.
	Updated body and brain imaging to include that Investigator	Primary endpoints of PFS and ORR by BICR assessment were

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	assessment will be used instead of BICR.	completed. Investigator tumor assessment will continue.
	Added that footnote b is not applicable per Protocol Amendment 03.	No further formal OS analyses will be conducted.
Section 3: Introduction	Added details on how Investigators can proceed with study treatments.	Participants are required to discontinue bempegaldesleukin.
Section 3.1.1: Research Hypothesis	Added that section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.
Section 3.3.3: Bempegaldesleukin and Nivolumab Benefit and Risk Assessment	Added that bempegaldesleukin did not show a benefit.	Given that additional toxicities with no added efficacy were observed in the experimental arm, the risk benefit was updated.
Section 4: Objectives and Endpoints	Added that secondary and exploratory endpoints except biomarker sample collection are not applicable per Protocol Amendment 03.	Additional data for secondary and exploratory objectives, except biomarker parameters, will not be captured.
Section 5.1: Overall Design	Added that original treatments are not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.
Figure 5.1-1: Study Schematic	Added that per Protocol Amendment 03 participants in Arm A are required to discontinue bempegaldesleukin and continue nivolumab monotherapy.	Participants are required to discontinue bempegaldesleukin.
	Adjusted maximum study duration from 5 years to 2 years +100 days.	Since further formal OS analyses will not be conducted the maximum study duration is being shortened to the nivolumab treatment period (2 years) +100 days for safety follow-up.
Section 5.1.2: Treatment Period	Added details on how Investigators can proceed with study treatments.	Participants receiving bempegaldesleukin plus nivolumab should discontinue

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		bempegaldesleukin and will receive nivolumab monotherapy.
Section 5.1.3: Long-term Follow-up	Adjusted maximum study duration from 5 years to 2 years +100 days.	Since further formal OS analyses will not be conducted the maximum study duration is being shortened to the nivolumab treatment period (2 years) +100 days for safety follow-up.
	Added that formal survival analysis is not applicable per Protocol Amendment 03.	No further formal OS analyses will be conducted.
Section 5.3: End of Study Definition	Added that OS analyses will not be performed.	No further formal OS analysis will be performed.
	Added text that the total duration of the study for the OS endpoint is not applicable per Protocol Amendment 03.	Since further formal OS analyses will not be conducted the maximum study duration is being shortened to the nivolumab treatment period (2 years) +100 days for safety follow-up.
Section 5.4.5: Rationale for Open-Label Design Section 5.5.1: Justification for Dose of Bempegaldesleukin Section 5.5.3: Rationale for Bempegaldesleukin/Nivolumab Combination Dose	Added that section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.
Section 5.4.7: Duration of Treatment with Nivolumab/ Bempegaldesleukin	Added that paragraph referring to bempegaldesleukin is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.
Section 5.5.2: Justification for Dose of Nivolumab	• Added that participants can continue on nivolumab monotherapy. • Updated dose of nivolumab to 480 mg IV Q4W. • Added that participants < 40 kg will be administered a	Changed dose for participants continuing nivolumab monotherapy to the approved nivolumab dose.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.	
Section 5.5.4: Justification for Dose for Adolescents	• Updated dose of nivolumab to 480 mg IV Q4W. • Changed weight base for nivolumab from 4.5 mg/kg IV Q3W (every three weeks) to 6 mg/kg IV Q4W.	Changed dose for participants continuing nivolumab monotherapy to the approved nivolumab dose.
Section 6.3: Lifestyle Restrictions	Added that section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.
Section 7: Treatment	• Added that participants can continue on nivolumab monotherapy. • Updated dose of nivolumab to 480 mg IV Q4W. • Added weight base for nivolumab of 6 mg/kg IV Q4W.	Changed dose for participants continuing nivolumab monotherapy to the approved nivolumab dose.
Section 7.1: Treatments Administered	• Added that participants can continue on nivolumab monotherapy. • Updated dose of nivolumab to 480 mg IV Q4W. • Changed weight base for nivolumab from 4.5 mg/kg IV Q3W to 6 mg/kg IV Q4W.	Changed dose for participants continuing nivolumab monotherapy to the approved nivolumab dose.
Section 7.1.1: Bempegaldesleukin Dosing Section 7.4.1.1: Dose Modification Criteria for Bempegaldesleukin and Nivolumab for Cycle 1 ALT/AST Elevations	Added that this section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.3.1: Bempegaldesleukin-induced Eosinophilia Section 7.4.3.2: Eosinophilic Disorders Section 7.4.5.2: Management Algorithm for Cytokine-Release Syndrome		
Section 7.1.1.1: Hydration Guidelines	Added that this section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin and hydration guidelines were only relevant for bempegaldesleukin administration.
Section 7.1.2: Nivolumab Dosing	• Added that participants can continue on nivolumab monotherapy. • Updated dose of nivolumab to 480 mg IV Q4W. • Changed weight-based dosage for nivolumab from 4.5 mg/kg IV Q3W to 6 mg/kg IV Q4W, and added details on infusion.	Changed dose for participants continuing nivolumab monotherapy to the approved nivolumab dose.
Section 7.3: Blinding	Added that treatment assignment will not be blinded to Sponsor.	Sponsor has been unblinded to treatment assignment since no further formal efficacy analyses have been conducted.
Section 7.4: Dosage Modification Section 7.4.1: Nivolumab and Bempegaldesleukin Dose Delay, and Discontinuation Criteria Section 7.4.6: Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions	Added that text related to bempegaldesleukin is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.6: Treatment Compliance Section 7.7.4.2: Restricted Treatments Section 7.7.5: Permitted Therapy		
Section 7.4.5.1: Management Algorithms for Immuno-Oncology Agents	• Added that text related to bempegaldesleukin is not applicable. • Adjusted that the management algorithm for bempegaldesleukin can be found in Appendix 7.	Participants are required to discontinue bempegaldesleukin.
[redacted]		
Section 7.7.4.2: Restricted Treatments	Added text stating that anticoagulation therapy will no longer be mandated for participants enrolled in this study.	Participants are required to discontinue bempegaldesleukin.
Section 7.7.4.4: Blood Pressure Precautions	Added that section is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin and blood pressure precautions were only relevant for bempegaldesleukin.
Section 7.8: Treatment After the End of the Study	Added that participants will receive SOC nivolumab after the end of the study.	Participants are required to discontinue bempegaldesleukin and will receive SOC nivolumab monotherapy.
Section 8.1: Discontinuation from Study Treatment	Removed that radiographic assessment needs to be submitted to a central imaging vendor.	Primary endpoints of PFS and ORR by BICR assessment were completed. Investigator tumor assessment will continue.
Section 8.1.1: Nivolumab and Bempegdesleukin Discontinuation Criteria Section 8.1.2: Criteria to Resume Bempegaldesleukin and/or Nivolumab	Added that text related to bempegaldesleukin is not applicable.	Participants are required to discontinue bempegaldesleukin.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.3: Treatment Beyond Progression	Removed that radiographic assessment needs to be submitted to a central imaging vendor.	Primary endpoints of PFS and ORR by BICR assessment were completed. Investigator tumor assessment will continue.
Section 8.1.4: Post Study Treatment Study Follow-up	Added to refer to Section 5.1 for details and that section is not applicable.	Since further formal OS analyses will not be conducted this section is not applicable.
Section 8.2: Discontinuation from the Study	Added that participants will be followed up to 100 days for protocol specified follow-up procedures with documentation of last overall survival.	Since further formal OS analyses will not be conducted the maximum study duration is being shortened to the nivolumab treatment period (2 years) +100 days for safety follow-up.
Section 9.1: Efficacy Assessments	BICR is replaced with Investigator assessment to determine response and disease progression.	Primary endpoints of PFS and ORR by BICR assessment were completed. Investigator tumor assessment will continue.
Section 9.1.1: Imaging Assessments for the Study Section 9.1.1.3: BICR Confirmation of Progression Section 9.1.2: Assessment for the Study	Added that imaging will not be submitted to imaging core lab.	Primary endpoints of PFS and ORR by BICR assessment were completed. Investigator tumor assessment will continue.
[redacted]		
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Removed reference to Appendix 7.	Since participants are required to discontinue bempegaldesleukin, Appendix 7 is not applicable.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.6: Pharmacodynamics	Added that in biomarker sample collection [redacted] Table 9.8.2-2 will not be applicable per Protocol Amendment 03.	Additional biomarker sample collection will not be applicable. However, exploratory biomarker analysis may be conducted.
Section 9.8: Biomarkers Section 9.8.1: Additional Research Collection	Added that in biomarker sample collection [redacted] Table 9.8.2-2 will not be applicable per Protocol Amendment 03. Additional Research collection is not applicable.	Additional biomarker sample collection will not be applicable. However, exploratory biomarker analysis may be conducted.
[redacted]		
Table 9.8.2-2: Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed	Added that in biomarker sample collection Table 9.8.2-2 will not be applicable per Protocol Amendment 03.	Additional biomarker samples will not be collected.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8.3: Tumor Tissue Specimens Section 9.8.4: Tumor Gene Expression and Mutation Analyses Section 9.8.5: Peripheral Biomarkers Section 9.8.6: Whole Blood for Genetic Analysis Section 9.8.7: Exploratory Serum and Plasma Biomarkers Section 9.8.8: Plasma ctDNA Section 9.8.9: Serum MicroRNA (miRNA) Section 9.8.10: Myeloid Derived Suppressor Cells Section 9.8.11: Peripheral Blood Mononuclear Cells and Whole Blood Immunophenotyping Section 9.8.12: Microbiome Analysis	Added that exploratory analysis of selected biomarkers as per Section 9.8 may be conducted.	Additional biomarker sample collection will not be applicable. However, exploratory biomarker analysis may be conducted.
[redacted]		
Section 10: Statistical Considerations	Added that OS analyses will not be conducted.	No further formal OS analysis will be performed.
Section 10.3: Statistical Analyses	Added that exploratory analysis of selected biomarkers as per Section 9.8 may be conducted.	This analysis may help to understand the mechanism of action.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3.4: Interim Analyses	Added that OS analyses will not be conducted.	No further formal OS analysis will be performed.
Appendix 7: Cerebrovacular Accident Adverse Event Management Algorithm for the Combination of Bempegaldesleukin with Checkpoint Inhibitors	Added that Appendix 7 is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin; therefore, algorithm is not applicable.
Appendix 10: Country Specific Requirements/Differences	Added Sweden to adolescent exclusion.	[redacted]
	Added that oral hydration is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin; therefore, oral hydration requirements are not applicable.
Appendix 11: Cytokine-Release Syndrome (CRS) Management Measures/Algorithm	Added that Appendix 11 is not applicable per Protocol Amendment 03.	Participants are required to discontinue bempegaldesleukin; therefore, CRS is not applicable.

TABLE OF CONTENTS

1 SUMMARY

Protocol Title: A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma

Study Phase: 3

Rationale:

Activation of programmed cell death protein-1 (PD-1) pathway inhibits the cluster of differentiation 28 (CD-28)-mediated upregulation of cytokines, inhibits T cell activation, and inhibits the expansion of previously activated cells. Blockade of the PD-1 pathway has demonstrated clinical activity across multiple tumor types including melanoma. An accumulating body of evidence supports that low levels of tumor infiltrating lymphocytes (TILs) in pretreatment biopsies predict poor clinical response to PD-1 pathway blockade. NKTR-214 (bempegaldesleukin) promotes biased signaling through the IL-2 intermediate affinity receptor (IL 2Rβγ) as opposed to the high affinity receptor (IL-2Rαβγ) found on regulatory T-cells (Tregs). Bempegaldesleukin increases intra-tumoral CD8+ lymphocytes and natural killer cells as well as the number of PD-1+ CD8+ cells in the tumor and peripheral blood. The biologic activity of bempegaldesleukin makes it a potentially promising immunotherapy to combine with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway.

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. The current study aims to demonstrate that treatment with bempegaldesleukin in combination with nivolumab will be efficacious in participants with unresectable or metastatic melanoma that is previously untreated.

[redacted]

The addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in PFS (HR 1.09, 97% CI, 0.88-1.35) or ORR compared to nivolumab monotherapy as assessed by Blinded Independent Central Review (BICR), and the significance threshold for OS was also not crossed at the combined first and second OS analyses. Furthermore, there was added toxicity with bempegaldesleukin plus nivolumab compared to nivolumab monotherapy including

a higher incidence of drug-related adverse events (AEs), drug-related serious adverse events (SAEs) and drug-related AEs leading to study treatment discontinuation.

Given that additional toxicities with no added efficacy were observed in the experimental arm, per Protocol Amendment 03, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.

Study Population: Males and females, ages 12 years or older, except where local regulations and/or institutional policies do not allow for participants < 18 years of age (pediatric population) to participate. For those sites, the eligible participant population is ≥ 18 years of age, or age of majority. Adolescents are not eligible for the [redacted] due to the blood sampling and biopsy requirements.

Key eligibility criteria

Inclusion

- Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (adults 18 years or older)/Lansky Performance Score ≥ 80% (minors ages 12-17 only)
- Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system, 8th edition
- Treatment-naïve participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) with the exception of prior adjuvant and/or neoadjuvant treatment for melanoma with approved agents (eg, proto-oncogene B-Raf [BRAF]/mitogen-activated protein [MEK] inhibitors, ipilimumab, nivolumab, pembrolizumab or interferon). Participants who have had recurrence within the 6 months of completing adjuvant or neoadjuvant treatment are not eligible.
- Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria
- All participants must have tissue submitted during the screening period to allow for participant enrollment into the study. Tissue submitted should be from an unresectable primary tumor lesion or any metastatic site. The tumor tissue should be from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment. Central lab must provide IRT with the results of PD-L1 testing prior to randomization. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission. Submission of an FFPE block is strongly preferred but unstained slides are also acceptable. Tissue may be from a core biopsy, punch biopsy, excisional or incisional biopsy, or surgical specimen; fine needle aspiration and other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission.

Medical Monitor (or designee) can be consulted for eligibility if subjects have less than 20 unstained slides.

  - In order to be randomized, a participant must be classified as PD-L1 positive (≥ 1% tumor cell membrane staining) vs PD-L1 negative (< 1% tumor cell membrane staining) or PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content) based on the PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay. If only an insufficient amount of tumor tissue from an unresectable or metastatic site is available from prior to the start of the Screening phase, then a fresh biopsy will be required during the screening phase for performance of biomarker analyses. Non-evaluable participants are not eligible for randomization.

- [redacted] Note: If the participant has > 1 lesion, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments. If the participant has only 1 lesion that is measurable and amenable to biopsy, the lesion must be greater than 2.0 cm and the biopsy cannot be excisional. (Note: These same lesion criteria apply for patients who consent to the optional biopsy in the main study.)
- Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards by approved methodology during the Screening period.

Exclusion

- Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to randomization. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Stable dose of anticonvulsants is allowed. Treatment for central nervous system (CNS) metastases may include stereotactic radiosurgery (eg, GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Participants with CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days prior to randomization are not eligible. Participants who received whole brain radiation therapy are not eligible.
- Uveal melanoma is excluded.

Objectives and Endpoints:

Per Protocol Amendment 03, the secondary and exploratory objectives except biomarker parameters are no longer applicable. Biomarker sample collection will not be applicable per

Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as per section 9.8 may be conducted.

Objective	Endpoint
Primary	
• To compare the objective response rate (ORR) using RECIST 1.1 of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• ORR by Blinded Independent Central Review (BICR)
• To compare progression-free survival (PFS) using RECIST 1.1 of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• PFS by BICR
• To compare overall survival (OS) of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• OS
Secondary	
• To evaluate efficacy of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy	• Clinical Benefit Rate (CBR) duration of response (DOR), time to response (TTR), evaluated by BICR per RECIST 1.1 • ORR, PFS, CBR, DOR, TTR - evaluated by investigator per RECIST 1.1
• To evaluate the association between PD-L1 expression on tumor cells (≥ 1% or < 1%/indeterminate) and efficacy measures including PFS and ORR by BICR and OS	• PFS and ORR by BICR and OS in biomarker population
• To evaluate the safety and tolerability of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy	• Safety and tolerability
Exploratory	
[redacted]	
• To characterize the effect of nivolumab when administered as monotherapy and in combination with	• Biomarker parameters

Objective	Endpoint
bempegaldesleukin on immune cell populations and markers of immune activation.	
• To assess efficacy of bempegaldesleukin combined with nivolumab and nivolumab monotherapy based on tumor mutation burden and blood-based tumor mutation burden	• PFS, OS, ORR in biomarker population
[redacted]	
• To evaluate PFS after the next line of treatment (PFS2) of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• PFS2 by investigator per RECIST 1.1

Overall Design:

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin in combination with nivolumab compared with nivolumab monotherapy in adult and adolescent (≥ 12 years of age) participants with previously untreated unresectable or metastatic melanoma. The study is divided into a Screening period, a Treatment period, and a Long-Term Follow-up period. [redacted]

Randomization (1:1) will be stratified by:

- PD-L1 tumor expression status (≥ 1% vs < 1% or indeterminate) based on the PD-L1 IHC 28-8 pharmDx assay
- BRAF mutation status (V600 mutation positive vs wild type)
- AJCC 8th edition M stage [M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs M1any[1] (Stage IV Elevated LDH)] based on the screening imaging and laboratory test results.

The treatment period of the study is divided into multiple treatment cycles with associated evaluations and procedures. One cycle of treatment is defined as 3 weeks. Results of the

assessments must be reviewed and documented before administering the first dose of the next cycle. In certain circumstances, participants with progressive disease (PD) per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see the full protocol for treatment beyond progression criteria.

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. The maximum total duration of the study is up to 2 years +100 days after randomization of the last participant.

Number of Participants:

Approximately 764 participants with previously untreated unresectable or metastatic melanoma will be randomized (1:1) to 1 of 2 treatment arms.

Treatment Arms and Duration:

Participants will be randomized (1:1) to 1 of 2 treatment arms:

- **Arm A: Bempegaldesleukin 0.006 mg/kg IV Q3W + nivolumab 360 mg IV Q3W (sequential)**
- **Arm B: Nivolumab 360 mg IV Q3W**

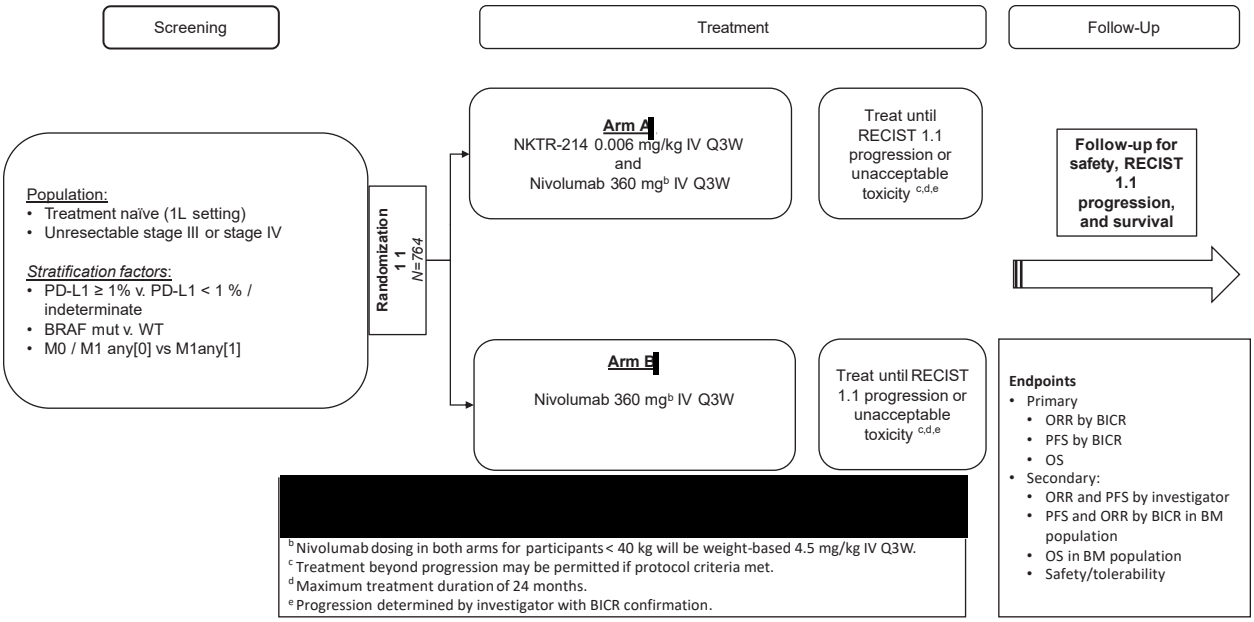
Note: Nivolumab dosing in both arms for participants < 40 kg will be 4.5 mg/kg (weight based).

Per Protocol Amendment 03, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.

Participants will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant is lost to follow up, BMS and Nektar Therapeutics decide to terminate the study, or for a maximum of 24 months of treatment. The total maximum duration of the study is up to 2 years +100 days after randomization of the last participant.

Study Schematic

This study schematic is not applicable per Protocol Amendment 03.



Per Protocol Amendment 03:

- Participants who have completed therapy and are currently in survival follow-up should discontinue from the study immediately if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.
- Participants who have completed therapy and are currently within the 100 days safety follow-up should discontinue from the study once they complete the safety follow up 100 days after the last dose of study treatment if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.
- Participants in Arm A are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants receiving treatment in Arm A and Arm B will receive nivolumab monotherapy on study at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.
- All participants will have 100 days safety follow-up or until AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation. The Sponsor will close the study once the last participant has completed the safety follow-up.

Study Treatment:

Study Drug for CA045001		
Medication	**Potency**	**IP/Non-IP**
***Not applicable per Protocol Amendment 03** Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	1.0 mg of rhIL-2 (IL-2) per vial	IP
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP

Note: For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule

Data Monitoring Committee: Yes

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA045001)

Procedure[a]	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response System to obtain participant number.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study including smoking history, alcohol use, AJCC M stage, and BRAF mutation status.
Tumor Sample Submission	X	All participants must have tissue submitted during the screening period to allow for participant enrollment into the study. Tissue submitted should be from an unresectable primary tumor lesion or any metastatic site. The tumor tissue should be from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment. Central lab must provide IRT with the results of PD-L1 testing prior to randomization. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission. Submission of an FFPE block is strongly preferred but unstained slides are also acceptable. Tissue may be from a core biopsy, punch biopsy, excisional or incisional biopsy, or surgical specimen; fine needle aspiration and other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission. The Medical Monitor (or designee) can be consulted for eligibility if subjects have less than 20 unstained slides. In order to be randomized, a participant must have quantifiable PD-L1 tumor expression (≥ 1% [positive] or < 1% [negative] tumor cell membrane staining) or be classified as PD-L1 indeterminate. Non-evaluable participants are not eligible for randomization. The analytical laboratory must provide IRT with confirmation of the related results prior to randomization. [redacted] Note: If the participant has > 1 lesions, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments. If the participant has only one lesion that is measurable and amenable to biopsy, the lesion must be greater than 2.0 cm and the biopsy cannot be excisional. Note: These same criteria that apply for lesion selection also apply to participants who consent to the optional biopsy in the main study. Please refer to Section 9.8.3 for additional information.

Table 2-1: Screening Procedural Outline (CA045001)

Procedure[a]	Screening Visit	Notes
Safety Assessments		
Physical Examination, Measurements, Vital Signs, Pulse Oximetry, Performance Status	X	Must be collected within 14 days prior to randomization. Includes height, weight, Performance Status (Appendix 5), BP, Heart rate, Temperature, Pulse Oximetry.
Prior and Concomitant Medication Use	X	Must be collected within 14 days prior to randomization. Document vaccine use within 30 days prior to randomization.
Serious Adverse Events Assessment	X	Collected from time of consent. All AEs (SAEs or non-serious AEs) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection collected from time of consent. See Section 9.2 and Appendix 3 for further details.
ECG	X	Within 14 days of randomization. See Section 9.4.2.
Echocardiogram or MUGA	X	Left Ventricular Ejection Fraction must be >45% within 60 days prior to randomization. The Investigator should further evaluate participants with other significant abnormalities on echocardiogram / MUGA. Decision regarding treatment should be based on Investigator's best clinical judgment.
Laboratory Tests		
Clinical Laboratory Testing	X	All laboratory assessments to be performed within 14 days prior to randomization, except for viral testing, which is to be completed within 28 days prior to randomization. Refer to Table 9.4.5-1 for a list of laboratory tests to conduct
Pregnancy Test	X	Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of HCG) is required to be done at Screening and within 24 hours prior to first dose of study therapy in women of childbearing potential (WOCBP).
BRAF mutation testing	X	Results from BRAF mutation testing per local institutional standard required for entry into IRT by the site prior to randomization. Note: Results from NRAS/CKIT mutation testing and prior gene expression profiles for risk stratification should be recorded if available.

Table 2-1: Screening Procedural Outline (CA045001)

Procedure[a]	Screening Visit	Notes
Tumor Assessment		
Body Imaging	X	Contrast-enhanced CT of the chest; contrast-enhanced CT or MRI of the abdomen, and pelvis; and all known sites of disease within 28 days prior to randomization. See Section 9.1.1 for further details.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants at baseline within 28 days prior to randomization. CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
[redacted]		

[a] Some assessments referred to in this section may not be captured as data in the CRF. These assessments are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
Study Drug							
Randomize	X						
Administer Study Drug	X			X		X	**Arm A:** Nivolumab 480 mg IV Q4W. **Arm B**: Nivolumab 480 mg IV Q4W. Note: Nivolumab dosing for participants < 40 kg on both arms will be 6 mg/kg IV Q4W. In both Arm A and Arm B: Participants may be dosed no less than 25 days from the previous dose.
***Not applicable per Protocol Amendment 03** Administer Study Drug	X			X		X	**Not applicable per Protocol Amendment 03.** The first dose must be administered within 3 calendar days following randomization. **Arm A:** Bempegaldesleukin 0.006 mg/kg IV Q3W + Nivolumab 360 mg IV Q3W. Refer to Section 7.1.1 for sequential dosing instructions. **Arm B**: Nivolumab 360 mg IV Q3W Note: Nivolumab dosing for participants < 40 kg on both arms will be 4.5 mg/kg IV Q3W. If the participant's weight on the day of dosing differs by > 10% from baseline or previous dose, the dose must be recalculated. For Nivolumab - All doses should be rounded to the nearest milligram. For bempegaldesleukin - All doses should be rounded to the second decimal digit (hundredths place). In both Arm A and Arm B: Participants may be dosed no less than 18 days from the previous dose.
***Not applicable per Protocol Amendment 03**	X			X		X	**Not applicable per Protocol Amendment 03.**

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
Administer fluids							Arm A only. May be withheld if deemed in the best interest of the participant by the Investigator. Refer to Section 7.1.1.1 for additional information.
***Not applicable per Protocol Amendment 03** Review Hydration Guidelines with Participants	X			X		X	**Not applicable per Protocol Amendment 03.** Arm A only. Hydration Guidelines should be reviewed at each dosing visit
***Not applicable per Protocol Amendment 03** Oral Hydration Follow-up		X			X		**Not applicable per Protocol Amendment 03.** For the first two doses of bempegaldesleukin, between Days 3 and 5 following infusion, site personnel must contact the participant (by telephone or clinic visit) to remind the participant of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion. For subsequent administrations of bempegaldesleukin, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin. See Section 7.1.1.1 for details.
Safety Assessments							
Targeted Physical Examination, Measurements, Vital Signs and Performance Status	X		Vital Signs Only	X		X	• Weight • BP • Heart rate • Temperature • Performance Status (Appendix 5)

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
							Arm A and Arm B: Day 1 vital signs for each cycle should be monitored at the following intervals: • Predose • Within 30 minutes of completion of nivolumab administration
Adverse Events Assessment (including SAEs)	Continuously						All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. Refer to Section 9.2.1 for the timing of AE/SAE collection.
Concomitant Medication Use	X		X	X		X	Record at each visit.
Laboratory Tests							
Pregnancy Test	X			X		X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) is required within 24 hours prior to treatment in women of childbearing potential (WOCBP).
Clinical Laboratory Testing	X			X		X	Refer to Section 9.4.5 Clinical Safety Laboratory Assessments for list of laboratory tests See Table 9.4.5-1. Hematology and chemistry assessments scheduled for the day of study drug(s) dosing must be available and assessed before dosing. Hematology and chemistry assessments can be drawn within 72 hours prior to dosing, though renal function (ie, serum creatinine) must be assessed within 24 hours prior to dosing with bempegaldesleukin or as soon as locally feasible. For the first dose visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility.

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
Efficacy Assessments							
Body Imaging	Prior to Protocol Amendment 03, contrast-enhanced CT of the chest, CT or MRI of the abdomen, pelvis, and all known and suspected sites of disease should be performed every 9 weeks (± 7 days) from randomization up to Week 54 and then every 12 weeks (± 7 days). Per Protocol Amendment 03, tumor assessments will continue per schedule of local standard of care (SOC). Tumor assessment for progression will not be based on imaging performed for biopsy in Cycle 2. Tumor assessment schedule should be maintained regardless of dose delays. Use same imaging method as was used at Screening.						Per Protocol Amendment 03, any participant remaining on treatment will continue imaging per Section 9.1.1. Imaging will be performed per SOC and images will no longer be submitted (BICR). All study treatment decisions will be based on the Investigator's assessment of tumor images. See Section 9.1.1 for additional details.
Brain Imaging	Prior to Protocol Amendment 03, participants with a history of brain metastasis or symptoms should have surveillance MRI with and without contrast per standard of care (first assessment at 9 weeks (± 7 days) from randomization, and then approximately every 12 weeks (± 7 days), or sooner if clinically indicated. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. Per Protocol Amendment 03, brain imaging will be done per schedule of local SOC.						Per Protocol Amendment 03, any participant remaining on treatment will continue imaging per Section 9.1.1. Imaging will be performed per SOC and images will no longer be submitted for BICR. See Section 9.1.1 for further details.
***Not applicable per Protocol Amendment 03** **Biomarker Assessments**	**Not applicable per Protocol Amendment 03.** [redacted] **Please review specimen collection schedule prior to each cycle as specified in Sections [redacted] 9.8**						

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
***Not applicable per Protocol Amendment 03** Biomarker Sample Collection	**Not applicable per Protocol Amendment 03.** See Notes						**Not applicable per Protocol Amendment 03.** See Section 9.8.2. [redacted] Table 9.8.2-2 Biomarker Sampling Schedule: All Participants not Enrolled into the [redacted]. Tumor biopsy: Required for the [redacted] during Cycle 1 but optional for subsequent participants. If clinically feasible, the lesion for biopsy during Cycle 1 would be the same lesion that was biopsied at baseline. If the participant has only one lesion that is measurable and amenable to biopsy, the lesion must be greater than 2.0 cm and the biopsy cannot be excisional. If the participant has > 1 measurable lesion, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments. Note: These same criteria that apply for lesion selection also apply to participants who consent to the optional biopsy in the main study. Please refer to Section 9.8.3 for additional information.
***Not applicable per Protocol Amendment 03** Stool sample collection	**Not applicable per Protocol Amendment 03.** See Notes						
***Not applicable per Protocol Amendment 03** Tumor biopsy	**Not applicable per Protocol Amendment 03.** See Notes						
[redacted]							

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
[redacted]							

Table 2-2: On-Study Activities (CA045001)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Procedure	Cycle 1 Only[a]			Cycle 2 Only[a]		Cycle 3 and Beyond[a]	Notes
	Day 1	Day 3-5	Day 8 (± 1 day)	Day 1 (± 3 days)	Day 3-5	Day 1 (± 3 days)	
[redacted]							

[a] If a dose is delayed, the procedures scheduled for that same time point, except body/brain imaging and pregnancy testing, should also be delayed to coincide with when the time point's dosing actually occurs.

Table 2-3: Long-term Procedural Follow-Up (CA045001)

Procedure	Follow-up Visit 1 (± 7 days)[a]	Follow-up Visit 2 (± 7 days)[a]	Survival Follow-up Every 3 months (± 14 days)[b]	Notes[c]
Safety Assessments				
Vital Signs	X	X		Vital Signs: BP, Heart rate, and temperature
Adverse Events Assessments (Including SAEs)	X	X		SAEs to be collected after the 100-day safety visit if the SAE is deemed to be related or residual toxicities are persisting. All AEs (SAEs or non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.
Performance Status	X	X		
Review of Concomitant Medications	X	X		
***Not applicable per Protocol Amendment 03** Subsequent Anti-Cancer Therapy	X	X	X	**Not applicable per Protocol Amendment 03.** Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression to subsequent anti-cancer therapies will be collected.
Laboratory Tests				
Pregnancy Test	X	X		WOCBP Only. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) is required.
Clinical Laboratory Testing	See Notes	See Notes		During Safety Follow-up Visit 1 and during Safety Follow-up Visit 2, if toxicities are present. Refer to Table 9.4.5-1, Clinical Safety Laboratory Assessments for list of laboratory tests

Table 2-3: Long-term Procedural Follow-Up (CA045001)

Procedure	Follow-up Visit 1 (± 7 days)[a]	Follow-up Visit 2 (± 7 days)[a]	Survival Follow-up Every 3 months (± 14 days)[b]	Notes[c]
[redacted]				
***Not applicable per Protocol Amendment 03 Biomarker Assessments**				
***Not applicable per Protocol Amendment 03** Blood PD Sampling	**Not applicable per Protocol Amendment 03.** See Notes			**Not applicable per Protocol Amendment 03.** See Section 9.8.2. [redacted]
***Not applicable per Protocol Amendment 03** Tumor biopsy	**Not applicable per Protocol Amendment 03.** See Notes			Table 9.8.2-2 Biomarker Sampling Schedule: All Participants not Enrolled into the [redacted] Tumor biopsy: Optional at progression.
Efficacy Assessments				
Body Imaging	Prior to Protocol Amendment 03,only for participants without Investigator-assessed progression. Contrast enhanced CT of the chest, CT or MRI of the abdomen, pelvis, and all known and suspected sites of			Per Protocol Amendment 03, any participant remaining on follow-up will continue imaging per

Table 2-3: Long-term Procedural Follow-Up (CA045001)

Procedure	Follow-up Visit 1 (± 7 days)[a]	Follow-up Visit 2 (± 7 days)[a]	Survival Follow-up Every 3 months (± 14 days)[b]	Notes[c]
	disease should continue every 9 weeks (± 7 days) from randomization up to Week 54 and then every 12 weeks (± 7 days). Per Protocol Amendment 03, tumor assessments will continue per the schedule of local standard of care (SOC).			Section 9.1.1. Imaging will be performed per SOC and images will no longer be submitted for BICR. See Section 9.1.1 for further details.
Brain Imaging	Prior to Protocol Amendment 03, only for participants without BICR-confirmed progression. Participants with a history of brain metastasis or symptoms should continue to have surveillance MRI with and without contrast per standard of care every 12 weeks (± 7 days), or sooner if clinically indicated. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. Per Protocol Amendment 03, brain imaging will be done per the schedule of local SOC.			Per Protocol Amendment 03, any participant remaining on follow-up will continue imaging per Section 9.1.1. Imaging will be performed per SOC and images will no longer be submitted for BICR. See Section 9.1.1 for further details.
Survival Status	X	X	X	
[redacted]				

Table 2-3: Long-term Procedural Follow-Up (CA045001)

Procedure	Follow-up Visit 1 (± 7 days)[a]	Follow-up Visit 2 (± 7 days)[a]	Survival Follow-up Every 3 months (± 14 days)[b]	Notes[c]
[redacted]				

[a] Participants must be followed for at least 100 days after the last dose of study treatment. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from the last dose of study treatment. Both follow-up visits should be conducted in person.

[b] **Not applicable per Protocol Amendment 03.** Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit 2. Survival visits may be conducted in person or by telephone. The study Sponsor may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] Some assessments referred to in this section may not be captured as data in the CRF. These assessments are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

3 INTRODUCTION

CA045001 is a Phase 3 randomized study of NKTR-214 (bempegaldesleukin) combined with nivolumab vs nivolumab monotherapy in participants with unresectable or metastatic melanoma that is previously untreated. Bempegaldesleukin consists of interleukin-2 (IL-2; See Appendix 1: Abbreviations), which has the same amino acid sequence as aldesleukin, conjugated at a defined region within the protein to releasable PEG chains. The six PEG chains render the molecule inactive. After administration in vivo, the PEG chains are slowly hydrolyzed to generate active cytokine conjugates. The most active IL-2 conjugates are 2-PEG-IL-2 and 1-PEG-IL-2. The location of the PEG chains on the active conjugated-IL-2 reduces affinity to the IL-2 receptor alpha subunit (IL-2Ra), reducing the activation of the high affinity IL-2 receptor (IL-2Rαβγ) found on Tregs. In the tumor, bempegaldesleukin preferentially activates CD8+ T and NK cells over Tregs. This Phase 3 study will allow for direct comparison of bempegaldesleukin combined with nivolumab vs nivolumab monotherapy as measured by ORR, PFS, OS, and other clinical endpoints in treatment naive participants with unresectable or metastatic melanoma.

Per Protocol Amendment 03, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and will receive nivolumab monotherapy.

3.1 Study Rationale

Activation of programmed cell death protein-1 (PD-1) pathway inhibits CD-28-mediated upregulation of cytokines, inhibits T cell activation, and inhibits the expansion of previously activated cells. Blockade of the PD-1 pathway has demonstrated clinical activity across multiple tumor types including melanoma. An accumulating body of evidence supports that low levels of tumor infiltrating lymphocytes (TILs) in pretreatment biopsies predicts for poor clinical response to PD-1 pathway blockade.[1,2,3] Bempegaldesleukin promotes biased signaling through the IL-2 intermediate affinity receptor (IL-2Rβγ) as opposed to the high affinity receptor (IL-2Rαβγ) found on regulatory T-cells (Tregs). Bempegaldesleukin increases intratumoral CD8+ lymphocytes and natural killer cells as well as the number of PD-1+ CD8+ cells in the tumor and peripheral blood. The biologic activity of bempegaldesleukin makes it a potentially promising immunotherapy to combine with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway.

The current study aims to demonstrate that treatment with bempegaldesleukin in combination with nivolumab will be efficacious in participants with unresectable or metastatic melanoma that is previously untreated. Additional objectives of the study include characterization of safety and tolerability, as well as [redacted] potential predictive biomarkers [redacted].

3.1.1 Research Hypothesis

This section is not applicable per Protocol Amendment 03.

Treatment with bempegaldesleukin combined with nivolumab will improve objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) when compared with

nivolumab monotherapy in participants with unresectable or metastatic melanoma that is previously untreated.

3.2 Background

3.2.1 Melanoma Background / Current Therapies

Melanoma is the most serious form of skin cancer and the incidence varies globally. Melanoma accounts for approximately 3% of all cancer deaths in Australia and 1% and 2% of all cancer deaths in Europe and the United States (US).[4,5] In 2020, it is estimated that approximately 29,000 patients worldwide will present with unresectable stage III and stage IV melanoma, where the 5-year survival rate is 18% for late-stage disease.[6]

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (dacarbazine) and immunotherapy (IL-2). Historically chemotherapy was used as palliative therapy for melanoma with modest response rates and responses that were usually short lived. Treatment of melanoma patients with high dose IL-2 demonstrated a response rate of 10%-15% with approximately 5% of patients developing a complete response and a portion of the responders achieved durable long-term responses.[7] The use of high dose IL-2 is restricted to specialized centers, as the treatment requires hospitalization for drug administration and toxicity management by a specially trained team.

Since 2011, agents in 3 new therapeutic classes received approval for the treatment of unresectable or metastatic melanoma as monotherapy or in combination. The approved agents include 1) anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibodies, such as ipilimumab; 2) anti-PD-1 receptor blocking antibodies, which include nivolumab and pembrolizumab; and 3) small molecules targeting the intracellular kinase pathways of BRAF and MEK in BRAF V600E positive melanoma. BRAF inhibitors (vemurafenib or dabrafenib) and MEK inhibitors (cobimetinib or trametinib) either alone or in combination, show improved OS or median PFS compared with chemotherapy, but patients often develop resistance to therapy.[8,9,10,11] Importantly, effective treatment with these agents is limited to patients with BRAF mutation positive tumors (approximately 40%-50% of patients).

According to the most recent National Comprehensive Cancer Network (NCCN) Guidelines, checkpoint immunotherapy with anti-PD-1 therapies, which are effective regardless of BRAF mutation status, is recommended first-line therapy for treatment of unresectable or metastatic melanoma. Options in this category include pembrolizumab, nivolumab, or nivolumab/ipilimumab combination therapy.[1] PD-L1 expression in pretreatment tumor biopsy correlates with clinical benefit to anti-PD-1 based treatment;[12] however, PD-L1 expression has not been recommended to guide melanoma treatment decisions given that low expressers may still have durable responses.[1,13] Although checkpoint inhibitors significantly improved clinical outcome, a significant portion of patients progress and treatment-related toxicities often require patients to discontinue therapy.

3.2.2 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[14,15,16] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the TCR.[17] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[18] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[19] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[20]

3.2.3 Bempegaldesleukin Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the interleukin-2 (IL-2) receptor and subsequent activation of effector T cells. As a PEGylated human recombinant IL-2 molecule of aldesleukin with an average of 6 releasable polyethylene glycol (PEG) chains, bempegaldesleukin can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. The polymer conjugation renders the cytokine initially inactive. Upon intravenous (IV) administration, the PEG chains slowly release to generate the active cytokine species (mainly 2-PEG-IL-2 and 1-

PEG-IL-2) that have a peak plasma concentration of 24 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1-PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2.

The polymer conjugation of bempegaldesleukin promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). Specifically, the location of the bempegaldesleukin PEG chains interferes with the binding to the IL-2 alpha receptor subunit responsible for the undesirable effect of activating regulatory T cells (Tregs) in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor. Upon infusion, bempegaldesleukin preferentially increases the proliferation, activation, and effector function of tumor antigen-specific CD8+ T cells and natural killer (NK) cells within the tumor microenvironment (TME) over expansion of unwanted intra-tumoral Tregs that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ).[21,22,23,24,25] Consistent with this mechanism of action, recent nonclinical studies demonstrate strong synergy of bempegaldesleukin with adoptive T cell therapy (ACT), with PD-1 checkpoint blockade, and with tumor antigen-specific vaccination, in a variety of mouse models.[24,25] This synergy was mediated by expansion of tumor-specific CD8+ T cells in the periphery and tumor, without strong expansion of Tregs in the tumor tissue.

Bempegaldesleukin also correspondingly promotes expression of PD-1 on the surface of CD8+ T cells and induction of a Type II interferon gene signature in the TME, driving cell surface expression of programmed cell death ligand 1 (PD-L1) on tumor cells.[26]

The immunological properties of bempegaldesleukin with the induction of tumor-infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes bempegaldesleukin a potentially promising combination therapy for use with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. Moreover, the safety profile of bempegaldesleukin generally does not overlap with that of checkpoint inhibitors, further supporting the use of bempegaldesleukin as a potentially complimentary combination partner with checkpoint inhibitors.

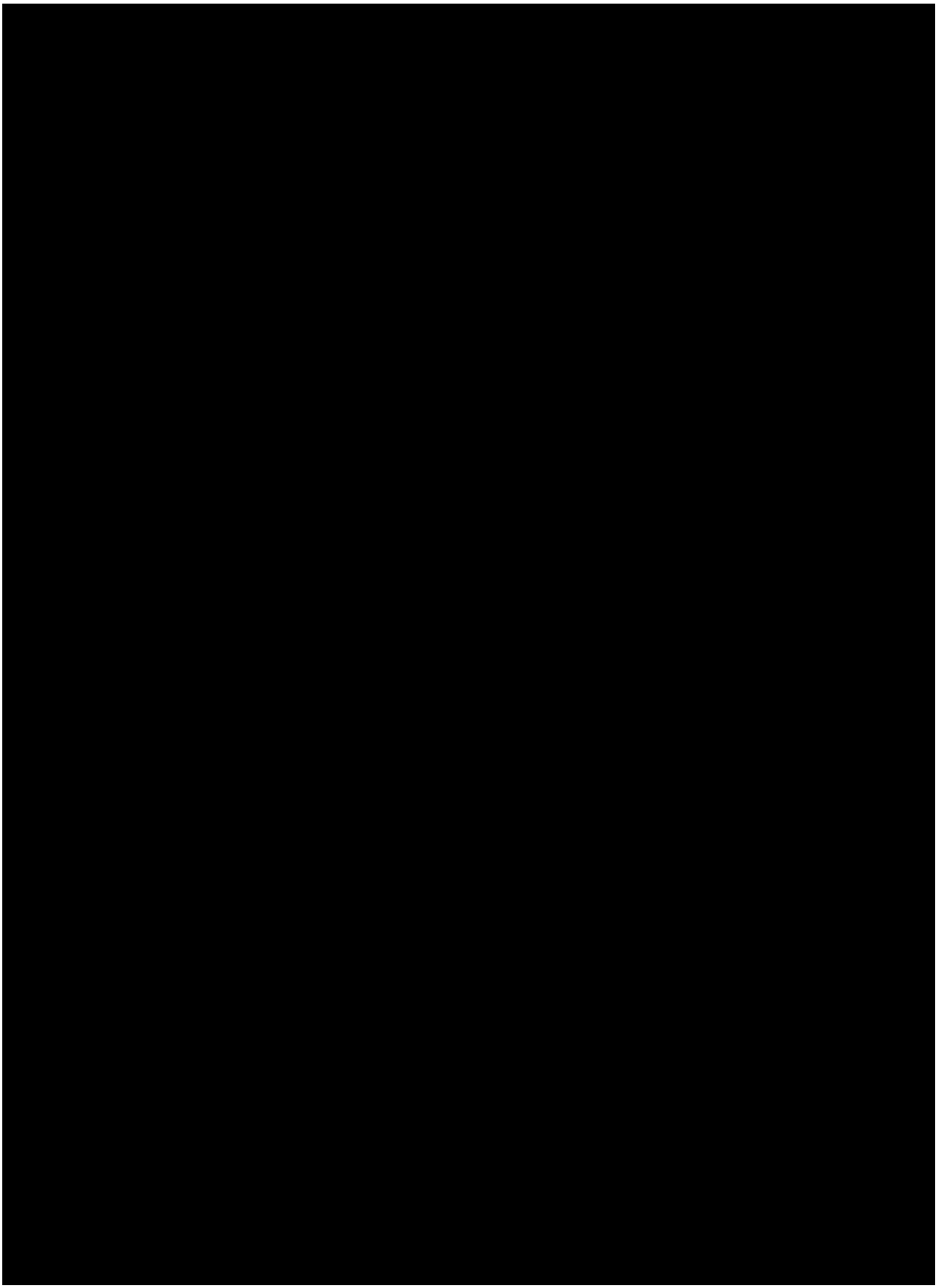
3.2.4 Clinical Experience with Nivolumab

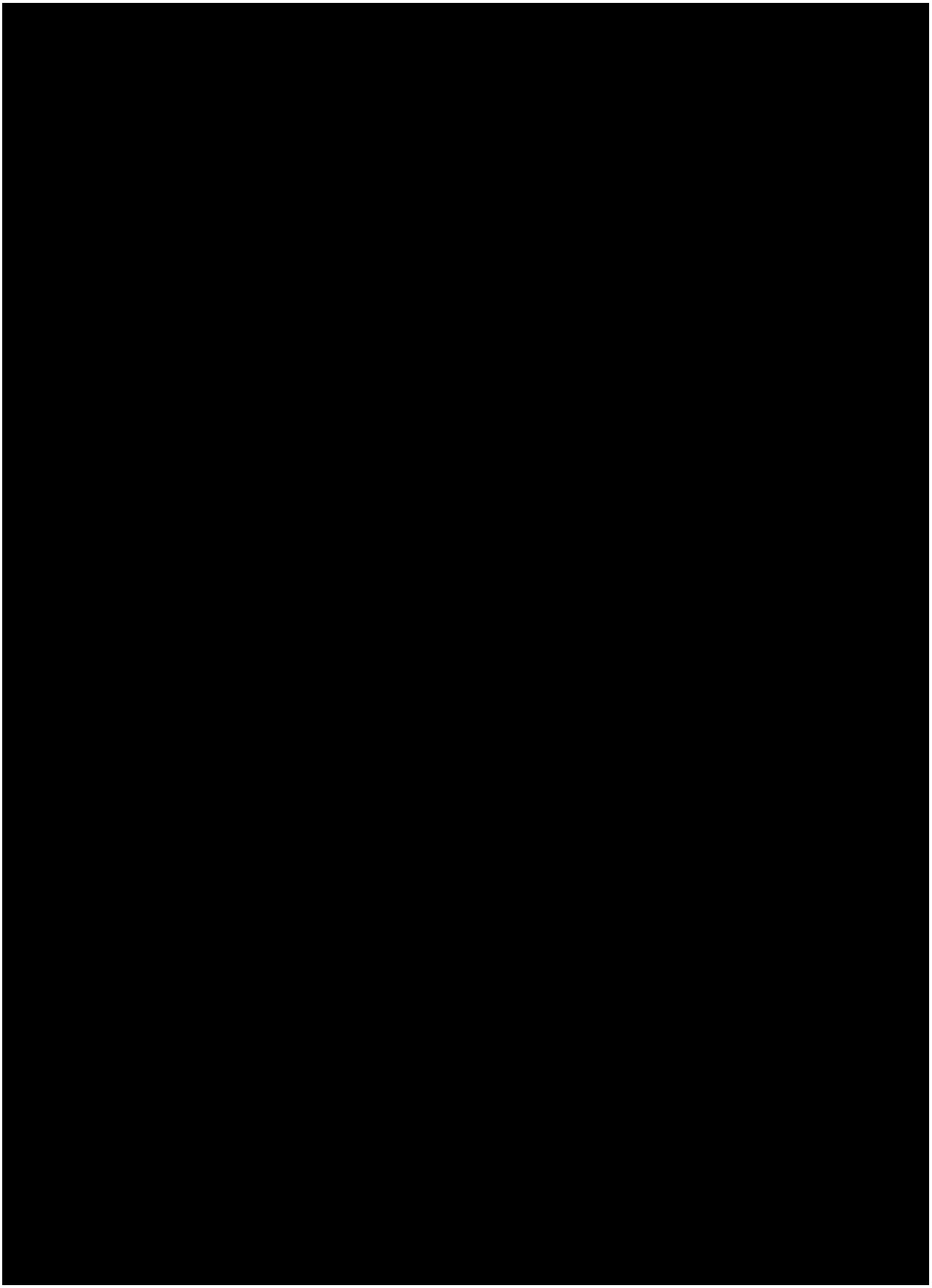
Nivolumab has demonstrated safety and efficacy as monotherapy in the treatment of advanced melanoma in treatment naive patients in two Phase 3 trials. In CheckMate-066 previously untreated melanoma patients with advanced melanoma without BRAF mutations were randomized treatment with either nivolumab versus dacarbazine. There was a 58% reduction in the risk of death with nivolumab treatment group (hazard ratio [HR] for death, 0.42 [99.79% CI, 0.25–0.73] $P < 0.001$).[27] CheckMate-067 was a double-blind, Phase 3 study to evaluate the efficacy and safety of nivolumab monotherapy and nivolumab plus ipilimumab combination therapy compared to ipilimumab monotherapy in metastatic or unresectable melanoma regardless of BRAF mutation status. Nine hundred forty-five participants were randomized 1:1:1 to receive either 3 mg/kg of nivolumab every 2 weeks (plus ipilimumab-matched placebo); 1 mg/kg of nivolumab every 3 weeks plus 3 mg/kg of ipilimumab every 3 weeks for 4 doses, followed by 3 mg/kg of nivolumab every 2 weeks; or 3 mg/kg of ipilimumab every 3 weeks for 4 doses (plus nivolumab-matched placebo). The overall response rate was 44% in the nivolumab monotherapy arm and 19% in the ipilimumab monotherapy arm. The hazard ratio for progression or death was 0.55 (95% CI, 0.45

to 0.66) with nivolumab versus ipilimumab. The rate of OS at 3 years was 52% in the nivolumab group, as compared with 34% in the ipilimumab group.[13] The median duration of response was not reached in the nivolumab monotherapy group and was 19.3 months in the ipilimumab group. These data led to FDA and EMA approval of nivolumab monotherapy as frontline treatment in patients regardless of BRAF mutation status.

[redacted]

[redacted]





3.3 Benefit/Risk Assessment

3.3.1 Bempegaldesleukin Safety Profile

Bempegaldesleukin was designed to mitigate the severe toxicities associated with rapid systemic immune activation seen with administration of aldesleukin. The identified risks of bempegaldesleukin include hypotension, IL-2 mediated AEs (eg, flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevations), infusion-related reactions/hypersensitivity reactions, thyroid dysfunction, eosinophilia, and arthralgia. The majority of these AEs are mild to moderate in severity and can be monitored and managed in the clinical setting. The goal of engineering a PEGylated form of IL-2 that reduces the treatment-limiting toxicities of aldesleukin, that is, those necessitating in-hospital administration, appears to have been realized with bempegaldesleukin at the doses tested.

Additional details on the clinical experience with bempegaldesleukin are provided in the bempegaldesleukin Investigator's Brochure.

3.3.2 Nivolumab Safety Profile

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable

with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

3.3.3 Bempegaldesleukin and Nivolumab Benefit and Risk Assessment

Bempegaldesleukin has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with nivolumab, with promising evidence of clinical efficacy and a potentially favorable benefit-risk profile. Bempegaldesleukin has been safely administered in an outpatient setting supported by appropriate clinical monitoring.

Hypotension has been identified as a clinically significant adverse effect of bempegaldesleukin, and can be effectively mitigated by prophylaxis and hydration guidelines. Other risks associated with bempegaldesleukin include IL-2 mediated AEs (eg, flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevation), infusion related reactions, thyroid dysfunction, eosinophilia, and arthralgia; these AEs are generally mild or moderate in severity, and can be monitored and managed in clinical setting. Cases of thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), dermatitis, pneumonitis, hepatitis, myocarditis, myositis/myasthenia gravis, and vitiligo/hypopigmentation consistent with immune-mediated mechanism have been observed in patients receiving bempegaldesleukin plus nivolumab, and some of these cases shared clinical characteristics consistent with immune-mediated AEs associated with checkpoint inhibitors.

The continued development of bempegaldesleukin in combination with nivolumab for the treatment of various cancers is warranted based on a positive benefit-risk profile. In addition, the early efficacy data along with the correlative biomarker showing conversion of PD-L1 negative patients to PD-L1 positive patients suggests that the addition of bempegaldesleukin to a checkpoint inhibitor (nivolumab) may change the tumor microenvironment in PD-L1 negative patients such that the combination may contribute to anti-tumor activity with an acceptable safety profile.

In conclusion, the currently available safety data demonstrates that bempegaldesleukin and nivolumab is a well-tolerated immuno-oncology combination therapy. Given the encouraging clinical activity and manageable and generally non-overlapping toxicity profile, the potential for direct benefit in patients warrants continued evaluation of the combination bempegaldesleukin and nivolumab in the clinical setting and supports further development of combination of bempegaldesleukin and nivolumab regimens in patients with cancer. If a participant had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the trial, then the benefit and risk considerations remain the responsibility of the Investigator.

The final ORR and PFS analyses, and the first OS interim analysis (combined with the second OS interim analysis) have been completed using the locked database with a database lock date of 01-Feb-2022. The addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in PFS (HR 1.09, 97% CI, 0.88-1.35) or ORR compared to nivolumab monotherapy, and the significance threshold for OS was also not crossed at the combined first and second OS analyses. Given there was no additional clinical benefit in the doublet therapy arm

compared to the monotherapy arm for the primary endpoints of PFS and ORR, the Sponsor, in consultation with the DMC, decided to unblind the trial and to perform no additional formal analyses for the OS endpoint.

After the Sponsor reviewed the topline results from the ORR and PFS final analysis, additional toxicities with no added efficacy were observed in the experimental arm. Therefore participants are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy for the remainder of the study treatment period.

4 OBJECTIVES AND ENDPOINTS

Table 4-1 presents the objectives and endpoints of the study. The final ORR and PFS analyses, and the first OS interim analysis (combined with the second OS interim analysis) have been completed using the locked database with database lock date of 01-Feb-2022. Given there was no additional clinical benefit in the doublet therapy arm compared to the monotherapy arm for the primary endpoints of PFS and ORR, the Sponsor, in consultation with the DMC, has decided to unblind the trial. No additional OS formal analyses will be performed. Any further efficacy analyses, if conducted, will be descriptive.

Per Protocol Amendment 03, the secondary and exploratory objectives except biomarker parameters are no longer applicable. Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected samples as per Section 9.8 may be conducted.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare ORR using RECIST 1.1 for bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• ORR by BICR
• To compare PFS using RECIST 1.1 of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• PFS by BICR
• To compare OS of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma	• OS
Secondary	
• To evaluate efficacy of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy	• CBR, DoR, TTR by BICR per RECIST 1.1 • ORR, PFS, CBR, DoR, TTR by Investigator per RECIST 1.1
• To evaluate the association between PD-L1 tumor expression on tumor cells (≥ 1% or	• PFS and ORR by BICR and OS in biomarker population

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
< 1%/indeterminate) and efficacy measures including PFS and ORR by BICR and OS.	
• To evaluate the safety and tolerability of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy	• Safety and tolerability
Exploratory	
[redacted]	
• To characterize the effect of nivolumab when administered as monotherapy and in combination with bempegaldesleukin on immune cell populations and markers of immune activation. Tumor tissue may also be explored for potential biomarkers of immune activation.	• Biomarker parameters
• To assess efficacy of bempegaldesleukin combined with nivolumab and nivolumab monotherapy based on tumor mutation burden and blood-based tumor mutation burden.	• PFS, OS, ORR in Biomarker Population.
[redacted]	
• To evaluate PFS after the next line of treatment (PFS2) of bempegaldesleukin combined with nivolumab and that of nivolumab monotherapy in participants with	• PFS2 by Investigator per RECIST 1.1

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
previously untreated unresectable or metastatic melanoma	

5 STUDY DESIGN

5.1 Overall Design

This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin in combination with nivolumab compared with nivolumab monotherapy in adult and adolescent (≥ 12 years of age) participants with previously untreated unresectable or metastatic melanoma. The study is divided into a Screening period, a Treatment period, and a Long-Term Follow-up period.

[redacted] Participants will be randomized (1:1) to 1 of 2 treatment arms:

The original treatments in Arm A and Arm B are not applicable per Protocol Amendment 03.

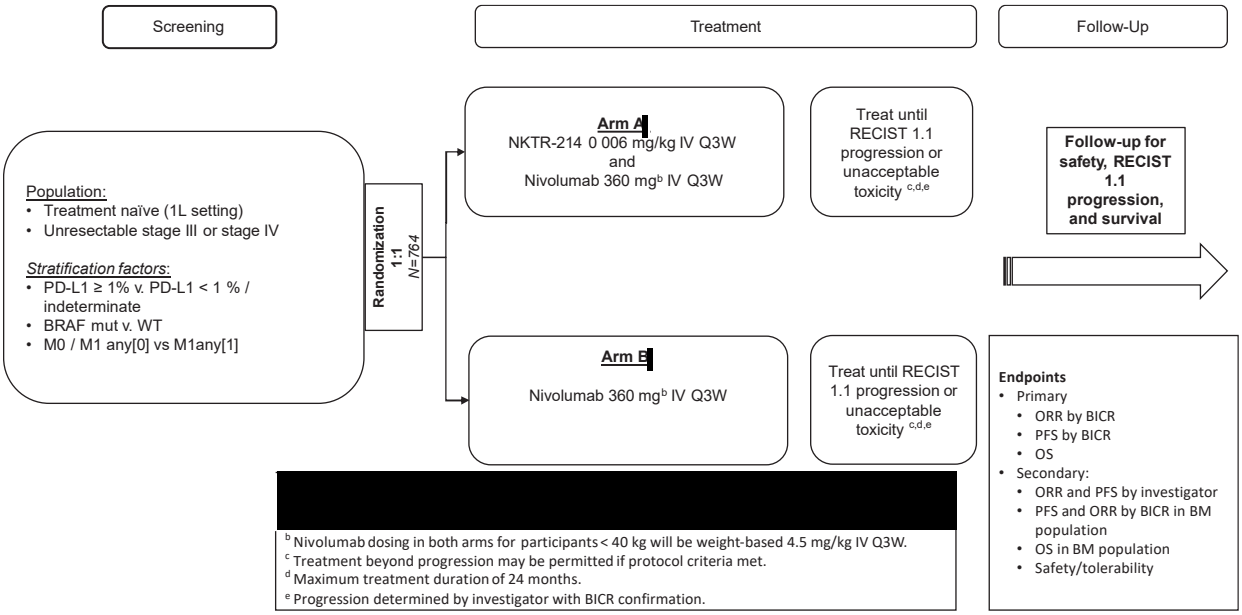
- **Arm A:** Bempegaldesleukin 0.006 mg/kg IV Q3W + nivolumab 360 mg IV Q3W (sequential dosing)
- **Arm B:** Nivolumab 360 mg IV Q3W
- Note:
- Bempegaldesleukin dose is based on IL-2 equivalent component.
- Nivolumab dosing in both arms for participants < 40 kg will be weight-based 4.5 mg/kg IV Q3W.

Randomization will be stratified by:

- PD-L1 tumor expression status (≥ 1% vs < 1% or indeterminate) based on the PD-L1 IHC 28-8 pharmDx assay)
- BRAF mutation status (V600 mutation positive vs wild type) based on local testing.
- AJCC 8th edition M stage [M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs M1any[1] (Stage IV Elevated LDH)] based on the screening imaging and laboratory test results.

This study schematic is not applicable per Protocol Amendment 03. Figure 5.1-1 provides the study schematic, and Section 2 outlines the study procedures in the Schedule of Activities.

Figure 5.1-1: Study Schematic



Per Protocol Amendment 03:

- Participants who have completed therapy and are currently in survival follow-up should discontinue from the study immediately if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.
- Participants who have completed therapy and are currently within the 100 days safety follow-up should discontinue from the study once they complete the safety follow up 100 days after the last dose of study treatment if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.
- Participants in Arm A are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants receiving treatment in Arm A and Arm B will receive nivolumab monotherapy on study at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.
- All participants will have 100 days safety follow-up or until AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation. The Sponsor will close the study once the last participant has completed the safety follow-up.

5.1.1 Screening Period

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants'

standard care. After signing the ICF, participants will be evaluated for entry criteria during the Screening period before administration of study drug(s). Rescreening after screen failure will be allowed. Imaging of the brain with MRI is required of all participants during Screening. CT of the brain (without and with contrast) can be performed if MRI is contraindicated

For participants whose BRAF mutation status is unknown, BRAF status must be determined by local testing prior to study randomization.

Sufficient, recent tumor tissue submitted should be from an unresectable primary tumor lesion or any metastatic site. The tumor tissue should be from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission. Tumor tissue should be obtained from core biopsy, punch biopsy, excisional or incisional biopsy, or surgical specimen and then submitted to the central laboratory. The Medical Monitor (or designee) can be consulted for eligibility if subjects have less than 20 unstained slides. The central laboratory must provide IRT with PD-L1 results from tumor tissue sample prior to randomization. All research sites will be blinded to the results of biomarker (PD-L1) testing. Participants must not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained.

5.1.2 Treatment Period

The treatment period of the study is divided into multiple treatment cycles with associated evaluations and procedures. One cycle of treatment is defined as 3 weeks. Results of the assessments must be reviewed and documented before administering the first dose of the next cycle. Every effort should be made to schedule visits within the protocol-specified windows. Assessments and frequency are described in Section 2.

[redacted] Participants will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant is lost to follow-up, BMS and Nektar Therapeutics decide to terminate the study, or for a maximum of 24 months of treatment. In certain circumstances, participants with progressive disease per RECIST 1.1, but with otherwise stable or improved performance and clinical status, may continue to be treated in the event of a perceived benefit per Investigator; see Section 8.1.3 for treatment beyond progression criteria.

Per Protocol Amendment 03, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.

Investigators have the following options for participants who are still on treatment:

1) Discontinue bempegaldesleukin and continue nivolumab monotherapy if the participant is assigned to the experimental arm (bempegaldesleukin plus nivolumab) for the protocol-specified duration
2) Continue assigned nivolumab monotherapy (i.e. nivolumab) for the protocol-specified duration
3) Discontinue the participant from assigned study treatment
4) Investigators should inform participants who are still on treatment and those on follow up about the study results and counsel them on treatment choices. Decisions regarding treatment options should be made jointly by Investigators and participants based on a risk/benefit analysis assessed individually for each participant. The counseling and decision should be clearly documented in the medical record of participant. All participants must be re-consented.

5.1.3 Long-Term Follow-Up

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. The total maximum duration of the study is up to 2 years +100 days from randomization of the last participant.

Timing for long-term follow-up will be as follows:

- Assessments should continue as described in Table 2-3.
- Participants must be followed for at least 100 days after the last dose of study treatment. Follow-up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up Visit 2 occurs approximately 100 days (± 7days) from the last dose of study treatment. Both follow-up visits should be conducted in person.
- Additional assessments may occur when the decision is made to discontinue treatment.
- **Not applicable per Protocol Amendment 03.** All participants will be contacted for survival every 3 months (± 14 days). BMS may request that survival data be collected on all treated participants outside of the 3 month specified window.
- Per clinical judgment, the participant may come in earlier.
- In case of a clinically significant AE, the participant will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs (bempegaldesleukin and/or nivolumab). If the participant discontinues study drug for a clinically significant AE, the participant will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

5.1.4 Data Monitoring Committee and Other External Committees

A Data Monitoring Committee will be established to provide oversight of safety and efficacy considerations in protocol CA045001 and to provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for bempegaldesleukin and nivolumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

Additional details concerning DMC oversight are provided in the DMC charter.

5.2 Number of Participants

It is expected that approximately 1,020 participants will need to be enrolled in order to randomize 764 participants, assuming a screen failure rate of approximately 25%. Approximately 764 participants with previously untreated unresectable or metastatic melanoma will be randomized (1:1) to 1 of 2 treatment arms.

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The first and second OS interim analyses have been completed using the locked database on 01-Feb-2022, and no additional OS formal analyses will be performed.

This paragraph is not applicable per Protocol Amendment 03. The total duration of the study for the OS primary endpoint will be determined by accrual of events and is expected to occur approximately 68 months after the date of the first participant to be randomized (See Section 10). Additional follow-up for PFS and OS may be conducted up to approximately 5 years after the randomization of the last participant.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for the Combination of Bempegaldesleukin and Immune Checkpoint Inhibitors

The ongoing PIVOT-02 study of nivolumab and bempegaldesleukin includes an expansion cohort in patients with treatment-naive melanoma. In the most recent analysis of the dose escalation part, the response rate in this cohort is 69% (11 out of 16 participants) with 1 complete response and 10 partial responses with all responders maintaining their response.[27] With 3 years of follow-up, nivolumab monotherapy in the CheckMate-067 study demonstrated an ORR of 44%, a 3-year PFS of 32% and a 3-year OS of 52%.[13] The 3-year analysis of CheckMate-067 reaffirmed that responses to checkpoint inhibitors continue to evolve with longer follow-up as the number of

participants achieving a complete response to nivolumab increased from 28 to 52 participants out of 316 total (9% to 16%) with a median duration of response that has still not been reached. It is anticipated that a similar evolution of responses will be seen in the combination of bempegaldesleukin and nivolumab as evolution of responses over time has been reported in the setting of high dose IL-2.

5.4.2 Rationale for Study Comparator and Study Population

PD-1 blockade is the recommended first-line therapy for treatment of BRAF WT and BRAF Mutant unresectable or metastatic melanoma in the NCCN Guidelines. Options in this category include pembrolizumab, nivolumab, or nivolumab / ipilimumab combination therapy.[12] Three year follow-up data from the CheckMate-067 study in which participants received nivolumab or the combination of nivolumab and ipilimumab demonstrated PFS rates of 32% and 39% and OS rates of 52% and 58%, respectively.[13] Although first-line treatment with checkpoint inhibitors significantly improved clinical outcome for melanoma patients, a significant portion of patients progress or discontinue treatment due to treatment-related toxicities.[1] These data support the need for combinations such as bempegaldesleukin and nivolumab that may yield greater clinical efficacy without adding significant treatment related toxicities.

5.4.3 Rationale for Inclusion of Adolescent Participants

Adolescent (generally aged 12-17 years) enrollment into clinical trials has been historically lower than enrollment of their pediatric counterparts. Lack of participation in pediatric trials may be due to differences in tumors observed in adolescent participants vs their pediatric counterparts, as tumors in adolescents may mirror those observed more often in adults. For trials in adult participants with tumor types that also occur in adolescents, adolescents are often excluded due to safety or regulatory concerns. Overall, this has led to a delay in the study of new therapies in adolescents, and most problematically, a delay in new efficacious therapies reaching this population. It has been recommended, therefore, that adolescents be considered for trials in adult populations for tumor types that are observed in adolescents and that share features common to those tumors that occur in adults.[31,32]

Although rare, the incidence of childhood and adolescent melanoma in the US has been increasing in the past 35 years. This trend is most prominent in the adolescent age range. A recent genomic analysis of pediatric melanoma demonstrates that conventional melanoma in children and adolescents shares many of the genomic features that have been described in adult melanoma, including BRAF mutations.[33] Given the similarities observed in adolescent melanoma compared to adult, as well as the overarching need for inclusion of adolescents in clinical trials of potentially new efficacious therapies, adolescents will be included in this study where locally permitted. Individual countries and sites have the option of opting out of adolescent eligibility.

5.4.4 Rationale for Choice of Endpoints

CA045001 will use the primary endpoints of ORR, PFS, and OS. ORR and PFS will be assessed per RECIST 1.1 by BICR. ORR will further be described by the durability and depth of responses, as those aspects are important characterizations of responses with immune-oncology treatments.

In the current melanoma clinical environment where multiple approved agents (ipilimumab and BRAF inhibitors) are available to treat the patients who progress on nivolumab with or without NKTR, PFS will not be confounded by subsequent therapy.

5.4.5 Rationale for Open-Label Design

This section is not applicable per Protocol Amendment 03. Due to the hydration program and the special restrictions for withholding anti-hypertensive medications in the bempegaldesleukin arm, a placebo-controlled, double-blinded study is not appropriate for this study.

5.4.6 Rationale for Stratification by M Staging, BRAF, and PD-L1

In order to minimize the potential for imbalances across treatment arms, there will be 3 stratification factors utilized in this trial: American Joint Committee on Cancer (AJCC) 8th edition M stage (M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs M1any[1] (Stage IV Elevated LDH)), BRAF mutation status (mutation positive vs wild type), and PD-L1 tumor expression (≥ 1% tumor cell surface expression [positive] vs < 1% tumor cell surface expression [negative]/indeterminate). Prognostic implications of M Staging are well established.[34] BRAF mutations have likewise been associated with adverse clinical outcomes in melanoma patients, as well as differences in PFS and OS in patients treated with nivolumab.[35]

Previous clinical studies with nivolumab monotherapy have shown patients with PD-L1 positive tumors may have higher response rates than those with negative or indeterminate expression.[36] Participants in the current trial will therefore be stratified by PD-L1 tumor expression status, as the effect of PD-L1 tumor expression on the response to nivolumab and bempegaldesleukin combination is not yet known.

5.4.7 Duration of Treatment with Nivolumab/Bempegaldesleukin

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months,[37,38,39,40,41,42] and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[43] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[44]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously-treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to

plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[45] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[46]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in participants with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, P = 0.00017) and pembrolizumab 10 mg/kg (HR 0.60, P < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[47]

Keynote-006 was a randomized Phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[48]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[49]

Collectively, these data suggest that there is minimal, if any, benefit derived from continuing immuno-oncology treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term

treatment. Therefore, in this study, treatment will be given for a maximum of 24 months from the start of study treatment (regardless of number of cycles administered).

This paragraph is not applicable per Protocol Amendment 03. Given the hypothesis that co-administration of bempegaldesleukin with nivolumab will potentiate the pharmacological effects of nivolumab, the duration of bempegaldesleukin therapy will be restricted to 24 months to match the duration of nivolumab therapy.

5.5 Justification for Dose

5.5.1 Justification for Dose of Bempegaldesleukin

This section is not applicable per Protocol Amendment 03. The dose for bempegaldesleukin is 0.006 mg/kg Q3W for participants taking in consideration the clinical safety profile associated with the robust immune system activation observed in the PIVOT-02 study. [redacted]

5.5.2 Justification for Dose of Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma, using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, cHL, SCCHN, and urothelial carcinoma, using a regimen of either nivolumab 240 mg Q2W, nivolumab 3 mg/kg Q2W, and nivolumab 480 mg Q4W.

Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg Q2W. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including nivolumab 360 mg Q3W. The simulated steady state average concentration (Cavgss) following administration of nivolumab 360 mg Q3W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants weighing 80 kg, the approximate median weight of participants with NSCLC, melanoma and RCC used in the PPK analyses. Given that the Cavgss estimates for nivolumab 360 mg Q3W are predicted to be similar to those for nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W, the efficacy is predicted to be similar for these regimens. It should be noted that the Cmaxss following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W providing sufficient safety margins. Further details on nivolumab 360 mg Q3W dosing can be found in the IB.

Finally, nivolumab 360 mg Q3W is currently being investigated in combination with a number of other agents, including bempegaldesleukin in Study 16-214-02 (PIVOT-02), and platinum-doublet chemotherapy dosing, with no new or increased safety events observed to date. Per Protocol Amendment 03, participants in Arm A should discontinue bempegaldesleukin and may continue

nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.

5.5.3 Rationale for Bempegaldesleukin/Nivolumab Combination Dose

This section is not applicable per Protocol Amendment 03. The safety of bempegaldesleukin as a single agent has been assessed in 5 monotherapy cohorts administered bempegaldesleukin Q3W (22 patients) at doses ranging from 0.003 mg/kg to 0.012 mg/kg; a dosing frequency of Q2W (6 patients) was further explored at 0.006 mg/kg.

Table 5.5.3-1: *Not applicable per Protocol Amendment 03 Patient Exposure supporting combination dose

	Bempegaldesleukin Dosing Frequency	Nivolumab (Flat Dose[a]) Dosing Frequency	Bempegaldesleukin Dose (mg/kg)	No. Patients Examined for Safety	Positive Biomarker Data and/or Evidence of Clinical Activity?
Bempegaldesleukin Monotherapy	Q3W	n/a	0.003, 0.006, 0.009, 0.012	22	Yes
	Q2W	n/a	0.006	6	Yes
Bempegaldesleukin+ Nivolumab	Q3W	Q2W	0.006	4	Yes
	Q2W		0.006	3	Yes
	Q3W		0.006	25	Yes
	Q2W		0.003	3	Yes
	Q3W		0.009	3	Yes

[a] Nivolumab Q2W = 240 mg, Q3W = 360 mg.
Abbreviations: Q2W = every 2 weeks; Q3W = every 3 weeks; n/a = not applicable.

- The Safety Review Committee reviewed the totality of data and concluded the following for all 5 combination dose cohorts with a data cut of 05-Oct-2017:
- Two patients at the bempegaldesleukin 0.009 mg/kg Q3W + nivolumab 360 mg Q3W dose level experienced dose limiting toxicities: Grade 3 hypotension and Grade 4 metabolic acidosis, each of which resolved within 5 days and the patients continued on treatment at a lower dose of bempegaldesleukin.
- There were no Grade ≥ 3 treatment-related adverse events (TRAEs) at bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W: the recommended Phase 2 dose.
- TRAEs that occurred in ≥ 50% of the patients included fatigue, flu-like symptoms (combined MedDRA preferred terms of influenza-like illness, pyrexia, and chills), rash (combined MedDRA preferred terms of rash, rash erythematous, rash macular, rash maculopapular, and rash pruritic), and pruritus.
- TRAEs were consistent across all five dose cohorts.

- Management guidelines implemented in the combination program for hypotension were effective to mitigate the risk for Grade ≥ 3 hypotension.
- No Grade ≥ 3 immune-mediated AEs were observed.
- Cytokine-related AEs such as fever, chills, pruritus, fatigue, and rash are predictable based on the mechanism of action and were generally of mild severity and short duration.
- The addition of bempegaldesleukin did not exacerbate nivolumab-related AEs that are commonly classified as immune-mediated AEs.
- Bempegaldesleukin alone or in combination with nivolumab did not produce capillary leak syndrome, which is commonly observed in patients treated with high-dose IL-2.

At the time of the data cut, tumor response data were available for 34 patients, including 10 with metastatic melanoma, 19 with RCC, and 5 with NSCLC. Of these 34 response-evaluable patients, 24 were treated at 0.006 mg/kg bempegaldesleukin with nivolumab 360 mg flat dose Q3W; 17 patients had partial or complete responses and 13 had stable disease.

Given the totality of data, including safety/tolerability, reproducible PK, dose-independent pharmacodynamic (PD) profile, immune cell activation, and promising efficacy data [redacted], the Safety Review Committee approved bempegaldesleukin 0.006 mg/kg Q3W plus nivolumab 360 mg Q3W as the recommended dose to be administered in the late phase studies.

5.5.4 Justification for Dose for Adolescents

The PK of drugs and many therapeutics proteins has been shown to be similar between adolescent and adults once the effect of body size on PK is taken into consideration. Therefore, in general, adult doses would be expected to achieve similar systemic exposures in adolescents. Population PK model based simulation has shown that exposures produced by nivolumab 360 mg Q3W were well below the exposure range of 10 mg/kg Q2W regimen, a clinically safe dose, over a dose range of 34-180 kg in adults. Therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures.[50,51]

Participants ≥ 40 kg will be administered nivolumab 480 mg IV Q4W. Participants < 40 kg body weight will be administered a weight-based dose of 6 mg/kg IV Q4W that is equivalent to adult dose (typical subject of 80 kg body weight). **The remainder of this paragraph is not applicable per Protocol Amendment 03.** Participants ≥ 40 kg will be administered nivolumab 360 mg Q3W. Participants < 40 kg will be administered body weight adjusted nivolumab dose 4.5 mg/kg Q3W.

Additional details on dosing are provided in the nivolumab IB.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, tumor biopsies, and other requirements of the study.

c) For adolescent participants unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the informed consent form approved for the study prior to clinical study participation. Each participant must be informed about the nature of the study to the extent compatible with his or her understanding. Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator. Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local requirements. Continued assent should be documented when important new information becomes available that is relevant to the participant's assent.

2) Type of Participant and Target Disease Characteristics

a) Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (adults 18 years or older) /Lansky Performance Score ≥ 80% (minors ages 12-17 only) (for details, see Appendix 5).

b) Histologically confirmed stage III (unresectable) or stage IV melanoma, as per AJCC staging system, 8th edition (Note: Mucosal melanomas will be considered M1 for stratification).[34]

c) Treatment-naïve participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) with the exception of prior adjuvant and/or neoadjuvant treatment for melanoma with approved agents (eg, BRAF/MEK inhibitors, ipilimumab, nivolumab, pembrolizumab or interferon). Participants who have had recurrence within the 6 months of completing adjuvant and/or neoadjuvant treatment are not eligible.

d) Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria

e) ***Not Applicable as of Amendment 02; see 2(l) for updated criterion:*** *All participants must have tissue submitted during screening. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 3 months prior to enrollment, with an associated pathology report, must be submitted to the core laboratory for inclusion. Biopsy should be excisional, incisional, punch biopsy, core needle or surgical specimen. Fine needle aspiration is unacceptable for submission. Biopsies of bone*

lesions that do not have a soft tissue component are also unacceptable for submission. Central lab must provide IRT with the results of PD-L1 testing prior to randomization.

i) *In order to be randomized, a participant must be classified as PD-L1 positive (≥ 1% tumor cell membrane staining) vs PD-L1 negative (< 1% tumor cell membrane staining)/PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content) based on the PD-L1 IHC 28-8 pharmDx assay. If only an insufficient amount of tumor tissue from an unresectable or metastatic site is available from prior to the start of the screening phase, then a fresh biopsy will be required during the screening phase for performance of biomarker analyses. Non-evaluable participants are not eligible for randomization.*

f) [redacted] If the participant has > 1 measurable lesion, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments.(Note: These same lesion criteria apply for patients who consent to the optional biopsy in the main study.)

g) Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards by approved methodology during the Screening period. The site is responsible for entering results of BRAF testing into the IRT prior to randomization. Participants with indeterminate or BRAF status not reported prior to randomization are not permitted to be randomized to a treatment arm.

h) Prior palliative radiotherapy must be completed at least 2 weeks prior to randomization. Participants must have recovered from all radiation-related toxicities. Note: radiated lesions cannot be used as measurable lesions unless there is clear evidence of progression.

i) Participants must be able and willing to comply with the study visit schedule and study procedures.

j) A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test.

k) ≥ 12 weeks life expectancy

l) All participants must have tissue submitted during screening period to allow for participant enrollment into the study. Tissue submitted should be from an unresectable primary tumor lesion or any metastatic site. The tumor tissue should be from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment. Central lab must provide IRT with the results of PD-L1 testing prior to randomization. Either a FFPE tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission. Submission of an FFPE block is strongly preferred but unstained slides are also acceptable. Tissue may be from a core biopsy, punch biopsy, excisional or incisional biopsy, or surgical

specimen; fine needle aspiration and other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission. The Medical Monitor (or designee) can be consulted for eligibility if subjects have less than 20 unstained slides.

i) In order to be randomized, a participant must be classified as PD-L1 positive (≥ 1% tumor cell membrane staining) vs PD-L1 negative (< 1% tumor cell membrane staining) or PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content) based on the PD-L1 IHC 28-8 pharmDx assay. If only an insufficient amount of tumor tissue from an unresectable or metastatic site is available from prior to the start of the screening phase, then a fresh biopsy will be required during the screening phase for performance of biomarker analyses. Non-evaluable participants are not eligible for randomization,

3) Age and Reproductive Status

a) Males and females, ages 12 years or older, except where local regulations and/or institutional policies do not allow for participants < 18 years of age (pediatric population) to participate. If adolescents are not allowed to participate then ≥ 18 years of age, or age of majority applies.

i) Adolescents are not eligible for the [redacted] due to the blood sampling and biopsy samples.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment and for 5 months post-treatment completion. Women should use an adequate method(s) of contraception as indicated in Appendix 4. NOTE: WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) and 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4 which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to randomization. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Stable dose of anticonvulsants is allowed. Treatment for CNS metastases may include stereotactic radiosurgery (eg, GammaKnife, CyberKnife, or equivalent) or neurosurgical resection. Participants with CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days prior to randomization are not eligible. Participants who received whole brain radiation therapy are not eligible.

b) Uveal melanoma is excluded.

c) Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (eg, a condition associated with diarrhea or acute diverticulitis).

d) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

e) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. (Note: Prophylaxis of contrast allergies with a brief course of corticosteroids is acceptable. See Section 7.7.5)

g) History of organ transplant or tissue that requires systemic use of immune suppressive agents

h) Active infection requiring systemic therapy within 14 days prior to randomization.

i) Need for > 2 antihypertensive medications (active components/ingredients) for management of hypertension (including diuretics). Participants with hypertension must be on a stable anti-hypertensive regimen for the 14 days prior to randomization. Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (eg, angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).

j) Known cardiac history including:

i) History of unstable or deteriorating cardiac disease within the previous 12 months prior to screening including but not limited to the following:
   (1) Unstable angina or myocardial infarction
   (2) Transient ischemic attack (TIA)/cerebrovascular accident (CVA)
   (3) Congestive heart failure (New York Heart Association [NYHA] Class III or IV)
   (4) Uncontrolled clinically significant arrhythmias

k) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

l) History of pulmonary embolism (PE), deep vein thrombosis (DVT), or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (eg, internal jugular vein thrombosis) within 3 months prior to randomization.
   i) Participants with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to randomization and must be receiving a stable regimen of therapeutic anticoagulation (low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]). Note: see Section 7.7.4.1 (Restricted Treatments) for further guidance.
   ii) Unless there is a new medical contraindication observed after Cycle 1 Day 1, a participant with a history of venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout participation on the treatment phase of the study.

m) Participants with inadequately treated adrenal insufficiency.

n) Previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to screening.
   i) Acute symptoms must have resolved and based on Investigator assessment in consultation with the Medical Monitor (or designee), there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

o) Participants currently in other interventional trials for coronavirus disease 2019 (COVID-19), including investigational COVID-19 vaccination trials that are not authorized or approved by relevant Health Authorities, should not participate in this clinical trial until the COVID-19 vaccine washout period is achieved, as defined in that study.

2) Prior/Concomitant Therapy

a) Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug

b) Participants who have received a live/attenuated vaccine within 30 days before first treatment. Replication incompetent virus vaccines are not considered live vaccines (live vaccines are defined as those that are capable of transmitting infectious viruses).

c) Prior treatment with IL-2 therapy.

d) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, agents that target IL-2 pathway or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways with the exception of treatment with adjuvant and/or neoadjuvant intent as described in inclusion 2c.

e) Participants with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis)

f) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1for prohibited therapies.

3) Physical and Laboratory Test Findings

a) WBC < 2000/µL

b) Neutrophils < 1500/µL

c) Platelets < 100*103/µL

d) Hemoglobin < 9.0 g/dL

NOTE: May not transfuse within 14 days of randomization to meet eligibility criteria 3.a through 3.d.

e) Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

$$\text{Female CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

f) AST/ALT: > 3.0 x ULN

g) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)

h) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

This section is not applicable per Protocol Amendment 03. Please see Section 7.1.1.1 for hydration guidelines and limitations on strenuous activities, long hot showers and sauna use.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized / has not been treated). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor (or designee) may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Testing for asymptomatic SARS-CoV-2 infection, for example by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the Investigator, there are no SARS-CoV-2 infection-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and

- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- **Not applicable per Protocol Amendment 03.** Bempegaldesleukin (NKTR-214) Powder for Solution for Injection
- Nivolumab Solution for Injection

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Per Protocol Amendment 03, all participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W for the remainder of the study treatment period. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV Q4W.

Table 7-1: Study Treatment for CA045001

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
***Not applicable per Protocol Amendment 03** Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	1.0 mg of rhIL-2 (IL-2) per vial	IP	Open-label	Vial (one or more vials per carton)	Store at -20°C ± 5°C. Protect from light, store in original packaging until use.
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Store at 2° - 8° C. Protect from light and freezing.

Abbreviations: C = Celsius; IL-2 = interleukin-2; IMP = investigational medicinal product; IP = investigational product; mg = milligrams; mL = milliliter

Note: ***Not applicable per Protocol Amendment 03.** For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Per Protocol Amendment 03, participants in Arm A are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy. Participants in Arm A and Arm B will receive nivolumab monotherapy at 480 mg IV Q4W for the remainder of the study treatment period.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	480 mg	Q4W	IV
***Not applicable per Protocol Amendment 03** Bempegaldesleukin (NKTR-214)[a]	0.006 mg/kg	Q3W	IV
***Not applicable per Protocol Amendment 03** Nivolumab	360 mg	Q3W	IV

[a] **Not applicable per Protocol Amendment 03.** Bempegaldesleukin dose is based on IL-2 content.
Abbreviations: IV = intravenous; Q3W = every three weeks.

Not applicable per Protocol Amendment 03. Nivolumab dosing in both arms for participants < 40 kg will be weight-based 4.5 mg/kg IV Q3W.

Nivolumab dosing in both arms for participants < 40 kg will be weight-based 6 mg/kg IV Q4W.

Study agent(s) should be administered in an area with access to resuscitation equipment.

All participants should begin study treatment within 3 calendar days of randomization.

7.1.1 Bempegaldesleukin Dosing

Per Protocol Amendment 03, participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab. **Therefore, this section is not applicable per Protocol Amendment 03.** Each participant's bempegaldesleukin dose will be determined by the participant's weight in kilograms, which will be determined before the start of each cycle. If the participant's weight is within 10% of the previous cycle Day 1 weight, the study drug doses do not need to be recalculated depending on institutional guidelines/preference.

Bempegaldesleukin will be administered first before nivolumab, and will be administered as an IV infusion over 30 (± 5) minutes at a starting dose of 0.006 mg/kg Q3W (± 3 days, Cycle 2 and beyond). Bempegaldesleukin infusion must be promptly followed by a flush of diluent to clear the line, and administration time should include the time required for flushing. Nivolumab

administration should start at least 30 minutes from the end of the bempegaldesleukin administration. Participants may be dosed no less than 18 days from the previous dose.

Participants should be carefully monitored for infusion reactions during bempegaldesleukin administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6. If the participant experiences a Grade ≥ 2 infusion-related reaction or hypotension during the days after bempegaldesleukin dosing, the participant may be monitored overnight at the discretion of the Investigator; longer periods of monitoring may be implemented at the discretion of the Investigator.

Treatment with bempegaldesleukin may be delayed or reduced as described in Section 7.4. In the event that nivolumab is permanently discontinued due to toxicities, see Section 8.1.1.

Bempegaldesleukin treatment can continue for participants randomized to the bempegaldesleukin and nivolumab combination arm in the event that nivolumab is permanently discontinued due to toxicities (see Section 8.1.1).

Bempegaldesleukin (NKTR-214) Powder for Solution for Injection, is to be administered as an IV infusion following reconstitution and dilution as described in the Pharmacy Manual. In-line filters (including in-line filter extension sets) must not be used to administer bempegaldesleukin due to the extent of drug losses by adsorption on the filter membrane. Bempegaldesleukin infusion must be promptly followed by a flush of diluent to clear the line. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Bempegaldesleukin infusions prepared in 0.9% NaCl solution or 5% Dextrose in water are compatible with polyvinyl chloride or polyolefin containers and infusion sets, as well as closed-system transfer devices (CSTDs) when following specific instructions to ensure prepared dose accuracy.

Please refer to the Pharmacy Manual/current Investigator's Brochure for details regarding preparation, storage, and administration.

7.1.1.1 Hydration Guidelines

This section is not applicable per Protocol Amendment 03. Important safety information and hydration instructions are to be provided to participants. Hydration and renal function should be assessed within 24 hours prior to study drug administration or as soon as locally feasible (Table 2-2). Underlying reasons for decreased oral intake (such as nausea) should be addressed and treatment (such as IV hydration) should be provided. Participants may receive additional hydration precautions in a participant card/handout.

Adult Hydration Guidelines:

For adult participants randomized to Arm A (ie, bempegaldesleukin in combination with nivolumab), administer at least 1 liter of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days (Days 2-4) after administration of bempegaldesleukin participants

are to be instructed to drink at least 2 liters per day of self-administered oral hydration (see Table 7.1.1.1-1).

Adolescent Hydration Guidelines:

Hydration guidance for adolescent participants is weight-based (see Table 7.1.1.1-1). Adolescents who weigh ≥ 40 kg follow the Adult Hydration Guidelines. For adolescent participants who weigh less than 40 kg randomized to Arm A administer 500 mL of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days after administration of bempegaldesleukin (Days 2-4), adolescents < 40 kg are to be instructed to drink at least 1 liter of fluids per day.

Table 7.1.1.1-1: Hydration guidelines for Adults and Adolescents

***Not applicable per Protocol Amendment 03.**

	Adults & Adolescents ≥ 40 kg	**Adolescents < 40 kg**
Day of infusion (IV)	1000 mL per day	500 mL per day
Days 2-4 (Oral)	2000 mL per day	1000 mL per day

Advise patients to refrain from activity that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 of each cycle of treatment with bempegaldesleukin. Advise participants with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.

Between Days 3 and 5, inclusive, following administration of the first two doses of bempegaldesleukin, site personnel must contact the participant (by telephone or clinic visit) at least once to remind the participant of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Table 2-2). Following subsequent administration of bempegaldesleukin, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin.

Per clinical judgment, IV fluids may be administered at any time. The Investigator may decide to forego administering IV fluids to a participant if this is deemed to be in the best interest of the participant (eg, evidence of fluid overload).

7.1.2 Nivolumab Dosing

Not applicable per Protocol Amendment 03. There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 18 days from the previous dose during Q3W (±3 days, Cycle 2 and beyond) cycles. Premedications are not recommended for the first dose of nivolumab.

Not applicable per Protocol Amendment 03. Participants should receive nivolumab at a dose of 360 mg as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first.

Not applicable per Protocol Amendment 03. Participants < 40 kg will be administered body weight adjusted nivolumab dose 4.5 mg/kg Q3W as a 30-minute infusion.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 25 days from the previous dose during Q4W (±3 days, Cycle 2 and beyond) cycles. Premedications are not recommended for the first dose of nivolumab.

Participants should receive nivolumab at a dose of 480 mg Q4W as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first.

Participants < 40 kg should be administered a body weight adjusted nivolumab dose of 6 mg/kg Q4W as a 30-minute infusion.

For participants (< 40 kg), dosing calculations for nivolumab should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. For nivolumab dosing in adolescents, all doses should be rounded up or to the nearest milligram per institutional standard. At the end of each infusion, flush the line with sufficient quantity of diluent.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed. Nivolumab treatment can continue for patients randomized to Arm A in the event that bempegaldesleukin is stopped due to toxicities.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Please refer to the current version of the pharmacy manual for complete preparation, storage, and handling information.

Not applicable per Protocol Amendment 03. In the event that bempegaldesleukin is permanently discontinued due to toxicities, see Section 8.1.1.

7.2 Method of Treatment Assignment

Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers will not be reassigned. An IRT will be employed to manage participant randomization. The Investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for participant randomization:

- Participant number
- Year of birth
- PD-L1 tumor expression status (PD-L1 positive vs PD-L1 negative/indeterminate), analyzed by the central laboratory vendor and transferred to the IRT
- BRAF V600 mutational status; local results to be entered into IRT by site.
- M Stage at screening (see Appendix 8)

- Participants meeting all eligibility criteria will be randomized in a 1:1 ratio and stratified by PD-L1 tumor expression status, BRAF status, and AJCC M stage as described below:

- PD-L1 tumor expression status
  - PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells) vs
  - PD-L1 negative (< 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- BRAF status
  - BRAF V600 mutation positive vs
  - BRAF V600 wild type
- AJCC 8th edition M stage at Screening (See Appendix 8)
  - M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs
  - M1any[1] (Stage IV Elevated LDH)

Note: All mucosal melanoma will be considered as M1 and the assignment of strata will be based on the baseline LDH level (M0 / M1any[0] for mucosal melanomas with normal LDH and M1any[1] for mucosal melanomas with elevated LDH).

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of PD-L1 tumor expression status (positive ≥ 1%, negative [< 1%]/indeterminate), BRAF V600 mutational status (BRAF mutation positive, BRAF wild type), and M Stage (M0 / M1any[0], M1any[1]). The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

Not applicable as this is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an Interactive Response Technology (IRT). Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples. [redacted]

[redacted]

Based on the CA045-001 study results showing lack of efficacy with bempegaldesleukin plus nivolumab compared to nivolumab monotherapy in the first line treatment of patients with metastatic or unresectable melanoma, treatment assignment will no longer be blinded to the Sponsor. Participants in Arm A will discontinue bempegaldesleukin, and may continue nivolumab monotherapy. The Sponsor unblinded the study as no further formal efficacy analyses will be conducted.

7.4 Dosage Modification

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. If bempegaldesleukin or nivolumab meets the criteria for dose delay which apply for all drug-related adverse events regardless of whether the event is attributed to nivolumab or bempegaldesleukin or both, then administration of both drugs must be delayed if any of the delay criteria in Table 7.4.1-1 and Table 7.4.1-2 are met.

SARS-CoV-2 infection, either confirmed or suspected, requires delay of nivolumab and bempegaldesleukin study treatment.

Delay bempegaldesleukin and nivolumab dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication until the criteria to resume are met (Section 8.1.2).

Note: Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Participants who require delay of nivolumab and bempegaldesleukin should be re-evaluated weekly or more frequently if clinically indicated and resume treatment with combination of bempegaldesleukin and nivolumab when re-treatment criteria are met. Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Bempegaldesleukin and nivolumab are considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Discontinuation criteria for nivolumab and bempegaldesleukin are found in Section 8.1.1.

AE grading should be based on CTCAE version 5.

7.4.1 Nivolumab and Bempegaldesleukin Dose Delay, Reduction, and Discontinuation Criteria

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. Nivolumab administration should be delayed for the following:

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication. AE criteria for delaying, reducing, and discontinuing nivolumab and bempegaldesleukin are available in Table 7.4.1-1 and Table 7.4.1-2.

- If a study participant has received an investigational COVID-19 vaccine prior to screening, enrollment should be delayed until the full dosing schedule of the vaccine has been completed and the impact of the vaccine is stabilized, unless a delay would compromise the participant's health or suitability for enrollment, as determined by the Medical Monitor (or designee).

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. Dose reductions for nivolumab are not permitted in this study.

Not applicable per Protocol Amendment 03. Dose delays and reductions are permitted for bempegaldesleukin. Bempegaldesleukin may be delayed or reduced to 0.003 mg/kg based on observed drug-related toxicities. If the bempegaldesleukin dose is reduced to 0.003 mg/kg, the dose level should remain at this level throughout the remainder of the study and will not be re-escalated.

Not applicable per Protocol Amendment 03. Bempegaldesleukin dosing may resume at the same bempegaldesleukin dose or at a lower bempegaldesleukin dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the participant. Medical Monitor (or designee) consultation is required for dose reduction.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 4	Permanently discontinue	-
Renal			
Serum Creatinine Increased See bempegaldesleukin-specific criteria in Table 7.4.1-2 for transient, non-inflammatory increased serum creatinine	Grade 2 or 3	Nivolumab: Delay dose[b]	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue	-
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to Grade ≤ 1.
	Grade 3 or 4	Permanently discontinue	-

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hepatic			
AST, ALT, or T.bili increased	AST or ALT > 3 × and ≤ 5 × ULN or T.bili > 1.5 × and ≤ 3× ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 × ULN or T.bili > 3 × ULN, regardless of baseline value	Permanently discontinue	ALT/AST elevations < 8.0 x ULN in Cycle 1 only, study treatment does not need to be discontinued (see Section 7.4.1.1 for dose modification criteria).
	Concurrent AST or ALT > 3 × ULN and T.bili > 2 × ULN, regardless of baseline value	Permanently discontinue	-
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor (or designee) needed prior to resuming nivolumab/bempegaldesleukin therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of nivolumab.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of nivolumab or bempegaldesleukin.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming nivolumab or bempegaldesleukin therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of nivolumab or bempegaldesleukin.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming nivolumab or bempegaldesleukin therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			replacement, participant may not require discontinuation of nivolumab or bempegaldesleukin.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area.
	Suspected SJS, TEN, or DRESS	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area.
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	-
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	-
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	-
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	-
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	-

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Neurological (other than GBS, MG, encephalitis, or myelitis) For CVA/TIA, see bempegaldesleukin-specific criteria in Table 7.4.1-2)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	-
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue	-
Other Clinical AEs			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	-
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	-

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Drug-related AE (**not listed above**) See bempegaldesleukin-specific criteria in Table 7.4.1-2 for further guidance) (not applicable per Protocol Amendment 03)	Grade 2 non-skin AE, except fatigue	Nivolumab: Delay dose[b]	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE: First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value (unless otherwise requiring permanent discontinuation, per Section 8.1.1) with the exception of fatigue where dosing may resume in the presence of Grade 2 fatigue.
	Grade 3 AE: First occurrence lasting > 7 days	Permanently discontinue	-
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	-
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	-

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**
(Note that bempegaldesleukin should be discontinued for participants receiving bempegdesleukin plus nivolumab)

Drug-related AE per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Laboratory Abnormalities			
Other Drug-related Laboratory Abnormality (**not listed above**)	Grade 3	Delay dose	Exceptions: No delay required for: • Grade 3 lymphopenia • Grade ≥ 3 asymptomatic amylase or lipase elevation Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity Reaction or Infusion Reaction	Grade 3 or 4	Permanently discontinue	See Section 7.4.6 (Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; CVA, cerebrovascular accident; DRESS, drug-reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre Syndrome; MG, myasthenia gravis; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; TIA, transient ischemic attack;ULN, upper limit of normal.

[a] Permanent discontinuation of study drug should meet the criteria (Section 8.1.1).

[b] **Not applicable per Protocol Amendment 03.** If dosing of one drug is delayed, then dosing of both drugs is delayed.

Table 7.4.1-2: Bempegaldesleukin-specific Adverse Event Criteria for Delay, Resumption, and Discontinuation[a] of Nivolumab and Bempegaldesleukin (if One is Delayed, Both are Delayed)

***Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable.**

Bempegaldesleukin-specific Criteria for Delay, Resumption, and Discontinuation			
Serum Creatinine Increased (transient, non-inflammatory)	Grade 2, 3, or 4	Delay dose[b]	For participants who must delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause, delay retreatment with study drug for approximately 3-5 days. After the dosing delay, the participant may resume study drug when serum creatinine has returned to Grade ≤ 1, as assessed within 24 hours prior to redosing (or as soon as locally feasible). If inflammatory etiology suspected, refer to renal AE management algorithm (Appendix 6) for further guidance.
Other Drug-related AE (not listed above)	Persistent Grade 2 toxicity, except fatigue and asthenia	Delay dose[b]	Dose delay at the discretion of the Investigator. Note: Persistent Grade 2 is defined as a Grade 2 AE lasting ≥ 3 weeks and ongoing at the time of subsequent dosing that is attributed as either "possibly related" or "related" to bempegaldesleukin.
TIA/CVA	All grades	Permanently discontinue both drugs	Any new CVA event confirmed by MRI with diffusion weighted imaging, regardless of neurological symptoms (e.g., cryptogenic CVA) and for suspected TIA without clear alternative etiology. See Appendix 7.*

Abbreviations: AE, adverse event; CVA, cerebrovascular accident; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

[a] Permanent discontinuation of study drug should meet the criteria (Section 8.1.1).

[b] Not applicable per Protocol Amendment 03. If dosing of one drug is delayed, then dosing of both drugs is delayed.

*Per Protocol Amendment 03, participants are required to discontinue bempegaldesleukin and may continue on nivolumab treatment. Advanced Cardiac Life Support (ACLS) and institutional guidelines should be followed for all CVA cases. For participants previously treated with bempegaldesleukin plus nivolumab who have a CVA or TIA, the Investigator should discuss risk/ benefit of continuing nivolumab. The managements algorithm for CVA or TIA (Appendix 7) is not applicable per Protocol Amendment 03.

7.4.1.1 Dose Modification Criteria for Bempegaldesleukin and Nivolumab for Cycle 1 ALT/AST Elevations

This section is not applicable per Protocol Amendment 03. These recommendations are for Cycle 1 only and are not intended to serve as rigid guidelines or to replace clinical judgement. Subsequent cycles should follow standard Hepatic Adverse Event Management Algorithm (Appendix 6).

Rule out non-inflammatory etiologies. If non-inflammatory cause, treat accordingly and continue bempegaldesleukin and nivolumab. Consider imaging for obstruction.

If during monitoring ALT/AST increases, follow the guidance for the highest levels.

If AST or ALT > 3.0 to ≤ 5 x ULN (Within first cycle of bempegaldesleukin and nivolumab)

- Increase frequency of LFT monitoring to approximately every 3 days and delay treatment until lab abnormalities resolve to Grade 1 or baseline

If no improvement within 7 days:

- Treat with 0.5-1 mg/kg/day prednisone equivalents, and taper steroids over at least 1 month before resuming treatment

If ALT or AST > 5.0 to ≤ 8.0 x ULN (Within first cycle of bempegaldesleukin and nivolumab)

- Increase frequency of monitoring to approximately every 3 days until lab abnormalities resolve to Grade 1 or baseline
- Treatment must be delayed until lab abnormalities resolve to Grade 1 or baseline

If no improvement within 7 days (follow Hepatic Adverse Event Management Algorithm):

- Discontinue bempegaldesleukin and nivolumab
- 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least one month
- Consult gastroenterologist
- Consider adding non-corticosteroid immunosuppressive medication if no improvement in > 3-5 days, worsens or rebounds while on steroids

If ALT or AST > 8.0 x ULN (follow Hepatic Adverse Event Management Algorithm)

- Discontinue bempegaldesleukin and nivolumab
- Increase frequency of monitoring to approximately 1-2 days
- 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least one month
- Consult gastroenterologist

- If no improvement in > 3-5 days, worsens or rebounds, add non-corticosteroid immunosuppressive medication

Please refer to Section 8.1 for discontinuation criteria.

7.4.2 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for both bempegaldesleukin and nivolumab. The elevations in hepatic transaminases associated with bempegaldesleukin typically occur at the time of peak active cytokine concentration in the blood (Day 8), and are often accompanied by IL-2 mediated AEs such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually asymptomatic, mild or moderate in severity, not associated with increased total bilirubin and alkaline phosphatase, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2. The transaminase elevations are considered to occur in the context of IL-2 mediated AEs. For transaminase elevations occurring in Cycle 1 consistent with a cytokine related effect without alternative etiologies, follow the Cycle 1 hepatic adverse event management guideline (Section 7.4.1.1 and Appendix 6).

Hepatic events, including elevated liver function tests, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher grade abnormalities are concerning for immune-mediated hepatitis, and typically occur with a later onset (median time to onset of 3.3 months). Immune mediated hepatitis generally results in a quick rise in liver function tests, and responds to corticosteroids or immune-modulating agents. For transaminase elevations occurring in Cycle 2 onwards potentially involving an immune-mediated mechanism, follow the immune-mediated hepatic adverse event management guidelines in the nivolumab IB or OPDIVO product labeling for appropriate management.

7.4.3 Monitoring and Management of Eosinophilia

7.4.3.1 Bempegaldesleukin-induced Eosinophilia

This section is not applicable per Protocol Amendment 03. Frequent and significant eosinophilia has been observed in patients receiving bempegaldesleukin, primarily starting at Cycle 2 with levels plateauing after Cycle 3, consistent with the known pharmacodynamic effect of IL-2 therapy. The eosinophilia pattern demonstrates a cyclic waxing and waning pattern whereby eosinophil levels peak approximately 7 days after each infusion and wane before the participant's next infusion.

Absolute eosinophil count (AEC) should be closely monitored per protocol. If a participant is suspected to have eosinophilic disorder (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous systems) with AEC at or above the 5,000/µL (5×10^9/L) level, delaying bempegaldesleukin treatment may be considered while evaluating and treating the participant as clinically indicated.

7.4.3.2 Eosinophilic Disorders

This section is not applicable per Protocol Amendment 03. Isolated cases of hypereosinophilic syndrome (HES) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. If there is clinical concern for an eosinophilic disorder, the Investigator is encouraged to contact the Medical Monitor (or designee).

Additional details regarding eosinophilia and eosinophilic disorders are provided in the bempegaldesleukin Investigator's Brochure.

7.4.4 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

Adrenal insufficiency and hypophysitis have been observed in participants receiving nivolumab and ipilimumab. Consider prompt evaluation when participants have signs or symptoms of hypophysitis or adrenal insufficiency which includes levels of early-morning ACTH, cortisol, thyroid stimulating hormone (TSH), and free thyroxine (T4). Co-management with an endocrinologist is recommended for participants with pre-existing adrenal insufficiency.

7.4.5 Management Algorithms for [redacted] Cytokine-Release Syndrome

[redacted]

7.4.5.2 Management Algorithm for Cytokine-Release Syndrome

This section is not applicable per Protocol Amendment 03. Cytokine-release syndrome (CRS) is a clinical diagnosis with a constellation of symptoms often characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. In addition, diarrhea and end organ dysfunction can be seen in CRS. Many of these symptoms overlap with known AEs seen in bempegaldesleukin and nivolumab combination therapy (ie, pyrexia and hypotension). These symptoms may be seen in infusion reactions as well as other known syndromes, such as tumor lysis syndrome and macrophage activation syndrome. For suspected CRS of Grade 3 or above, the Investigator is encouraged to contact the Medical Monitor or designee. An algorithm for the management of CRS is provided in Appendix 11 (not applicable per Protocol Amendment 03).

7.4.6 Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. Infusion reactions have been reported during bempegaldesleukin and nivolumab infusions. If such a reaction were to occur with either the bempegaldesleukin or nivolumab infusion, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, myalgia, hypotension, hypertension, bronchospasm, or other hypersensitivity/allergic-like reactions.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at the bedside and monitor the participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes before subsequent infusions. Subsequent infusions may be administered at a reduced rate (eg, 50% of the original infusion rate).

For **Grade 2** symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the bempegaldesleukin or nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at the bedside and monitor the participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. If symptoms recur after restarting the bempegaldesleukin or nivolumab infusion, then no further bempegaldesleukin or

nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at the bedside, and monitor the participant until resolution of symptoms.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of methylprednisolone or equivalent) may be used. Subsequent infusions may be administered at a reduced rate (eg, 50% of the original infusion rate) (see Section 7.7.4.1 for corticosteroid dose equivalents).

For **Grade 3** or **Grade 4** symptoms (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of bempegaldesleukin or nivolumab. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Nivolumab and bempegaldesleukin will be permanently discontinued. The participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational products are only dispensed to study Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes

documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability as well as participant's medical records and electronic case report form (eCRF). Study drug will be administered in the clinic by trained personnel. Drug accountability should be reviewed by the site study staff at each visit.

This paragraph is not applicable per Protocol Amendment 03 as bempedaledesleukin is discontinued from Arm A. Arm A: At least once between Days 3 and 5 (inclusive) following the first two infusions of bempegaldesleukin, site personnel must contact the participant (by telephone or clinic visit) to remind the participant of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion (Table 2-2). For subsequent doses, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.5)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of melanoma)
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Low dose acetylsalicylic acid (approximately 81 mg/day) should not be combined with LMWH or DOAC due to an increased risk of hemorrhage (except as stated in Section 7.7.4.1).

7.7.2 Palliative Therapy

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted. If radiologic progression per RECIST 1.1 has been identified by the Investigator prior to the start of palliative treatment, the criteria for treatment beyond progression (Section 8.1.3) must be met in order for study treatment to continue after the completion of palliative treatment.

7.7.3 Prior and Concomitant Medications

Recording of prior medications should include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, OTC medications, herbs, and dietary supplements.

All medications (prescription and OTC), vitamin and mineral supplements, and/or herbs taken by the participant from screening through the follow-up (100 days from the last dose of the study treatment) will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (eg, biopsy) should also be included.

7.7.3.1 COVID-19 Vaccination

A decision to vaccinate individuals is up to the individual and the treating physician unless prohibited by the protocol. Of note, COVID-19 vaccine response and safety may have the potential to be affected by administration of a particular IP.

When feasible, the full vaccination series (eg, both doses of a two-dose series) should be completed prior to treatment until the vaccine-associated symptoms of the vaccine are stabilized and a delay in treatment would not put the study participant at risk.

If a participant is already in the study, the full vaccination series is allowable. Study dose administration must be delayed until the vaccine-associated symptoms of the vaccine are stabilized. The appropriate information should be captured to assess any potential vaccine-related adverse events.

There does not need to be a minimum duration between the last administration of IP and administration of COVID-19 vaccine. If possible, avoid overlap of administration (eg, at least 2 days, preferably 7 days apart).

COVID-19 vaccines have the potential to impact immunological pharmacodynamic biomarkers.

[redacted]

7.7.4 Other Restrictions and Precautions

7.7.4.1 Restricted Treatments

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

7.7.4.2 Restricted Treatments

The guidance for anticoagulation and antithrombotic therapy for the prevention and treatment of venous thromboembolic disease was included to mitigate the potential increased risk of ischemic cerebrovascular events (ICEs) observed in participants treated with bempegaldesleukin plus nivolumab. Per Protocol Amendment 03, participants will receive nivolumab monotherapy only. Nivolumab monotherapy does not appear to be associated with an increased risk of ICE, and anticoagulation therapy will no longer be mandated for participants enrolled on the study. There are no data suggesting how long the duration of potential increased risk of ICE persists after the discontinuation of bempegaldesleukin. Decisions regarding antithrombotic therapy should be based on the Investigator's assessment of the benefit/risk for each individual participant.

The remainder of this section is not applicable per Protocol Amendment 03. Participants with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation (preferably LMWH or DOAC). Unless there is a new medical contraindication observed after Cycle 1 Day 1, a participant with a history of a venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the participant's time on study treatment.

Anticoagulation options include the following:

- Low molecular weight heparin (LMWH).
- Oral factor Xa inhibitors (direct oral anti-coagulants [DOAC] such as rivaroxaban, apixaban, or edoxaban).
- Use of warfarin (Coumadin) is permitted; however, therapeutic dosing should target a specific INR stable for at least 4 weeks prior to enrollment. Because bempegaldesleukin has the potential to down-regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of bempegaldesleukin, frequent monitoring of INR and ongoing consideration of warfarin dose adjustments are warranted throughout the participant's participation on study.

If anticoagulation is being newly introduced or adjusted, the Investigator may consider consulting the Medical Monitor (or designee) for guidance.

7.7.4.3 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast

regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the Investigator and the standard set by the local Ethics Committee.

7.7.4.4 Blood Pressure Precautions

This section is not applicable per Protocol Amendment 03. Consideration should be given to discontinuing antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hypertrophy) prior to each dose of bempegaldesleukin, particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of bempegaldesleukin. Participants who are on medications with antihypertensive effects for the treatment of coronary artery disease (CAD; eg, beta-blockers, Ca channel blockers, nitrates, etc) should be able to withhold these drugs prior to initiation of treatment.

Antihypertensive medications may be reinstituted in between doses of bempegaldesleukin at any time as clinically indicated (eg, based on blood pressure monitoring results).

In participants receiving beta-blockers, consider a step-wise tapering of doses before initiation of bempegaldesleukin to avoid reflex tachycardia. If Grade 2 or higher hypertension is observed in any cycle, participants should be monitored more frequently (at least weekly until a new stable antihypertensive regimen is identified). Participants may be monitored more frequently at the discretion of the Investigator as clinically warranted.

7.7.5 Permitted Therapy

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily of prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Prophylaxis for flu-like symptoms with either acetaminophen or ibuprofen is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms should be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed.

Prophylaxis for rash and/or pruritus with anti-histamines is permitted on study per the Investigator's discretion. Prophylaxis for rash and/or pruritus should be initiated on either Day 1

or Day 2 after dosing of bempegaldesleukin or nivolumab and may continue through Day 5 or longer as needed.

Administration of red blood cell (RBC) transfusions is allowed for participants with anemia.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration in Protocol Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab and bempegaldesleukin is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

Per Protocol Amendment 03, BMS is terminating the development of bempegaldesleukin in combination with nivolumab. If BMS decides to terminate the study all sites will be notified and given a period of time to discontinue study treatment and transition all participants to commercially available SOC treatment. The Sponsor may provide alternative mechanisms to receive treatment for participants who cannot afford or access commercially available SOC treatments.

8 DISCONTINUATION AND RESUMPTION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Disease progression in the absence of clinical benefit as determined by the Investigator.

- Clinical disease progression in the absence of radiologically confirmed progression by RECIST 1.1
- See Section 8.1.1 for Nivolumab and Bempegaldesleukin Discontinuation Criteria.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the Investigator and Sponsor

If a participant has not progressed following discontinuation of study drug(s), every effort should be made to continue to obtain radiographic tumor assessments until Investigator confirmed progression.

A participant may also be withdrawn from investigational product/study by the Sponsor, Regulatory Authorities, or Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs).

Participants may choose to discontinue the study at any time, for any reason, and without prejudice to further treatment.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In all cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8.1.1 Nivolumab and Bempegaldesleukin Discontinuation Criteria

Per Protocol Amendment 03, participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and will receive nivolumab monotherapy.

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. Participants meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, with Medical Monitor (or designee) approval, treatment with bempegaldesleukin or nivolumab alone may continue if the toxicities listed below are considered related to bempegaldesleukin or to nivolumab only and once the criteria to resume are met (Section 8.1.2).

Nivolumab and bempegaldesleukin treatment should be permanently discontinued per criteria in Table 7.4.1-1 and Table 7.4.1-2.

Discontinue study treatment for participants receiving bempegaldesleukin in combination with nivolumab:

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab and bempegaldesleukin dosing.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1.2 Criteria to Resume Bempegaldesleukin and/or Nivolumab

Per Protocol Amendment 03, the text below related to bempegaldesleukin is not applicable. Participants may resume treatment with study intervention if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.1-1 and Table 7.4.1-2.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following:

1) At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen),
2) Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications),
3) Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and
4) Consultation by the Medical Monitor (or designee).

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

If the toxicity resolves to ≤ Grade 1 or baseline > 8 weeks after the last dose, but the participant does not otherwise meet the criteria for permanent discontinuation (see Section 8.1.1), and the Investigator believes that the participant is deriving clinical benefit, then the participant may be eligible to resume the study drug(s) following the approval of the Medical Monitor (or designee).

8.1.3 Treatment Beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[20,52]

Participants, regardless of study arm, will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease or clinical progression, assessed by the Investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Radiographic assessment should continue as per schedule (Table 2-2) during treatment beyond progression. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

If the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities, Table 2-2.

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial progressive disease. Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.4 Post Study Treatment Study Follow-up

In this study, ORR, PFS, and OS are key endpoints of the study. **Please refer to Section 5.1 for follow-up details. Per Protocol Amendment 03, the remainder of this paragraph is not**

applicable. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5.1.3 until death or the conclusion of the study. The total duration of the study is up to 5 years after randomization of the last participant.

The Sponsor may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window (Schedule of Activities, Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

Per Protocol Amendment 03, this paragraph is not applicable. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy will be collected.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed up to 100 days for protocol specified follow-up procedures with documentation of last overall survival. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

- If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator's Brochure.

Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Per Protocol Amendment 03, BICR assessment of imaging will be discontinued. Response and progression will be determined by the Investigator.

9.1.1 Imaging Assessments for the Study

As of Protocol Amendment 03, images will no longer be submitted to an imaging core lab. Sites should be qualified prior to scanning the first participant and understand the image acquisition guidelines as outlined in the CA045001 Imaging Manual provided by the imaging core lab.

Screening and follow-up images should be acquired as outlined in Section 2, (Schedule of Activities).

Evaluate any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) for RECIST 1.1 tumor assessment. X-Ray and bone scans that clearly demonstrate interval progression of disease, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be included in tumor assessment.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be included for RECIST 1.1 tumor assessment.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same Investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography-computed tomography (PET-CT) scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care,

and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

MRI of brain without and with contrast should be acquired as outlined in Section 2 (Schedule of Activities). CT of the Brain without and with contrast can be performed if MRI is contraindicated.

Bone scans may be collected per local standards, as clinically indicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same Investigator using RECIST 1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the CRF based on the Investigator's assessment using RECIST 1.1 criteria (See Appendix 9 for specifics of RECIST 1.1 criteria to be utilized in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response (BOR) of stable disease (SD) requires a minimum of 42 days on study from randomization to the date of the first imaging assessment.

9.1.1.3 BICR Confirmation of Progression

Per Protocol Amendment 03, BICR will be discontinued and all study treatment decisions will be based on the Investigator's assessment of tumor images.

Not applicable per Protocol Amendment 03. Sites should submit all scans to the imaging core lab on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and Investigator assessment of submitted scans. When progression per RECIST 1.1 criteria is assessed by the Investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be performed. The BICR review will be completed and the results provided to the site as specified in imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Not applicable per Protocol Amendment 03. Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to

the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2, until progression has been confirmed by BICR.

All study treatment decisions will be based on the Investigator's assessment of tumor images and not on the BICR assessment. The BICR assessment of progression is only relevant for determining when tumor assessments for a given participant are no longer required to be submitted to the imaging vendor.

9.1.2 Imaging Assessment for the Study

Per Protocol Amendment 03, BICR assessment of imaging will be discontinued and imaging assessment will be performed only by the Investigator.

All study treatment decisions will be based on the Investigator's assessment of tumor images.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment.

[redacted]

[redacted]

[redacted]

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE), per CTCAE version 5, can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection and all SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 100 days of discontinuation of dosing.

- Cerebrovascular accident (CVA; any grade) is considered an adverse event of special interest (AESI/AEOSI) and should be assessed as an SAE. All CVAs are required to follow the timelines for SAE reporting (eg, 24 hours).

SAEs to be collected after the 100-day safety visit if the SAE is deemed to be related or residual toxicities are persisting.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF modules.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of updated information being available.

For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known adverse events, when appropriate for the program or protocol.

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

[redacted]

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled out as per institutional policy on SARS-CoV-2.

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Serum or urine pregnancy tests will be performed on women of childbearing potential (WOCBP) according to the Schedule of Activities. A negative pregnancy test result must be obtained before the administration of the study drug(s).

A pregnancy test does not need to be performed on women who are postmenopausal. A definition of post-menopausal can be found in Appendix 4.

If a female participant becomes pregnant, administration of the study drug(s) must be discontinued. Requirements for reporting a pregnancy are provided in Appendix 3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor

or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

[redacted]

This paragraph is not applicable per Protocol Amendment 03. Additional information may also be collected on select AEs primarily related to bempegaldesleukin, including hypotension, capillary leak syndrome, and eosinophilic disorders. A list of relevant AE terms will be maintained by the Medical Surveillance Team/Drug Safety Committee or equivalent.

9.2.7 Adverse Events of Special Interest (AESI/AEOSI)

Cerebrovascular accident (CVA; any grade) is considered an adverse event of special interest (AESI/AEOSI) and should be assessed as an SAE. All CVAs are required to follow the timelines for SAE reporting (eg, 24 hours). CVA management guidelines are provided in Appendix 7.

9.2.8 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting Investigator (eg, anemia versus low hemoglobin value).

9.2.9 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) Treatment-emergent ALT or AST > 3 times ULN,

AND

2) Total bilirubin > 2 times ULN or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of elevated liver enzymes and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.10 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3). All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record CRF.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Vital Signs and Oxygen Saturation

Vital sign measurements will be recorded according to the Schedule of Activities (Section 2). Vital signs include pulse rate, systolic and diastolic blood pressure, and temperature. Pulse oximetry will also be included at baseline only. It is preferred that the same arm be used for all blood pressure readings, if possible. Instructions for more frequent vital sign monitoring after completion of study drug administration are provided in Section 2.

9.4.2 Electrocardiograms

All participants will have 12-lead electrocardiogram (ECG) done during Screening as specified in the Schedule of Activities (Section 2).

9.4.3 Echocardiogram

Standard echocardiogram will be performed to assess cardiac function and LVEF according to the Schedule of Events (Section 2). A MUGA scan can be performed to assess cardiac function and LVEF if a standard echocardiogram cannot be performed. Participants who are found to have other significant abnormalities on echocardiogram should be discussed with the Medical Monitor (or designee) prior to randomization.

9.4.4 Pregnancy Tests

Serum or urine pregnancy tests will be performed on women of childbearing potential according to the Schedule of Activities. A negative pregnancy test result must be obtained within 24 hours prior to the administration of the study drug(s).

A pregnancy test does not need to be performed on women who are postmenopausal. A definition of post-menopausal can be found in Appendix 4.

If a female participant becomes pregnant, administration of the study drug(s) must be discontinued. Guidelines to be followed in case of pregnancy and reporting requirements are provided in Section 9.2.5.

9.4.5 Clinical Safety Laboratory Assessments

A list of the clinical laboratory analyses to be tested is provided in Table 9.4.5-1.

All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2).

The Investigator or qualified Sub-Investigator will review all results for clinical significance. Any laboratory result deemed clinically significant (ie, is associated with signs and symptoms, requires treatment, or requires follow up) will be recorded as an AE as described in Section 9.2.8.

Table 9.4.5-1: Clinical Safety Laboratory Assessments

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Creatinine clearance (Screening only) Blood Urea Nitrogen (BUN) or serum UREA Glucose	Albumin Sodium Potassium Chloride Calcium Phosphorus CK TSH, free T3 and free T4 - Screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Lipase and/or amylase
Serology	
Hepatitis B/C (HBsAg, HCV antibody or HCV RNA) - Screening only (Testing for HIV-1 and HIV-2 must be performed where mandated by local requirements)	

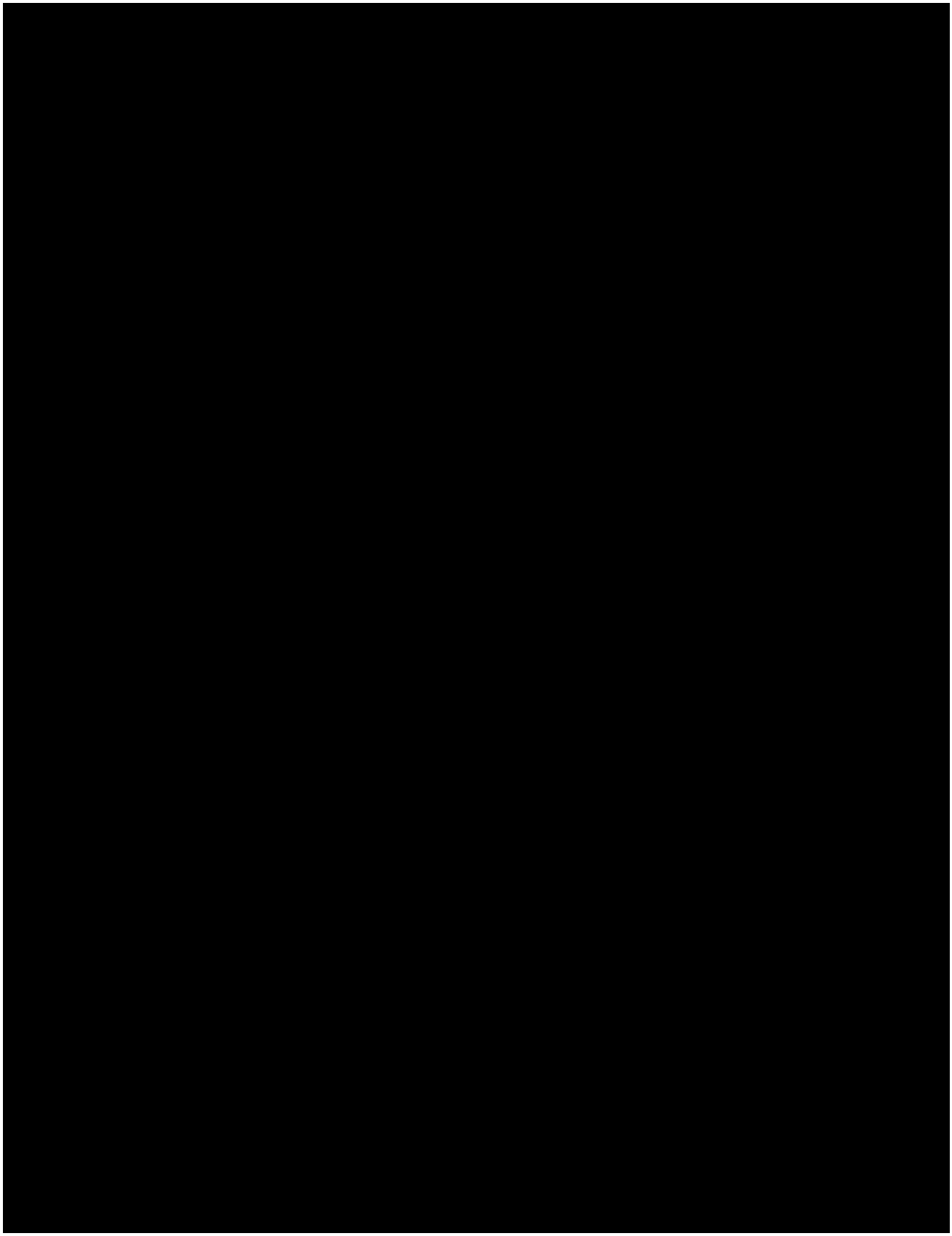
Table 9.4.5-1: Clinical Safety Laboratory Assessments

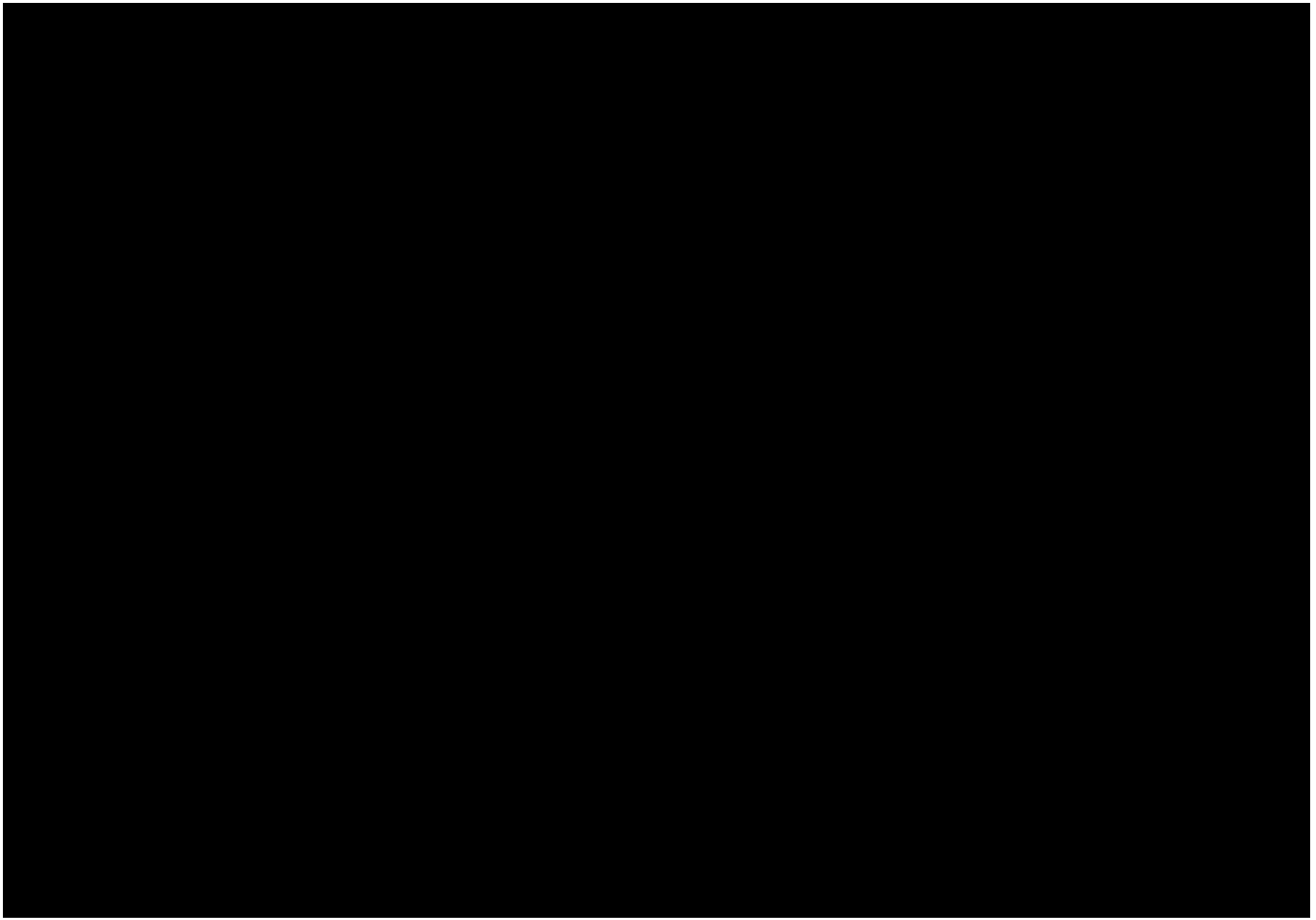
Other Analyses
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG). Urine or serum.
Follicle stimulating hormone (FSH) Screening -only required to confirm menopause in women < age 55)
Urinalysis - Screening only and as clinically indicated. Urine dipstick can be done and if abnormal perform microanalysis

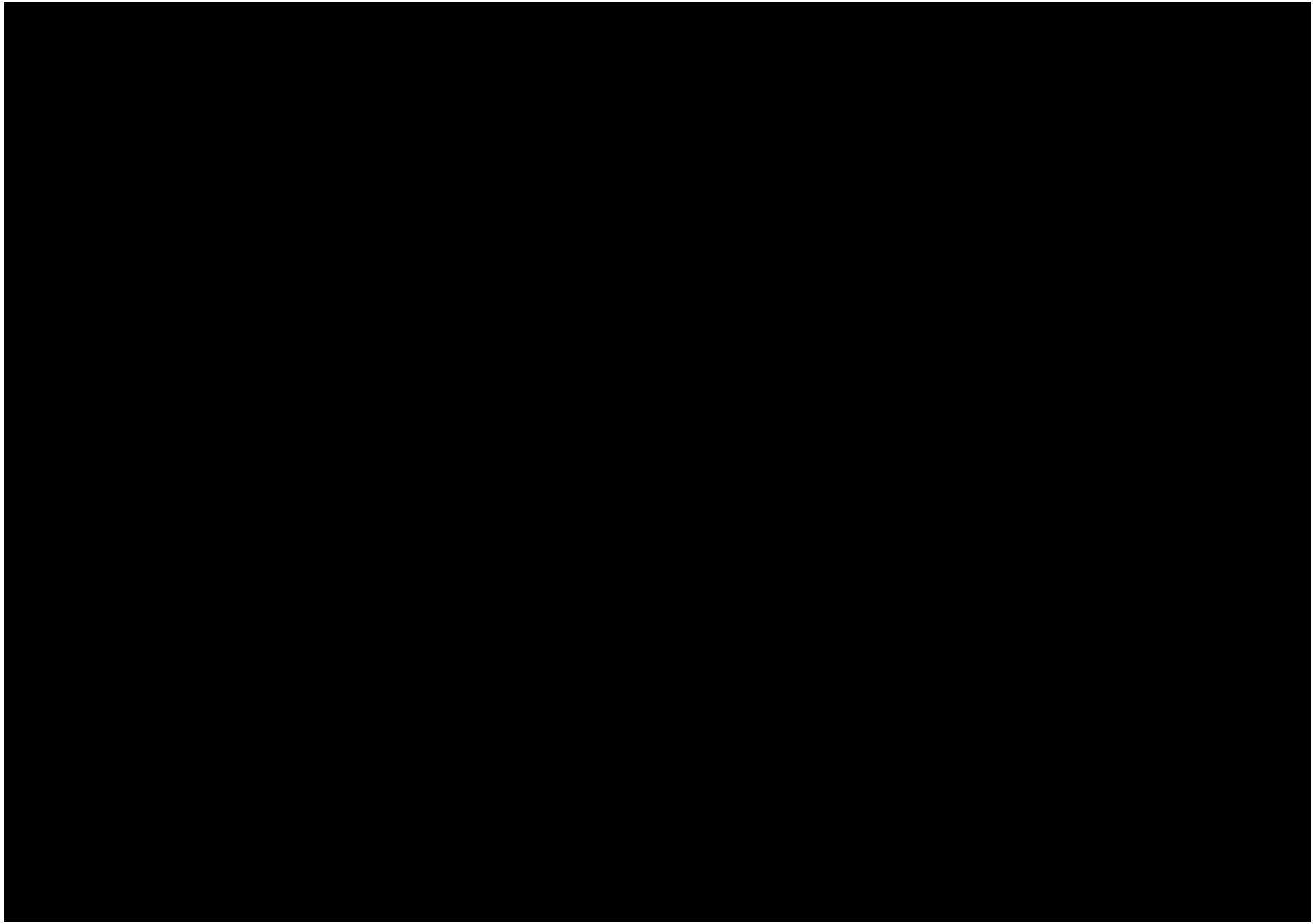
9.4.6 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

[redacted]







9.6 Pharmacodynamics

Biomarker sample collection ([redacted] Table 9.8.2-2) will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as per Section 9.8 may be conducted.

Exploratory analysis of selected biomarkers in relationship with exposure of nivolumab and bempegaldesleukin, and with efficacy may be explored with the data permitted. For more details, please see Section 9.8, Biomarkers.

9.7 Pharmacogenomics

Not applicable.

9.8 Biomarkers

Various factors that could potentially predict clinical response and inform on the incidence and/or etiology of AEs to treatment with nivolumab in combination with bempegaldesleukin will be investigated in peripheral blood and in pre-, on-treatment, and upon recurrence tumor specimens (Table 9.8.1-1). Data from these investigations will be evaluated for associations with clinical efficacy (eg, ORR, PFS, OS) and safety/toxicity (AE) data. All samples collected may also be used for exploratory analyses to assess biomarkers associated with melanoma and/or with immunotherapy treatment. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in the Laboratory Manual.

Biomarker sample collection in [redacted] Table 9.8.2-2 **are not applicable per Protocol Amendment 03.** The biomarker sampling schedules are provided [redacted] Table 9.8.2-2: Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Any remaining tissue collected for this study will be used to further understand and investigate the mechanism of action and progression/relapse of disease in participants treated with nivolumab in combination with bempegaldesleukin (Section 9.8.3). Also, the samples will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

Residual blood (or blood derivatives such as serum, plasma, plasma circulating tumor DNA [ctDNA], PBMCs, and extracted RNA/DNA) or tumor tissue (archival or fresh biopsy and extracted RNA/DNA) from tumor biopsy and biomarkers collections (Table 9.8.1-1) will also be retained for additional research purposes.

9.8.1 Additional Research Collection

This section is applicable only for samples collected prior to Protocol Amendment 03. This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research participation is required for all investigational sites in the US.

If the IRB and investigative site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research collection as a requirement for participation in the study.

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual [redacted] serum, [redacted] and plasma biomarkers, PBMCs, whole blood and extracted DNA/RNA, and tumor biopsy collections Table 9.8.1-1 will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided in Table 9.8.1-1 to the site in the procedure manual.

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for which residual samples will be retained
[redacted]	
Serum and Plasma Biomarkers	All
Plasma ctDNA	All
PBMCs	All
Isolated DNA/RNA	All
Whole Blood DNA/RNA	All
Tumor Biopsy	All
Stool Microbiome	All

9.8.2 Biomarker Sampling Schedule

[redacted]

Table 9.8.2-2: Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed

***Not applicable per Protocol Amendment 03.**

Collection Timing[a]	Tumor Biopsy	Myeloid Derived Suppressor cells (US/Canada only)	PBMC (Not collected in Brazil)	Flow Cytometry	Absolute Lymphocyte Count	Serum	Plasma ctDNA	Plasma Biomarkers	Whole Blood RNA Gene Expression	Whole Blood DNA	Stool Microbiome (Optional)[b]
Screening	X										
Cycle 1 Day 1 Pretreatment		X	X	X	X	X	X	X	X	X	X[c]
Cycle 1 Day 3[d]				X	X	X					
Cycle 1 Day 8		X	X	X	X	X					
Cycle 1 Day 21[e]	X	X	X	X	X	X					
Cycle 2 Day 1		X	X	X	X	X	X	X			
Cycle 3 Day 1						X		X			
Cycle 4 Day 1						X	X	X	X		
Cycle 5 Day 1		X	X	X	X	X	X	X			
Day 1 of every other cycle starting at Cycle 7, (eg, C7D1, C9D1, C11D1, etc) until EOT						X		X			
Day 1 of every 3 cycles starting at Cycle 8 for 1 year (eg, C8D1, C11D1, C14D1, etc); then every 4 cycles until EOT (eg, C24D1, C28D1 etc)							X				
Upon occurrence of Grade ≥ 3 drug related AE or lab abnormality regarded as a drug related AE[f]			X	X		X		X			

Table 9.8.2-2: Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed

***Not applicable per Protocol Amendment 03.**

Collection Timing[a]	Tumor Biopsy	Myeloid Derived Suppressor cells (US/Canada only)	PBMC (Not collected in Brazil)	Flow Cytometry	Absolute Lymphocyte Count	Serum	Plasma ctDNA	Plasma Biomarkers	Whole Blood RNA Gene Expression	Whole Blood DNA	Stool Microbiome (Optional)[b]
Upon occurrence of a radiographically documented CVA or a TIA event[g]						X		X			
Upon Progression[h]	X	X	X	X	X	X	X	X	X		X[c]

[a] Biomarker sampling occurs prior to dosing of study drug. From Cycle 2 onward, collections can occur ± 3 days from the scheduled time. During cycle 1, biomarker collection timeframes will match [redacted] collections.

[b] If the baseline stool microbiome is not collected, then the remaining samples are not needed.

[c] Optional. Stool collections can be done up to 1 week before dosing day/cycle.

[d] If patients are dosed on a Thursday, Day 3 samples can be collected on Day 2 (Friday). If participants are dosed on a Friday, Day 3 samples can be collected on Day 4 (Monday).

[e] Biopsy is optional. If a biopsy is taken between C1D15 and C1D21, indicated samples should be collected during this visit. If biopsy is not taken, the collection of indicated blood samples are not required.

[f] For Grade 3 or greater AEs, indicated blood samples should collected within 48 hours of onset of AE, if feasible.

[g] Collect indicated blood specimens if feasible, and as close to the CVA or TIA event date as possible.

[h] Sample collection, including tumor biopsy, upon disease progression is optional but highly recommended.

9.8.3 Tumor Tissue Specimens

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

All participants must have tumor tissue submitted during the screening period to allow for participant enrollment into the study. Tissue submitted should be from an unresectable primary tumor lesion or any metastatic site. The tumor tissue should be from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment. Central lab must provide IRT with the results of PD-L1 testing prior to randomization. Either a FFPE tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission. Submission of an FFPE block is strongly preferred but unstained slides are also acceptable. Tissue may be from a core biopsy, punch biopsy, excisional or incisional biopsy, or surgical specimen; fine needle aspiration and other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission.

The Medical Monitor (or designee) can be consulted for eligibility if participants have less than 20 unstained slides.

PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor and immune cells if a minimum of a hundred (100) evaluable tumor cells are present. Participants with tumor samples containing less than 100 cells per tissue section will not be randomized, but participants with positive, negative, or indeterminate (membrane staining is obscured by high cytoplasmic staining or melanin content) PD-L1 tumor expression will be stratified based on their expression.

In addition, this pre-treatment tumor sample may be used to assess other putative predictive biomarkers of nivolumab and bempegaldesleukin efficacy and/or to better characterize the tumor-immune microenvironment.

Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, bempegaldesleukin, and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, TILs or subpopulations of TILs and any immune mRNA expression signature. These pre-treatment tumor samples may also be used to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab and bempegaldesleukin, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3), intratumoral immune cell subsets, including macrophages, natural killer (NK) cells, T cells and B cells and other molecules, ie, cytokines and chemokines.

[redacted]

[redacted] If the participant has > 1 measurable lesion, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments. These same criteria that apply for lesion selection also apply to patients who consent to the optional biopsy in the main study.

It is also highly recommended that tumor tissue samples be collected on-treatment and upon recurrence when safe and feasible. These samples may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab and bempegaldesleukin on the expression of potentially relevant predictive and/or prognostic melanoma biomarkers, including, but not limited to BRAF mutation and PD-L1 tumor expression and other immuno-oncology-related events such as upregulation/downregulation of chemokines and cytokines. Both the pre-treatment tumor sample and the sample collected on-treatment and upon recurrence may be retrospectively assessed for BRAF mutation status, N-RAS mutation status, as well as for the expression of other immune or melanoma related genes, RNAs and/or proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to, IHC, qRT-PCR, genomics, genetic mutation, methylation detection and fluorescent in-situ hybridization (FISH).

9.8.4 Tumor Gene Expression and Mutation Analyses

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Tumor Mutational Burden (TMB) refers to the total number of nonsynonymous somatic mutations that exist within a tumor's genome. A subset of these mutations, termed neo-antigens, may result in an expressed protein that is not recognized by the host's immune system as self, and therefore has the potential to be immunogenic, leading to an anti-tumor immune-mediated response. Tumors with a high mutation burden may have a higher rate of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutation burden.[54] Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with immuno-oncology therapies. This hypothesis has been supported in multiple publications across immuno-oncology therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al (2014), where high TMB was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy.[55] Further studies by Rizvi et al reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients.[55] Additional studies of pembrolizumab and atezolizumab in NSCLC have been generally consistent with these results.[56]

Recently, TMB was evaluated in an exploratory post hoc analysis in the BMS-sponsored first-line NSCLC study, CheckMate-026, which represents the first Phase 3 study to demonstrate the impact of TMB on efficacy of a PD-1/L1 inhibitor.[57] This analysis demonstrated that in patients with high TMB, ORR was numerically higher in the nivolumab arm versus the chemotherapy arm (47% vs 28%) and median PFS was longer in the nivolumab arm compared to the chemotherapy arm (9.7 vs 5.8 months, HR 0.62; 95% CI 0.38, 1.00). OS was notable, though similar (18.3 vs 18.8 months and 1 year OS rates of 64% vs 60%, respectively), between the arms in patients with high TMB, although of note, 68% of patients in the chemotherapy arm received subsequent nivolumab.[58] Interestingly, the ORR and mPFS rates observed in the high TMB subgroup within CheckMate-026 were similar to those reported in the first line NSCLC study of pembrolizumab (Keynote-024), where ORR and mPFS were 45% and 10.3 months, respectively, in patients with ≥ 50% PD-L1 expression treated with pembrolizumab monotherapy.[58]

The available data to date suggest that, in addition to PD-L1, TMB is also a biomarker of clinical efficacy to immuno-oncology therapy. Therefore, TMB will be included as an exploratory biomarker of clinical efficacy of nivolumab with and without bempegaldesleukin combination therapy.

To explore the potential association of tumor mutation burden with clinical outcomes, tumor tissue will be evaluated by targeted and/or whole exome sequencing.

Exploratory analyses of mRNA (and/or miRNA) will be completed using RNA isolated from tumor tissue. Targeted and/or whole transcriptome RNA-seq, microarrays, and/or similar methodologies will be used to assess gene expression signatures, such as but not limited to those associated with inflammatory processes and/or immune related signaling, for potential association with clinical outcomes.

9.8.5 Peripheral Biomarkers

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

A variety of biomarkers that may predict or impact the treatment efficacy with bempegaldesleukin and nivolumab will be investigated in peripheral blood specimens taken from all participants prior to and during treatment. Several analyses will be completed and are described briefly below. Additional biomarker assessments may also be performed if samples are available.

9.8.6 Whole Blood for Genetic Analysis

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Whole blood will be collected from all participants prior to treatment to generate genomic DNA and RNA for Single Nucleotide Polymorphism (SNP)/WES and gene expression analyses, respectively. These analyses will focus on SNPs within genes associated with PD-1, CTLA-4, and

other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab and bempegaldesleukin treatment and/or with AEs. Also, whole blood RNA will be collected on-treatment to assess for potential changes in peripheral gene expression due to treatment with nivolumab and bempegaldesleukin combinations.

9.8.7 Exploratory Serum and Plasma Biomarkers

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Blood samples for exploratory serum and plasma biomarker analyses will be drawn at the specified time points indicated in the biomarker table. Additionally, serum and plasma samples will be collected when clinically safe and feasible, upon occurrence of a Grade 3 drug-related AE that results in a dose delay. Separate blood samples will be collected and processed for serum and plasma and then put in frozen storage. Serum and plasma samples may be assessed by ELISA, seromics, microRNA profiling, ctDNA measurements, metabolomics and/or other relevant multiplex-based protein assay methods for immune -related factors that may predict for nivolumab and/or bempegaldesleukin benefit or AEs; such factors may include, but are not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (eg, soluble MICA), circulating tumor DNA, SARS-CoV-2 serologic status, and microRNAs (eg, angiopoietin-2 and fibronectin). Serum and plasma may also be assessed for additional factors that may inform on the etiology of CVA events; such factors may include, but are not limited to those associated with vascular damage (eg, vWF, soluble P-selectin), coagulation and platelet activation (D-dimer, prothrombin 1.2, fibrinogen, solCD40L), eosinophil activation (eosinophil cationic protein) and inflammatory markers relevant to CVA (eg, CRP, TNFα, IL-6, VCAM/ICAM).

9.8.8 Plasma ctDNA

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Circulating tumor DNA (ctDNA) are small fragments of DNA that are shed from tumor and can be found circulating in the peripheral bloodstream. ctDNA derived from malignant cells can be isolated and analyzed from blood-derived plasma for genetic features including, but not limited to somatic mutations using targeted sequencing-based methods (eg, Next Generation sequencing). To complement the planned genomics analyses outlined for tumor assessments, plasma will be collected at baseline and on-treatment to isolate ctDNA. Mutational data derived from these samples will be compared to those identified directly in the tumor. Baseline and on-treatment changes in mutational burden (either global or individual genes) will be evaluated for association with treatment outcomes. Correlation between mutational burden in blood and the tumor will be explored.

9.8.9 Serum MicroRNA (miRNA)

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

MicroRNAs (miRNA) are widely-expressed, small RNAs that regulate the abundance of mRNA transcripts and their translation into protein. Global miRNA expression profiling has become increasingly common in cancer research, and miRNA signatures that are correlated to stage of disease or to clinical outcomes are now available for a variety of cancer types. Expression profiling of miRNA may be useful also in identifying molecular markers for the prediction of drug responses and for prospective stratification. Intriguingly, miRNAs are stable in serum and may represent miRNAs over-expressed in tumors and/or reflect immune system activity. Serum taken at baseline and during treatment from participants randomized to each treatment arm will be analyzed for miRNA content by microarray or similar methodology. The resulting miRNA profiles will be evaluated for changes in miRNA abundance that occurs following treatment and for associations with response and survival data. Ultimately, the goal will be to determine if unique immunerelevant and/or disease-specific miRNA signatures exist and if they are potentially useful for identifying participants who are likely (or unlikely) to respond to nivolumab treatment.

9.8.10 Myeloid Derived Suppressor Cells

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Myeloid derived suppressor cells (MDSCs) are an immune cell population capable of suppressing T cell activation and proliferation. Low pre-treatment MDSC levels in peripheral blood may be associated with better overall survival in melanoma participants treated with nivolumab combination. MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic changes or associations with outcome.

9.8.11 Peripheral Blood Mononuclear Cells and Whole Blood Immunophenotyping

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

Whole-blood samples will be collected for isolation and cryopreservation of peripheral blood mononuclear cells (PBMCs) in both arms of the study. These cryopreserved samples may be used for functional activation tests, additional immunophenotyping assays, T-cell receptor sequencing, and DNA methylation.

Whole blood immunophenotyping by flow cytometry will be used to assess pre-treatment and serial on-treatment changes in composition/activation status of peripheral immune cell subsets to determine PD changes and/or association with outcome. Cellular subsets evaluated will include, but not limited to, T, B, NK, natural killer T cell (NKT), and T-regulatory cells. Cellular subsets

may be defined in terms of, but not limited to, memory phenotype, activation, exhaustion, signaling markers, and proliferation status before and after treatment. Several markers may be used to assess this including, but not limited to, Ki-67, human-leukocyte antigen-antigen D-related, CTLA-4, PD-1, ICOS, CD39, etc.

9.8.12 Microbiome Analysis

Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens as detailed below may be conducted.

The potential influence of the gut microbiome on melanoma treatment outcome is not known. It is known that the microbiome can affect treatment of certain cancer types (ie, colorectal cancer) through several mechanisms, including promotion of disease via induction of chronic inflammation or catabolism of polyamines on other carcinogenic digestible material. In addition, the innate and adaptive immune system activation state and repertoire may be altered based on local microbiota leading to differential activity of nivolumab in cancer participants. DNA will be extracted from fecal samples taken prior to therapy and on-treatment with nivolumab and nivolumab/bempegaldesleukin combination (Table 9.8.2-2). A gene-sequencing approach will be utilized to survey microbial species in the gut in order to define microbiota as a function of efficacy and safety. Overall changes in the gut microbiota will also be characterized in individual participants that receive therapy.

9.9 Medical Resource Utilization and Health Economics

This section is not applicable per Protocol Amendment 03. Healthcare resource utilization data will be collected for all randomized participants using an internal CRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

10 STATISTICAL CONSIDERATIONS

In general, continuous data will be summarized by descriptive statistics, including number of participants, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of participants. Unless otherwise specified, data will be summarized by treatment arm.

All efficacy evaluations will be analyzed using the intent-to-treat (ITT) population, and all safety endpoints will be summarized using the Safety population.

A detailed description of analysis methods will be provided in the statistical analysis plan (SAP).

The final ORR and PFS analyses, and the first OS interim analysis (combined with the second OS interim analysis) have been completed using the locked database with database lock date of 01-Feb-2022. Given there was no additional clinical benefit in the doublet therapy arm compared to the monotherapy arm for the primary endpoints of PFS and ORR, the Sponsor, in consultation with

the DMC, has decided to unblind the trial, and no additional OS formal analyses will be performed. Any further efficacy analyses, if conducted, will be descriptive.

10.1 Sample Size Determination

The sample size of the study accounts for the three primary efficacy endpoints: ORR, PFS and OS. The overall alpha for this study is 0.05, which is split with 0.001 to evaluate ORR, 0.03 to evaluate PFS and 0.019 to evaluate OS. All alphas are two-sided. ORR will be analyzed when the first 480 randomized participants have a minimum follow-up of 6 months. PFS will be evaluated for treatment effect at an alpha of 0.03 with at least 90% power; no interim analysis of PFS is planned. OS will be evaluated for treatment effect at an alpha level of 0.019.

A fallback approach will be used to test ORR, PFS, and OS. If ORR is significant, the alpha of 0.001 allocated to ORR will be passed to OS. If PFS is significant, the alpha of 0.03 allocated to PFS will pass to OS. That is,

- If both ORR and PFS are significant, then OS will be tested at 0.05 level
- If PFS is significant but ORR is not, then OS will be tested at 0.049 level
- If ORR is significant but PFS is not, then OS will be tested at 0.02 level
- If neither ORR nor PFS is significant, then OS will remain to be tested at 0.019 level

It is estimated that approximately 764 previously untreated metastatic melanoma subjects will be randomized into two arms in a 1:1 ratio. Table 10.1-1 summarizes sample size design parameters and schedule of primary endpoint analyses planned in this study.

Table 10.1-1: Summary of Sample Size Parameters and Schedule of Analyses

Endpoints	ORR	PFS	OS
Sample size	480: 240 vs 240	764: 382 vs 382	764: 382 vs 382
Power	90%	90%	90%
Alpha	0.1% (2-sided)	3% (2-sided)	1.9% (2-sided)
Alternative Hypothesis: Experimental vs Control	ORR: 66% vs 45%	PFS rates for nivolumab arm: 63% (3 months) 52% (6 months) 46% (9 months) 37% (18 months) HR=0.7	mOS: 53.7 months vs 37.6 months HR=0.7
ORR Final	~35.9 months (29.9 months of accrual + 6 months of follow-up)	--	--
PFS Final Analysis/OS Interim #1	--	~39.8 months 375 PFS events Critical HR: 0.799	~39.8 months Critical HR corresponds to two-sided alpha = 0.0001,

Table 10.1-1: Summary of Sample Size Parameters and Schedule of Analyses

Endpoints	ORR	PFS	OS
			and depends on the number of OS events observed
OS Interim #2	--	--	~47.9 months 230 OS events (55% of OS Information) Critical HR: 0.646
OS Interim #3	--	--	~59 months 314 OS events (75% of OS Information) Critical HR: 0.729
OS Final Analysis	--	--	~76.3 months 419 OS events Critical HR: 0.792

Note: Analysis time projections are updated based on updated enrollment projection in February, 2021. If final ORR and final PFS analyses occur close enough, they may be combined into one analysis conducted at the final PFS analysis time. In this case, the ORR formal analysis will only be conducted for the ORR population.

10.1.1 Sample Size Justification for ORR Estimate

Given a two-sided alpha of 0.001, 480 subjects in nivolumab+bempegaldesleukin and nivolumab arms will provide approximately 90% power to detect 21% ORR difference between the 2 treatment arms, assuming ORRs of 66% and 45%, respectively, using a Chi-square test. If observed ORR difference is greater than 14.9%, it will result a statistically significant result.

This ORR formal comparison will occur when the first 480 randomized participants have a minimum follow-up of 6 months. In the original protocol, the ORR formal comparison was projected to occur approximately 15.6 months after the first subject's randomization date (9.6 months of accrual of 480 subjects and 6 months of ORR follow-up). That projection was based on the assumption that the accrual duration of the study was approximately 15 months.

Based on actual enrollment and updated projection in February 2021, where the accrual duration of the study is projected to be approximately 38.8 months, the ORR formal comparison is projected to occur approximately 35.9 months from the first subject's randomization date (~29.9 months of accrual of 480 subjects and 6 months of ORR follow-up). If final ORR and final PFS analyses occur close enough, they may be combined into one analysis conducted at the final PFS analysis time. In this case, the ORR formal analysis will only be conducted for the ORR population.

10.1.2 Sample Size Justification for PFS Comparison

Based on the PFS results for nivolumab from BMS Study CA209067 (ie, the CheckMate-067 Study,[36] a non-constant PFS hazard was observed. Thus, for the sample size calculation, a piecewise exponential distribution was assumed in each treatment arm with a constant HR of 0.7. Specifically, in the nivolumab arm we assume PFS rates of 63%, 52%, 46%, and 37% at 3, 6, 9,

and 18 months, respectively. Under the assumptions of piecewise exponential distribution for each arm and a constant HR of 0.7, the calculated median progression-free survival (mPFS) are 6.96 months and 17.8 months for the nivolumab and nivolumab+bempegaldesleukin arms, respectively. At a two-sided alpha level of 0.03, a total of 375 PFS events are needed to detect a PFS hazard ratio (HR) of 0.7 with 90% power. In the original protocol, under the assumption of 15 months of enrollment period, 7-months of minimum follow-up, and a 10% annual drop-out rate, a total sample size of 764 subjects is required to observe the needed 375 PFS events at 22 months. Under updated projection in February 2021, with 764 subjects and 10% annual drop-out rate, the PFS analysis time, ie, to observe approximately 375 PFS events, is projected to occur at approximately 39.8 months from the first subject's randomization date. It is projected that an observed HR of 0.799 or less would result in a statistically significant improvement in the final analysis of PFS.

10.1.3 Sample Size Justification for OS Comparison

For OS, at a two-sided alpha level of 0.019, a total of 419 events are needed to detect a HR of 0.70 with 90% power. Assuming a median OS time for the nivolumab arm (Arm B) of 37.6 months, with a total sample size of 764, in the original protocol it is projected the total study duration is 59 months (15 months for accrual and 44 months for follow up), with a critical boundary hazard ratio of 0.792. With updated enrollment projection in February 2021, it is projected the total study duration (corresponding to the final OS analysis time) is approximately 76.3 months from the first subject's randomization date. All projected OS interim analysis times are updated accordingly. However, all PFS and OS analysis times are driven by the required number of events. The actual analysis times depend on actual enrollment speed and events accrual, thus may be different from projections.

Three formal interim analyses of OS are planned for this study. The first OS interim analysis is planned at the time point of the final PFS analysis, where OS will be tested at 0.0001 level, regardless of the outcome of the final PFS analysis. For instance, if 150 OS events are observed at the time point of the final PFS analysis, then the critical boundary on hazard ratio for the first OS interim is 0.53.

All other formal OS analyses will be conducted when planned number of OS events specified below are observed.

The second OS interim analysis is planned when 230 OS events are observed (55% of the targeted OS events for final analysis, projected to happen 47.9 months from FPFV), and the third OS interim analysis is planned after observing 314 OS events (75% of targeted OS events needed for final analysis, projected to happen 59 months from FPFV). Accounting for the alpha = 0.0001 spent at the first OS interim, the remaining alpha level will be the overall OS alpha level (as described below) minus 0.0001 depending on the ORR and PFS results. If neither ORR nor PFS is significant, the remaining alpha level of 0.0189 (alpha=0.019-0.0001) will be spent on the rest of the OS interim analyses and the final OS analysis. The stopping boundaries for the second OS interim, the third OS interim, and the final OS analyses will be derived based on the actual number of deaths using the O'Brien and Fleming alpha-spending function in software EAST 6.4.1. If the

numbers of events are exactly the same as planned, the critical boundary on hazard ratios for the second, third OS interim analyses and the final OS analysis are 0.646, 0.729, and 0.792, respectively.

If the final ORR analysis is statistically significant, the significance level of 0.001 spent in the ORR analysis will be passed on to the OS analysis. Similarly, if the final PFS analysis is statistically significant, the significance level of 0.03 spent in the PFS analysis will also be passed on to the OS analysis. The alpha spent at the second, third OS interim analyses and the final OS analysis will be adjusted accordingly and the overall alpha level for OS is described at the beginning of Section 10.1.

If there are at least 230 OS events at the time point of the final PFS analysis, then the first planned OS interim analysis and the second planned OS interim analysis (at 230 OS events) will be merged into one OS interim analysis, and will occur at the time point of the final PFS analysis. In this case, there will be no extra spending of two-sided alpha = 0.0001 for the first OS interim analysis, and the stopping boundaries for all OS analyses will be derived based on the actual number of deaths using the O'Brien and Fleming alpha-spending function in software EAST 6.4.1.

If the 419th OS event has not occurred 60 months after randomization of the last participant, then the final OS analysis will take place at that time. In such case, the final analysis boundary will be re-calculated based on the observed final number of events using all remaining alpha for OS.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who signed an informed consent form and were registered into the IRT.
Intent-to-Treat (ITT) Population/All Randomized Participants	All participants who were randomized. Participants are grouped within the ITT Population by the treatment to which they were randomized. This is the primary analysis set for baseline characteristics and all efficacy analyses.
ORR Population	All randomized participants who have at least 6 months of follow-up at the time point of the final ORR analysis. A participant's follow-up time is defined here as the time between randomization date and clinical data cut-off date regardless of participant disposition (ie, intent-to-treat principle). This is the primary analysis set for the final ORR analysis, which will occur when approximately the first 480 randomized participants have at least 6 months of follow-up.
Safety Population/All Treated Participants	All participants who receive at least 1 dose (or partial dose) of study drug. Participants are grouped within the Safety population according to the treatment they actually received. This is the analysis set for all safety analyses, as well as, study drug administration.
[redacted]	
Biomarker Population	For predictive biomarkers, biomarker population includes all randomized participants who have biomarker data available at baseline. For pharmacodynamic biomarkers, the biomarker population incudes all

Population	Description
	randomized participants who have baseline and at least one post-baseline biomarker data available.
All PD-L1 evaluable participants	All randomized participants with quantifiable PD-L1 expression.
[redacted]	

10.3 Statistical Analyses

A description of the participant population will be included in the statistical output reported, including subgroups of age, gender and race.

Per Protocol Amendment 03, the secondary and exploratory objectives are not applicable. However, exploratory analyses of biomarkers on previously collected samples as per Section 9.8 may be conducted. Any analyses of secondary objectives will be descriptive.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary ORR	ORR is defined as the proportion of participants with a confirmed best overall response of CR or PR in the ITT population by RECIST 1.1 per BICR. A pre-planned analysis of blinded independent central review (BICR)-assessed ORR (using RECIST v 1.1; confirmed at least 4 weeks later) and duration of response is intended for both arms to evaluate the clinical activity of bempegaldesleukin in combination with nivolumab relative to nivolumab. BICR-assessed ORR will be compared using a Cochran-Mantel Haenszel (CMH) two-sided test stratified by the three stratification factors (PD-L1 status, BRAF status, and AJCC M stage) at 0.001 level to control the overall study type I error. An associated odds ratio and 95% and 99.9% confidence interval (CI) will be calculated. The ORR difference between the two treatment arms with its 95% and 99.9% CI will be reported. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each randomized arm.
Primary Progression-Free Survival	Progression-free survival (PFS) is defined as the time between the date of randomization and the first date of documented tumor progression using RECIST 1.1 per BICR (see Section 9.1.1.3), or death due to any cause, whichever comes first. A log-rank test stratified by PD-L1 tumor expression status, BRAF mutation status, and M stage will be used to compare PFS between the 2 treatment arms in the ITT Population at 0.03 level. A Cox proportional hazards model with treatment as the single covariate, stratified by the above factors, will be used to estimate the hazard ratio and corresponding 97% CI. The Kaplan-Meier method will be used to further summarize PFS, including PFS curves, medians with corresponding 95% CIs. The PFS rates at 6 and 12 months will also

Endpoint	Statistical Analysis Methods
	be estimated. In addition, to account for potential non-proportional hazard for PFS, sensitivity analyses will be conducted to compare PFS per BICR between treatment groups using weighted log-rank test. Technical details will be given in the SAP. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who do not have any on-study tumor assessments and do not die will be censored on their date of randomization. Participants who started a new anticancer treatment regimen prior to disease progression will be censored on the date of their last evaluable tumor assessment prior to receiving the new antineoplastic regimen. Participants who are lost to follow up will be censored on the date of their last evaluable tumor assessment.
Primary Overall Survival	Overall survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. Participants who do not have a date of death will be censored on the last date for which a participant was known to be alive. OS will be analyzed using the stratified log rank test, Cox proportional hazards model, and Kaplan Meier method, similar to PFS. The OS rates at 12 and 24 months will also be estimated. In addition, similar sensitivity analyses to account for potential non-proportional hazard for OS will also be conducted.
Secondary Clinical Benefit Rate, Duration of Response, Time to Response	The clinical benefit rate (CBR), defined as the proportion of participants with CR, PR, or SD per RECIST 1.1 by BICR will be summarized similarly to ORR. Duration of response (DOR) is defined for participants who have a confirmed CR or PR as the date from first documented CR or PR per RECIST 1.1 to the date of the documentation of disease progression by BICR or death due to any cause, whichever is earlier. Participants who do not have disease progression or die will be censored on the date of their last evaluable tumor assessment. The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. Time to response (TTR) is defined for participants who had a confirmed CR or PR as the time from the date of randomization to date of first documented CR or PR per RECIST 1.1 as assessed by BICR. The median TTR will be estimated using the Kaplan-Meier method with corresponding 95% CI and range. ORR, PFS, CBR, DoR, TTR assessed by Investigator per RECIST 1.1 will be analyzed similarly to these endpoints assessed by BICR. PFS per BICR, ORR per BICR, and OS in biomarker population (by PD-L1 status) will be analyzed similarly as stated above.
Exploratory PFS2 [redacted]	PFS2 is defined as the time from randomization to objectively documented progression after the next line of therapy, per Investigator assessment, or to death, whichever occurs first. Participants who were alive and without progression after the next line of therapy can be censored at last known alive date. Details on the PFS2 analysis will be described in the SAP. [redacted]

10.3.2 Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary Safety and Tolerability	Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v5 criteria by system organ class and preferred term. On study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v5 criteria.

10.3.3 Other Analyses

[redacted]

10.3.3.3 Missing Data

Statistical considerations and methodology for handling missing data, including sensitivity analyses for PFS and ORR, will be detailed in the SAP.

10.3.4 Interim Analyses

Several interim analyses are planned for this study. Table 10.3.4-1 gives an overview of their purposes and timing. The final ORR and PFS analyses, and the first OS interim analysis (combined with the second OS interim analysis) have been completed using the locked database with a database lock date of 01-Feb-2022. Given there was no additional clinical benefit in the doublet therapy arm compared to the monotherapy arm for the primary endpoints of PFS and ORR, the Sponsor, in consultation with the DMC, has decided to unblind the trial. No additional OS formal analyses will be performed. Any further efficacy analyses, if conducted, will be descriptive.

Table 10.3.4-1: Interim Analyses Schedule

Analysis	Purpose	Analysis Trigger
Final ORR Analysis	Demonstrate significant improvement in ORR	Approximately the first 480 randomized participants have a minimum of 6-month of follow-up
Final PFS Analysis, Interim OS Analysis #1	Demonstrate significant improvement in PFS and OS	~375 PFS events
Interim OS Analysis #2	Demonstrate significant improvement in OS	~230 OS events
Interim OS Analysis #3		~314 OS events
[a]Final OS Analysis		~419 OS events

[a] If the 419th OS event has not occurred 60 months after randomization of the last participant, then the final OS analysis will take place at that time. In such case, the final analysis boundary will be re-calculated based on the observed final number of events using all remaining alpha for OS.

The Statistical Analysis Plan will further describe the planned interim analyses.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ACLS	Advanced Cardiac Life Support
[redacted]	[redacted]
AE	adverse event
AESI/AEOSI	adverse event of special interest
ACLS	advanced cardiac life support
AEC	absolute eosinophil count
AI	accumulation index
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	additional research
AST	aspartate aminotransferase
AT	aminotransaminase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BICR	Blinded independent central review
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb

Term	Definition
BOR	best overall response
BP	blood pressure
BRAF	proto-oncogene B-Raf
BTLA	B and T lymphocyte associated
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
CBR	clinical benefit rate
CD8+	CD8 positive
CD 122	interleukin-2 receptor subunit beta
CD-28	cluster of differentiation 28
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
Cl^-	chloride
CLcr	creatinine clearance
Cm	centimeter
[redacted]	[redacted]
Cmaxss	steady state peak concentrations
[redacted]	[redacted]
CMH	Cochran-Mantel Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal carcinoma
CRF	Case Report Form, paper or electronic
CRS	cytokine-release syndrome

Term	Definition
CSTD	closed-system transfer device
CT	computed tomography
CTAg	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA 4	cytotoxic T-lymphocyte–associated antigen 4
[redacted]	[redacted]
CV	coefficient of variation
CVA	cerebrovascular accident
Cavgss	simulated steady state average concentration
ctDNA	circulating tumor DNA
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DLT	dose-limiting toxicity
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulant
DOR	duration of response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
DVT	deep vein thrombosis
EA	extent of absorption
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
Eg	exempli gratia (for example)
ELISA	enzyme-linked immunosorbent assay
EMA	European Medical Agency
ESR	Expedited Safety Report

Term	Definition
[redacted]	[redacted]
F	bioavailability
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FPFV	first participant first visit
FSH	follicle stimulating hormone
G	gram
CAD	coronary artery disease
CBR	clinical benefit rate
COVID-19	coronavirus disease 2019
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CVA	cerebrovascular accident
FDG	fluorodeoxyglucose
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
H	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
H&N	head and neck
HR	hazard ratio
HRT	hormone replacement therapy

Term	Definition
IA	interim analysis
ICD	International Classification of Diseases
ICE	ischemic cardiovascular events
ICU	intensive care unit
ICH	International Conference on Harmonisation
ICOS	inducible T-cell costimulator
IDMC	Independent Data Monitoring Committee
Ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL-2	interleukin-2
IL-2Rα	IL-2 receptor alpha subunit
IL-2Rβ	IL-2-receptor beta subunit
IL-2Rαβγ	high affinity IL-2 receptor
IL-2Rβγ	intermediate affinity IL-2 receptor
IND	Investigational New Drug
IFN-γ	interferon-γ
[redacted]	[redacted]
IP	investigational products
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K^+	potassium
Kg	kilogram
L	liter
LAG3	lymphocyte-activation gene 3
LAM	lactation amenorrhea method

Term	Definition
LC	liquid chromatography
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
Ln	natural logarithm
LVEF	left ventricular ejection fraction
MEK	mitogen-activated protein
Mg	milligram
Mg++	magnesium
Min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
MR	medical research
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
MUGA	multigated acquisition
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
Ng	nanogram
NIMP	non-investigational medicinal products
NK	natural killer
NKT	natural killer T cell
NKG2D	natural-killer group 2, member D
NKTR	Nektar Therapeutics
[redacted]	[redacted]

Term	Definition
[redacted]	[redacted]
N-RAS	neuroblastoma RAS viral oncogene homolog
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over the counter
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PD-1	programmed cell death protein-1
PD-L1	programmed death ligand 1
PE	pulmonary embolism
PEG	polyethylene glycol
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PFS2	PFS time from randomization to progression after the next line of therapy
PK	pharmacokinetics
PPK	population pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
[redacted]	[redacted]
QC	quality control
QD, qd	quaque die, once daily
Q3W	every three weeks
Q4W	every four weeks
R^2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RNA	ribonucleic acid

Term	Definition
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SAP	statistical analysis plan
SOC	standard of care
SOP	Standard Operating Procedures
T	Temperature
T	Time
T cell	regulatory T cell
TCR	T cell receptor
TIA	Transient ischemic attack
TILs	tumor infiltrating lymphocytes
Tim-3	T cell immunoglobulin and mucin domain 3
[redacted]	[redacted]
[redacted]	[redacted]
TID, tid	ter in die, three times a day
[redacted]	[redacted]
TMB	tumor mutation burden
TME	tumor microenvironment
TRAE	treatment related adverse events
Tregs	regulatory T cells
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States of America
[redacted]	[redacted]
W	Washout
WBC	white blood cell
WHO	World Health Organization

Term	Definition
WOCBP	women of childbearing potential
[redacted]	[redacted]
x g	times gravity

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The Investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

The Investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, Investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the Investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The Investigator, or a person designated by the Investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

Minors who are judged to be of an age of reason must also give their written assent.

Subjects/participants unable to give their written consent (eg, stroke or subjects/participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an

opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/ biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The Investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The Investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The Investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The Investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the Investigator (or head of the study site in Japan) when the study records are no longer needed.

If the Investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another Investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the Investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the Investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the Investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the Investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the Investigator or designee.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal Investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year [6 months for studies including pediatric population] of the end of trial in EU/European Economic Area and third countries.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose as a verbatim term (as reported by the Investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.8 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.6 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same Investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: [redacted]

SAE Facsimile Number: Will be provided by local site monitor.

SAE Telephone Contact (required for SAE and pregnancy reporting): **Will be provided by local site monitor.**

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the Investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly.[a]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral (birth control pills)
  - intravaginal (vaginal birth control suppositories, rings, creams, gels)
  - transdermal
- Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy

- Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral
  - injectable
- Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c]
- Bilateral tubal occlusion

- Vasectomized partner

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.

• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 ECOG (ADULT) AND LANSKY (ADOLESCENTS) PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	**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 alight or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only 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.

PERFORMANCE STATUS CRITERIA: Lansky	
Score	**Lansky Description**
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Substantial restriction of, and less time spent, in play activity
60	Out of bed, but minimal active play; keeps busy with quiet activities
50	Gets dressed, but inactive much of day; no active play, able to participate in quiet play
40	Mostly in bed; participates in some quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play limited to passive activities
10	No play; does not get out of bed
0	Unresponsive

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v5)	Management	Follow-up
Grade 1 Creatinine > ULN to ≤ 1.5x ULN	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> • Treat as Grade 2 to Grade 4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1-2 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u>: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections <u>If no improvement or worsening</u>, add additional immunosuppression.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

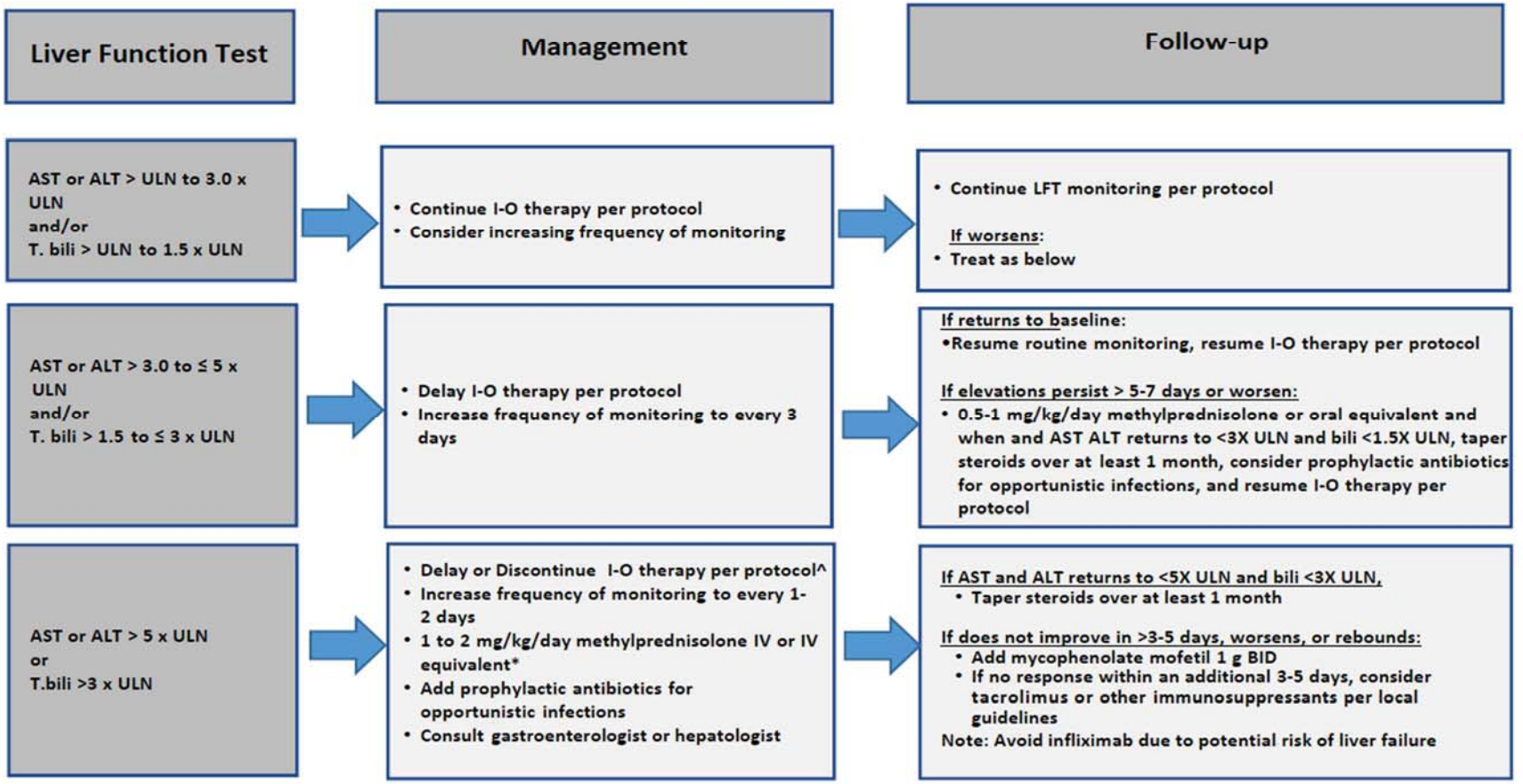
Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

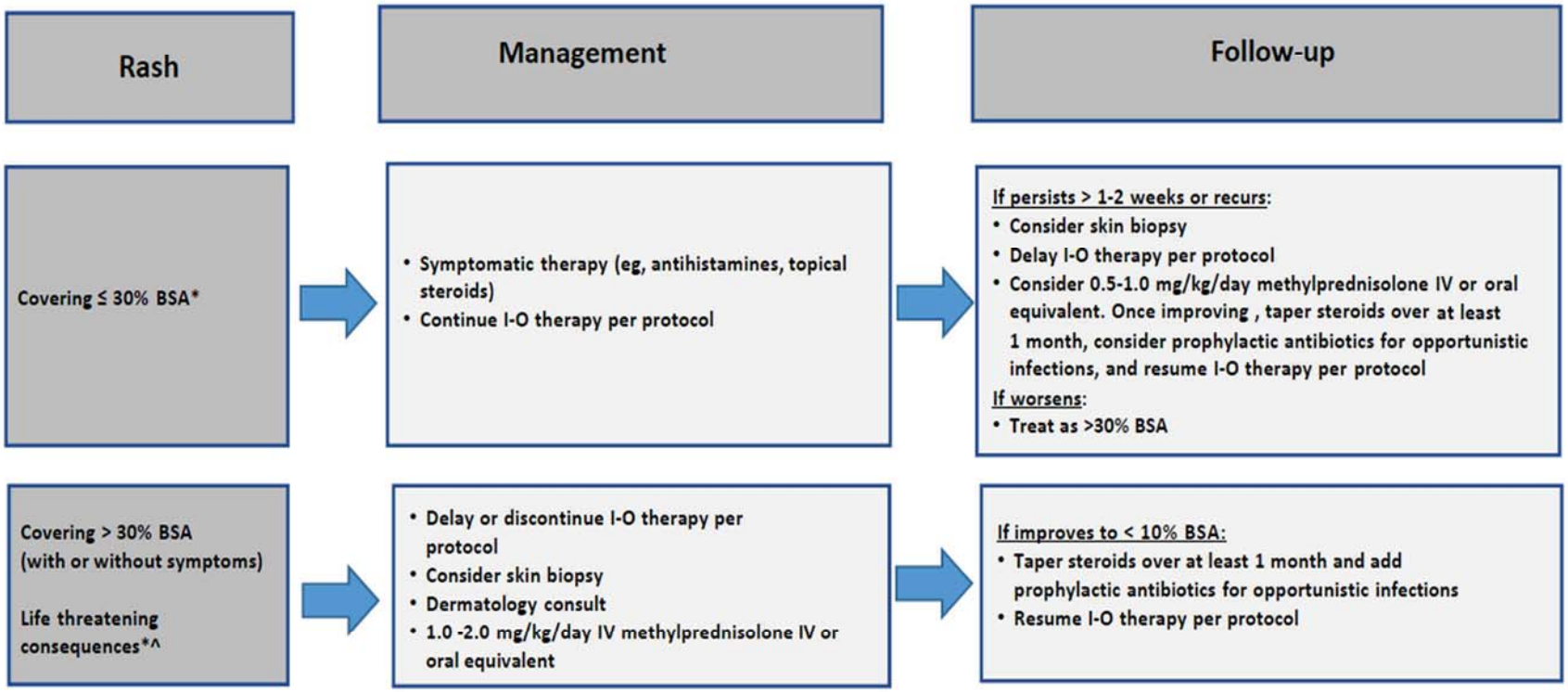
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Myocarditis	Management	Follow-up

Symptoms with mild to moderate activity or exertion	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP. as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  ○ Troponin and B-type natriuretic peptide monitoring
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for life threatening myocarditis:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider anti-thymocyte globulin as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

28-Sep-2020

APPENDIX 7 *NOT APPLICABLE PER PROTOCOL AMENDMENT 03 CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM FOR THE COMBINATION OF BEMPEGALDESLEUKIN WITH CHECKPOINT INHIBITORS

Appendix 7 is not applicable per Protocol Amendment 03. The table below provides a management algorithm for possible signs/symptoms of CVA for patients treated with the combination of bempegaldesleukin with a checkpoint inhibitor. This general guideline constitutes guidance to the Investigator and may be supplemented by clinical judgment of the Investigator and/or discussions with the Medical Monitor representing the Sponsor.

CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM **This guideline pertains to all participants receiving bempegaldesleukin (NKTR-214) in combination with nivolumab**	
For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: • Recommend following the Advanced Cardiac Life Support (ACLS) Adult Suspected Stroke Algorithm that includes time-sensitive assessment and rtPA use guidance[a]. • Perform neurological imaging with DWI MRI soon as feasible after the initial presentation of symptoms, preferably within 24 hours, or as indicated following an acute intervention. DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used. If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA event confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (eg, cryptogenic CVA), and for suspected TIA without clear alternative etiology: o Discontinue study treatment for patients receiving bempegaldesleukin in combination with a checkpoint inhibitor (ie, nivolumab[b]).
2	Neurology consultation recommended.
3	Perform pertinent laboratory assessments including coagulation (D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine) and exploratory biomarkers, preferably by central laboratory testing. Local laboratory testing is allowed when central laboratory testing is not possible.
4	Consider cardiac echocardiogram (trans-esophageal as appropriate) to evaluate for potential source of emboli.

Abbreviations: ACLS = Advanced Cardiac Life Support; CVA = cerebrovascular accident; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; rtPA = recombinant tissue plasminogen activator; TIA = transient ischemic attack.

[a] ACLS-algorithms.com. Adult Stroke Algorithm, (ACLS) Advanced Cardiac Life Support [Internet]; 2021 [cited 5 May 2021]. Available from: https://acls-algorithms.com/adult-stroke-algorithm/.

Additional consideration to the above CVA management guidelines for adolescent study population: rtPA use is not approved in this age group for acute ischemic stroke indication. Follow age-appropriate institutional guidelines for antithrombotic therapies for emergency ischemic stroke management.

[b] For other treatment combinations, refer to the relevant protocol(s).

APPENDIX 8 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

[From AJCC Cancer Staging Manual, 8th Edition. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. editors. Springer International Publishing. 2017 (pages 577 & 578)]

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of Distant Metastasis (M)

M Category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or non-regional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated

M Category	Anatomic site	LDH level
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
Suffixes for M category: (0) LDH not elevated; (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

Definition of Regional Lymph Node (N)

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes with or without in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected, and/or presence any number of matted nodes	Yes

AJCC Prognostic Stage Groups

Clinical (cTNM)

Clinical stage includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

When T is....	And N is.....	And M is....	The clinical stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

PATHOLOGICAL (pTNM)

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

When T is....	And N is.....	And M is....	The pathological stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA

When T is....	And N is.....	And M is....	The pathological stage is...
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a-N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N >N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Ant T, Tis	Any N	M1	IV
Pathological Stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

Mucosal Melanoma of the Head and Neck TNM definitions

Definition of Primary Tumor (T)

T Category	T Criteria
T3	Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension: for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx or larynx.
T4a	Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin.
T4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures.

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present

Definition of Distant Metastasis (M)

M Category	M criteria
M0	No distant metastasis
M1	Distant metastasis present

AJCC 7 Prognostic Stage Groups for Mucosal Melanoma of the Head and Neck

When T is....	And N is.....	And M is....	The Clinical stage is...
T3	N0	M0	III
T4a	N0	M0	IVA
T3–T4a	N1	M0	IVA
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Reference: AJCC Cancer Staging Manual, 7th Edition. Edge SB, Byrd DR, Compton CC, et al. editors. Springer International Publishing. 2010; Chapter 9 (page 97)

APPENDIX 9 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [redacted].[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviaitons: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 10 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Argentina, Czech Republic, Germany, Peru and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

Section	Country-specific language
Section 2 Flow Chart/Time and Events Schedule Table 2-1: Screening Assessments - Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 1k	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"**to be replaced** with "Positive test for HIV".

Germany, Sweden- Inclusion criteria were modified to [redacted] to clarify that no minor participants will be enrolled in the study or participate in the [redacted]. Adolescent hydration guidelines [redacted] are not applicable to adolescent participants in Germany and Sweden as no adolescents will be enrolled in Germany or Sweden.

Section Number & Title	Country-specific language
Section 6.1 Inclusion Criteria Inclusion criterion 1c	Not applicable to participants in Germany and Sweden as no minor participants will be enrolled in Germany or Sweden
Inclusion criterion 3a	Note: no minor participant will be enrolled in Germany or Sweden
Inclusion criterion 3a i)	Note: no participants will be enrolled in the intensive PK and Biomarker sub-study in Germany and Sweden
This section is not applicable per Protocol Amendment 03. Section 7.1.1.1 Hydration Guidelines. Adolescent Hydration Guidelines	Note: not applicable to participants in Germany and Sweden as no adolescents will be enrolled in Germany or Sweden
[redacted]	[redacted]

Ireland - Hypertension precautions were modified to reinforce blood pressure medication guidance

Section	Country-specific language
Section 7.7.4.3 Hypertension Precautions	"Eligible participants who are on medications with antihypertensive effects for treatment of CAD (eg, b-blockers, CCBs, nitrates, etc) are those for whom it is considered safe to temporarily discontinue these drugs prior to initiation of treatment. If the Investigator considers temporary discontinuation of such medications may have an adverse effect on the patient, such patients should not be included in the trial." to be replaced with "Participants who are on medications with antihypertensive effects for the treatment of CAD (eg, b-blockers, CCBs, nitrates, etc) are only eligible to enrol if their physician considers it safe to temporarily discontinue these drugs prior to initiation of treatment. If the Investigator considers temporary discontinuation of such medications may have an adverse effect on the patient, such patients should not be included in the trial"

APPENDIX 11 *NOT APPLICABLE PER PROTOCOL AMENDMENT 03 CYTOKINE-RELEASE SYNDROME (CRS) MANAGEMENT MEASURES/ALGORITHM

Appendix 11 is not applicable per Protocol Amendment 03. A management algorithm for cytokine-release syndrome (CRS) for participants treated with bempegaldesleukin is provided below. This general guideline constitutes guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor.

As a general principle, differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

For patients with suspected CRS:

- For Grade 1 or Grade 2 events, implement supportive care, including management of isolated symptoms based on institutional practices
- Consider admitting the patient for monitoring and to provide supportive care, including management of isolated symptoms based on institutional practices and protocol management guideline (eg, hydration management guidelines in Section 7.1.1.1).
- For patients with a persistent or worsening clinical condition after initial treatment of CRS, re-evaluate for other contributing conditions. It is particularly important to reassess the patient for coexisting infections, cardiac, pulmonary, thromboembolic, and other complications.

Grading Assessment per CTCAE Version 5.0		**Treatment Measures Recommended**
CRS Grade 3	• Hypotension managed with 1 pressor • Hypoxia requiring > 40% O_2	• Vasopressin administration should be considered if the hypotensive event is refractory to > 3 L of fluid resuscitation. • Oxygen therapy (nasal canula, non-invasive positive pressure ventilation, etc.) for respiratory symptoms with consideration of intubation for a patient with severe respiratory manifestations. • Supportive care for renal, hepatic, and other organ function deteriorations. • Steroid therapy should be considered (eg, hydrocortisone 100 mg every 8 hours, dexamethasone 10 mg up to 4 times daily, 1 to 2 mg/kg/day methylprednisone IV or PO equivalent). • High-dose steroid (eg, solumedrol 2 mg/kg up to 1 gram daily for 3 days) may be considered for severe CRS that failed to respond after repetitive steroid treatments. • For severe CRS cases that require simultaneously aggressive management of hypotension, oxygenation, and cardiac telemetry, consult Intensivist for ICU evaluation.
CRS Grade 4	• Life-threatening consequences • Pressor or ventilatory support indicated	

APPENDIX 12 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 26-Aug-2021

The purpose of this protocol amendment is to update the sample size justification for progression-free survival (PFS) comparison, add sensitivity analyses to account for potential non-proportional hazard for PFS and overall survival (OS) in the efficacy analyses, update analysis time projection based on updated enrollment projection, and add provisional languages to trigger OS final analysis at 60 months of minimum follow-up if the total planned number of OS events are not reached by then. Other updates have been made to align with changes to safety assessments including the implementation of National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (CTCAE v5), a revised cerebrovascular accident (CVA) algorithm, and the addition of a cytokine-release syndrome (CRS) algorithm. Guidance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status and coronavirus disease 2019 (COVID-19) vaccine has also been included. Details have been provided to add clarity and consistency about aging of tumor biopsy between the inclusion criteria and tumor tissue specimen sections. Modifications to the bempegaldesleukin and nivolumab program standards have been addressed and protocol inconsistencies corrected.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Administrative Letter 03 and Administrative Letter 04 were incorporated into Amendment 02.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Added contact information for the Clinical Scientist and new Clinical Trial Physician	To provide current contact information for the study
Synopsis	Changes were made to match relevant protocol revisions below	For consistency throughout the protocol
Throughout the protocol	"NKTR-214" changed to "bempegaldesleukin"	To update with International Nonproprietary Name (INN)
2 Schedule of Activities 5.1.1 Screening Period 6.1 Inclusion Criteria (2e and 2l) 9.8.3 Tumor Tissue Specimens	Revised tumor tissue requirements. • Clarified that tissue submitted for screening should be from an unresectable primary tumor lesion or any metastatic site • Either a FFPE tissue block or 20 unstained tumor tissue sections, with an associated pathology report, must be submitted to the core	To clarify tissue biopsy requirement for screening

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission	
2 Schedule of Activities 3.3.3 Bempegaldesleukin and Nivolumab Benefit and Risk Assessment 6.2 Exclusion Criteria (1n,1o; 2b) 6.4.1 Retesting During Screening or Lead-In Phase 7.4 Dose Modification 7.7.3.1 COVID-19 Vaccination 8.1.2 Criteria to Resume Bempegaldesleukin and/or Nivolumab 9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.2.3 Follow-up of AEs and SAEs 9.8.7 Exploratory Serum and Plasma Biomarkers	Added or modified text to address SARS-CoV-2 infection and vaccination during study participation NOTE: No additional samples will be collected. Samples already planned for collection will be utilized, if needed	Participant safety due to SARS-CoV-2 infection
3.2.3 Bempegaldesleukin Mechanism of Action	Updated references and preclinical and clinical data	Updated references to reflect final publications
[redacted] 3.3 Benefit/Risk Assessment and related Subsections	Added pooled safety analyses of participants who received bempegaldesleukin and nivolumab and pooled safety analyses of CVA events	Added and updated data and information to align with Bempegaldesleukin Investigator's Brochure (IB v9.2)
[redacted]		

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.4.7 Duration of Treatment with Nivolumab/Bempegaldesleukin	Added that treatment is for a maximum of 24 months, "regardless of number of cycles administered"	For clarity
6.2 Exclusion Criteria (1i)	Added protocol-specific text for stable anti-hypertensive regimen and clarified anti-hypertensive medications with 2 drugs	Clarified exclusion criterion
7.4 Dose Modification and related Subsections Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinue of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) Table 7.4.1-2 Bempegaldesleukin-specific Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both are Delayed) 8.1.1 Nivolumab and Bempegaldesleukin Discontinuation Criteria 8.1.2 Criteria to Resume Bempegaldesleukin and/or Nivolumab	• Clarified text on dose delay for nivolumab or bempegaldesleukin or both • Added Table 7.4.1-1 and Table 7.4.1-2 for nivolumab and bempegaldesleukin AE criteria and subsequent delay, resumption, and discontinuation • Modified text to align criteria for dose delay, resume, and discontinuation with new Table 7.4.1-1	Updated study treatment dose delay, resume, and discontinuation criteria to align with the current CTCAE version (v5) and to align with Bempegaldesleukin IB v9.2 and Nivolumab IB v19 Addendum 01
7.4.3 Monitoring and Management of Eosinophilia and Subsections	Reworded heading title and added two new subsections	Updated to align with Bempegaldesleukin IB v9.2
Table 7.4.1-2 Bempegaldesleukin-specific Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both are Delayed) [redacted] 8.1.1 Nivolumab and Bempegaldesleukin Discontinuation Criteria	• Added permanent discontinuation criteria for bempegaldesleukin treatment related to CVA and TIA • Added that a management algorithm for possible signs of CVA/TIA and follow-up for participants treated with bempegaldesleukin in combination with nivolumab is provided in Appendix 7 and updated the appendix	To clarify CVA and TIA algorithms and to align with Bempegaldesleukin IB v9.2, Appendix 3

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.2.7 Adverse Events of Special Interest (AESI/AEOSI) Table 9.8.2-2 Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed	• Clarified that CVA (any grade) should be assessed as a serious adverse event (SAE) • In Table 9.8.2-2 footnote, changed blood specimen from "mandatory" to "if feasible, and as close to the CVA or TIA event date as possible"	
7.4.5.2 Management Algorithm for Cytokine-Release Syndrome	Added management algorithm of CRS in new Appendix 11	To align with Bempegaldesleukin IB v9.2 on the management of this potential risk
7.4.6 Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions	• Added myalgia and hypersensitivity to list of possible symptoms of infusion reaction with bempegaldesleukin and nivolumab • Added text regarding increasing infusion time for subsequent infusions for participants with previous Grade 1 or 2 infusion reactions	Participant safety during infusions with both medications
7.6 Treatment Compliance	Clarified frequency for contacting participant following first 2 infusions	To align with Bempegaldesleukin IB v9.2
7.7.3 Prior and Concomitant Medications	Clarified all medications, supplements, and/or herbs will be documented and recorded for 100 days from the last dose of study treatment	Updated for clarification
[redacted]		
7.7.4.2 Restricted Treatments	Added section on anti-coagulation guidance	Participant safety during anti-coagulation treatment
8.1 Discontinuation from Study Treatment	• Added discontinuation due to clinical disease progression in the absence of	Participant safety

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.1.3 Treatment Beyond Progression	radiologically confirmed progression by RECIST 1.1 • Clarified that documented progression is "BICR-confirmed" progression and removed starting alternate cancer therapy • Added that participants with clinical progression can continue treatment beyond progression	
[redacted]		
Table 9.8.2-2 Biomarker Sampling Schedule: All Participants after Randomization into [redacted] is Completed	• Revised Cycle "5" to "7" for serum and plasma biomarkers and changed collections to every "other" cycle • Clarified that tumor biopsy upon disease progression is recommended, but optional	To reduce participant and site burden and to add clarity

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Clarified footnote "e" that if biopsy is not taken, then other samples are preferred but not required	
9.8.11 Peripheral Blood Mononuclear Cells and Whole Blood Immunotyping	Added paragraph with detail on whole blood immunotyping	To clarify purpose of flow cytometry and provide examples of biomarkers interrogated
10.1 Sample Size Determination and related Subsections Table 10.1-1 Summary of Sample Size Parameters and Schedule of Analyses 10.3.1 Efficacy Analyses	• Updated projection of analysis times based on updated enrollment projection • Added provisional language for combining ORR and PFS final analysis if they occur close enough in time • Added additional information on PFS assumptions and provided the estimated median PFS by arm • Added provisional language for conducting OS final analysis at 60 months after last participant randomized if the planned OS event number is not reached by then • Added additional sensitivity analyses for PFS and OS to account for potential non-proportional hazards	• To provide update of analysis time projection • To streamline the ORR and PFS final analyses if they occur close enough in time • To provide estimation of median PFS, and demonstrate that magnitude of treatment effect targeted for PFS is clinically meaningful • To account for a slowdown in the OS events rate observed after 60 months in historical nivolumab data, which could prevent the final OS analysis from being performed in a reasonable time window • To help quantify treatment effect under potential non-proportional hazards for PFS or OS
Table 10.3.4-1 Interim Analyses Schedule	• Clarified that the analysis trigger for the final ORR analysis is for "randomized" participants to have a minimum of 6 months follow-up • Added footnote to clarify the final overall survival analysis will take place if the 419th overall survival event has not occurred 60 months after randomization of the last participant	Clarification

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
APPENDIX 2 Study Governance Considerations	Updated first paragraph in Monitoring section to include remote monitoring; added new subsection on dissemination of study data	Clarified expectations
APPENDIX 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Updated SAE contact information	To provide current contact information for the study
APPENDIX 6 Management Algorithms for Studies Under CTCAE Version 5.0	Updated the IO agent management algorithms to align with CTCAE v5	Updated IO management algorithms for immune-mediated AEs to align with current CTCAE v5 and the updated Nivolumab IB v19 Addendum 01
APPENDIX 7 Cerebrovascular Accident Adverse Event Management Algorithm for the Combination of Bempegaldesleukin with Checkpoint Inhibitors	Revised text	To clarify CVA and TIA algorithms and to align with Bempegaldesleukin IB v9.2
APPENDIX 10 Country Specific Requirements/Differences	• Revised title for greater clarity • Removed HIV requirement for France and Spain • Added Germany specific changes from CA045001-revprot00a-de and CA045001-revprot0000b-de that are not part of current global protocol	Added changes to facilitate use of CA045001 Protocol Amendment 02 as the global protocol
APPENDIX 11 Cytokine-Release Syndrome (CRS) Management Measures/Algorithm	Added new appendix	To align with Bempegaldesleukin IB v9.2 on the management of this potential risk
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for Revised Protocol 01, 24-Feb 2020

Program updates were added and internal inconsistencies were corrected. Updates as per Admin Letters 01 and 02 were also made.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout	In reference to dosing the term "adolescents" was changed to "participants".	In the event that an adult has a weight of < 40 kg which will meet criteria for Nivolumab weight based dosing.
Title Page	The Protocol Number was corrected to CA045001/17-214-08.	As per Admin Letter 01
[redacted]		
Synopsis, Inclusion Criteria	Added "neoadjuvant" treatment to criterion 'c' Clarification was made to criterion 'e(i)' regarding tumor tissue sample. Lesion criterion was added to inclusion criterion 'f'	Clarification of treatments. Test diagnostic provided. Clarification of lesion criteria.
Synopsis, Exclusion Criteria	Text in criterion 'a' was updated to include that MRI of the brain is now required within 28 days prior to randomization, and participants with CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days prior to randomization are not eligible.	Clarification to the timing.
Synopsis, Objective and Endpoints	Duration of complete response (DoCR) was removed. [redacted]	To simplify the list of endpoints, given the presence of the endpoint "Duration of Response (DoR)" [redacted]
Synopsis, Overall Design	Clarified evaluable vs enrolled participants in the PK and Biomarker subset. [redacted]	[redacted] Clarification of AJCC stages. Format for stratification clarified to match IRT categories:

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
		M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs M1any[1] (Stage IV Elevated LDH).
Synopsis, Study Treatment	The international nonproprietary name (INN) was added to the table. Potency was updated for bempegaldesleukin.	Compound name added. To align with Program Essential Protocol Elements.
Table 2-1, Tumor Sample Submission	Lesion criteria was added.	Clarification of lesion criteria.
Table 2-1, Physical Exam and Vital Signs (new name for row)	Targeted Physical Exam changed to Physical Exam and under the 'Notes' section removed that heart rate, pulse oximetry, etc will be recorded at Baseline only.	To align with the Program Essential Protocol Elements and study procedure.
Table 2-1, Assessment of Signs and Symptoms	Row was deleted.	To align with the Program Essential Protocol Elements
Table 2-1, Prior and Concomitant Medication	"Prior and" was added to the line item.	To align with the Program Essential Protocol Elements
Table 2-1, Echocardiogram or MUGA procedure	Added language in notes section; The Investigator should further evaluate participants with other significant abnormalities on echocardiogram / MUGA. Decision regarding treatment should be based on Investigator's best clinical judgement.	To align with the Program Essential Protocol Elements
Table 2-1, CBC with differential, chemistry, endocrine, viral, urinalysis	CBC with differential, chemistry, endocrine, viral, urinalysis row now called "Clinical Laboratory Testing"	To align with Program Essential Protocol Elements
Tale 2-1, Pregnancy Test	The 'Notes' section, added that pregnancy test was done at Screening as well.	Provide more clarifications/guidance on procedures to be followed.
Table 2-1, BRAF mutation testing	Added in note section: results from NRAS/CKIT mutation testing and prior gene expression profiles for risk stratification should be recorded if available.	Provide more clarifications/guidance on results collected in CRFs.
Table 2-1, Brain Imaging	Brain imaging is required within 28 days prior to randomization.	As per Admin Letter 02.
[redacted]		
Table 2-2, Timepoints	Added timepoints of Day 3-5 in Cycle 1 and Cycle 2 and added Cycle 3 and beyond.	To align with Program Essential Protocol Elements

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2, Administer Study Drug	Added an administration timepoint at Cycle 3 and Beyond, Day 1 (± 3 days). In 'Notes' added that study drug administration for nivolumab dose should be rounded to the nearest mg and for bempegaldesleukin to the second decimal digit.	Provide more clarifications/guidance on procedures to be followed.
Table 2-2, Rows Administer Fluids and Review Hydration Guidelines with Participants	Added an administration timepoint at Cycle 3 and Beyond, Day 1 (± 3 days).	Provide more clarifications/guidance on procedures to be followed.
Table 2-2, Oral Hydration Follow-up	New row added with follow-up at Cycle 1 Day 3-5 and Cycle 2 Day 3-5.	To align with Program Essential Protocol Elements
Table 2-2, Targeted Physical Examination, Measurements, Vital Signs and Performance Status	Changed Cycle 1 Day 8 assessments to "Vital Signs only" Clarified that vital signs should be monitored within 30 mins of completion of nivolumab administration	To align with the Program Essential Protocol Elements Provide clarification/guidance on procedures to be followed.
Table 2-2, Concomitant Medication Use	Added a timepoint at Cycle 3 and Beyond, Day 1 (± 3 days).	To align with the Program Essential Protocol Elements
Table 2-2, Pregnancy Test	Added a timepoint at Cycle 3 and Beyond, Day 1 (± 3 days). Added that serum or urine pregnancy test is required within 24 hours prior to treatment in women of childbearing potential	To align with the Program Essential Protocol Elements Provide more clarifications/guidance on procedures to be followed.
Table 2-2, Clinical Laboratory Testing (new name for row)	In Clinical Laboratory Testing, added testing at Day 1 Cycle 2 and Day 1 Cycle 3 and in 'Notes' added language "For the first dose visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility."	Provide more clarifications/guidance on procedures to be followed.
Table 2-2, Body Imaging	In Body Imaging it was clarified that tumor assessments will occur until BICR confirmed disease progression and treatment discontinuation.	Provide more clarifications/guidance on procedures to be followed.
Table 2-2, Brain Imaging	Added that CT of the brain (without and with contrast) can be performed if MRI is contraindicated.	Provide more clarity.
Table 2-2, Tumor Biopsy	Added in notes section; If clinically feasible, the lesion for biopsy during Cycle 1 would be the same lesion that was	Provide more clarity of lesion criteria.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	biopsied at baseline. Note: If the participant has > 1 lesions, the lesion planned for biopsy while on treatment cannot be designated as a target lesion at baseline. Additional target lesions should be available for radiographic efficacy assessments. If the participant has only one lesion that is measurable and amenable to biopsy, the lesion must be greater than 2.0 cm and the biopsy cannot be excisional. Note: These same criteria apply for lesion selection applies to patients who consent to the optional biopsy in the main study. Please refer to Section 9.8.3 for additional information.	
[redacted]		
Table 2-3 overall	To Follow-up Visit 1 and Follow-up Visit 2 added ± 7 days	To provide a window.
Table 2-3, Vital signs	In 'Notes' section provided the vital signs that will be recorded	To align with the Program Essential Protocol Elements
Table 2-3, Adverse Event Assessments (Including SAEs):	Updated notes section that SAEs to be collected after the 100-day safety visit if the SAE is deemed to be related or residual toxicities are persisting.	Provide clarity.
Table 2-3, Performance Status	Added an assessment at Follow-up Visit 2	To align with the Program Essential Protocol Elements
Table 2-3, Review of Concomitant Medications	From 'Notes' removed "In Survival Follow-up, subsequent cancer treatment only."	To align with the Program Essential Protocol Elements
Table 2-3, Subsequent Anti-Cancer Therapy	Added new row; Subsequent Anti-Cancer Therapy to be reviewed at Follow-up Visit 1, Follow-up Visit 2 and Survival Follow-up. Added in the notes section; Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen and date of progression to subsequent anti-cancer therapies will be collected.	To align with the Program Essential Protocol Elements

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3, Pregnancy Test	Added that serum or urine pregnancy test is required in women of childbearing potential	Provide more clarifications/guidance on procedures to be followed.
Table 2-3, Clinical Laboratory Testing	Clinical laboratory testing at Visit 1 was done only if toxicities were present.	Provide more clarifications/guidance on procedures to be followed.
Table 2-3, Body Imaging	In Body Imaging it was clarified that tumor assessments will occur until BICR confirmed disease progression and treatment discontinuation.	Provide more clarifications/guidance on procedures to be followed.
Table 2-3, Brain Imaging	Added that CT of the brain (without and with contrast) can be performed if MRI is contraindicated.	Provide more clarity
[redacted]		
Section 3.2.3, NKTR-214 Mechanism of Action	INN was added and text was updated for NKTR-214 mechanism of action.	Compound named and data updates as per the Program.
[redacted]		
Section 3.3.1, NKTR-214 Safety Profile	Identified risks of NKTR-214 were added.	Data updates
Section 3.3.3, NKTR-214 and Nivolumab Benefit and Risk Assessment	The NKTR-214 and nivolumab benefit/risk assessment was updated.	Data updates
Section 4, Objectives and Endpoints	DoCR was removed from Table 4-1 [redacted]	To simplify the list of endpoints, given the presence of the endpoint "Duration of Response (DoR)" [redacted]

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1, Overall Design	[redacted] Study schematic was updated.	[redacted] Format for stratification clarified to match IRT categories: M0 / M1any[0] (Stage III any LDH or Stage IV Normal LDH) vs M1any[1] (Stage IV Elevated LDH)
[redacted]		
Section 5.1.4, Data Monitoring Committee and Other External Committees	Standard text for when a study will have a DMC was added.	Template language added.
Section 5.3, End of Study Definition	It was clarified that the total duration of the study for the OS primary endpoint was expected to occur approximately "68" months after the date of the first participant to be randomized	Clarification of the estimated OS final analysis time.
Section 5.4.6, Rationale for Stratification by M Staging, BRAF, and PD-L1	M stage stratification was clarified.	Clarification made.
Section 5.4.7, Duration of Treatment with Nivolumab/NKTR-214	Wording modification in the last paragraph for the duration of NKTR-214 therapy.	Clarification of text.
Section 5.5.1, Justification for Dose of NKTR-214	NKTR-214 dose based on IL-2 equivalent component was removed.	To reflect the Nektar Program Essential Protocol Elements
Section 6.1, Inclusion Criteria	A 'Note' on mucosal melanoma stratifications was added to criterion '2b' Clarification was made to criterion '2c' to add neoadjuvant Clarification was made to criterion '2e(i)' regarding tumor tissue sample. Additional text was included in the Note in criterion '2f' to state that "If the participant has only 1 lesion that is measurable and amenable to biopsy, the lesion must be greater than 2.0 cm and the biopsy cannot be excisional".	Provide clarifications/guidance and program updates.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	In criterion '2j', MUGA was NOT required to be performed within 60 days prior to randomization. Criterion '3a(i)', '3d' and '3e' were updated.	
Section 6.2, Exclusion Criteria	Criterion '1a' was updated to reflect that there should be no MRI evidence of progression within 28 days prior to randomization and participants with CNS metastases treated or brain biopsy performed within 28 days prior to randomization were not eligible. In criterion '1f', a Note was added "Prophylaxis of contrast allergies with a brief course of corticosteroids is acceptable." Criterion '1j(i)(4)' was updated to remove arrhythmias requiring medication for rate control. Criteria '1l' and '1m' were added as per program updates. In criterion '2d', added "agents that target IL-2" and "neoadjuvant". In criterion '5a', added regarding prisoners who were incarcerated, that it was only in countries where local regulations permit.	As per Admin Letter 02. Provide clarifications/guidance and program updates.
Section 6.3, Lifestyle Restrictions	Added that there were limitations on strenuous activities, long hot showers.	Program updates.
Section 7, Treatment	The international nonproprietary name (INN) was added and updates were made to the 'Potency' and 'Storage Conditions' for NKTR-214 in Table 7-1. Abbreviation definitions and a clarification 'Note' added below the table.	Compound named and updates made to the drug information.
Section 7.1, Treatments Administered	The international nonproprietary name (INN) and abbreviations were added to Table 7.1-1.	Compound named.
Section 7.1.1, NKTR-214 Dosing	Updates were made to the section based on program updates.	Program updates.
Section 7.1.1.1, Hydration Guidelines	Updates were made to the section based on program updates.	Program updates.
Section 7.1.2, Nivolumab Dosing	This section was updated based on program updates.	Program updates.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2, Method of Treatment Assignment	M stage stratification was updated and a 'Note' was added on mucosal melanoma stratifications.	Clarification was made.
Section 7.3, Blinding	Standard template language was added for this open label study.	Template language updates.
Section 7.4, Dosage Modification	Standard language as per NKTR Program Essential Protocol Elements was added	Program updates.
Section 7.4.1, Nivolumab and NKTR-214 Dose Delay and Reduction Criteria	Language adapted to match NKTR Program Essential Protocol Elements	Program updates.
Section 7.4.1.1, Dose Modification Criteria for NKTR-214 and Nivolumab for Cycle 1 ALT/AST Elevations	New section added.	Program updates.
Section 7.4.2, Monitoring and Management of Elevated Hepatic Transaminases	New section added as per program requirement. As a result, consequent section numbering is changed.	Based on Clinical data from PIVOT 02
Section 7.4.3, Monitoring and Management of NKTR-214-induced Eosinophilic Disorder	New section added as per program requirement.	Program updates.
Section 7.4.4, Monitoring and Management of Adrenal Insufficiency and Hypophysitis	New section added as per program requirement.	Program updates.
Section 7.4.5, Management Algorithms for Immuno-Oncology Agents	"Myocarditis" was added to the list of management algorithms.	Program updates.
Section 7.4.6, Treatment of NKTR-214-Related or Nivolumab-Related Infusion Reactions	Text regarding reporting Grade 3 and 4 infusion reactions has been removed. Bullet point with text regarding Grade ≥ 2 infusion-related reactions or hypotension was removed.	Program updates.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.5.1, Retained Samples for Bioavailability / Bioequivalence / Biocomparability	Added "Biocomparability" to section heading.	Additional information to align with model document template.
Section 7.6, Treatment Compliance	Language was updated about the monitoring of treatment compliance. Language was added regarding oral hydration follow-up.	Program updates.
Section 7.7.1, Prohibited and/or Restricted Treatments	Added a bullet point that "Low dose acetylsalicylic acid (approx 81 mg/day) should not be combined with low molecular weight heparins (LMWH) or direct oral anticoagulants (DOAC) due to an increased risk of hemorrhage	Program updates.
[redacted]		
Section 7.7.4.1, Restricted Treatments	Added language for participants with a history of a venous or arterial thromboembolic event.	Program updates
Section 7.7.4.3, Blood Pressure Precautions	Section name modified and language was updated based on program updates	Program updates.
Section 7.7.5, Permitted Therapy	Stated that prophylaxis for flu-like symptoms and rash/pruritis "should" be initiated on Day 1 or Day 2 after NKTR-214 dosing.	Changed guidance.
Section 8.1, Discontinuation from Study Treatment	To bullet #4 added language that "only in countries where local regulations permit", a participant who has been imprisoned may be permitted to continue as a participant. Text was updated to state that in all cases of pregnancy the study treatment will be permanently discontinued and the updated Pregnancy section (Section 9.2.6) was referred to.	Program update.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.1, Nivolumab and NKTR-214 Discontinuation Criteria	Added "except adrenal insufficiency" to the drug-related endocrinopathy bullets. Added a 'Note' for Grade ≥ 3 adrenal insufficiency or Grade ≥ 4 hypophysitis. Added language for CVA and transient ischemic attack (TIA). Added "elevation" to the bullet point regarding Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase Added that for "cytokine related ALT/AST elevations < 8 x ULN in Cycle 1 only, study treatment does not need to be discontinued".	Program updates. Based on Clinical data from PIVOT-02.
Section 8.1.2, Criteria to Resume NKTR-214 and/or Nivolumab	Removed language in the beginning of this section. Added an exception for participants who delay study treatment due to Grade ≥ 2 creatinine increase due to a non-inflammatory cause. Added grade 4 hypophysitis and the sentence "Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms should not require discontinuation" to the bullet for drug-related endocrinopathies.	Redundant guidance covered in other sections. Program updates. Program updates.
Section 8.1.3, Treatment Beyond Progression	Added a statement that activities for the duration of the treatment beyond progression should be submitted to the central imaging vendor.	Additional guidance added.
Section 8.1.4, Post Study Treatment Study Follow-up	Added text for subsequent cancer therapy details that will be collected.	Additional guidance added.
Section 9.1.1, Imaging Assessments for the Study	Added bone scans in addition to X-rays.	Additional guidance added.
Section 9.1.1.2, Imaging and Clinical Assessment	Clarified that the BOR of stable disease requires a minimum of 42 days.	Changed from 35 to 42 days.
[redacted]		

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Added a bullet that CVA (any grade) is considered an adverse event of special interest.	Updates to the Nektar program.
Section 9.2.5, Pregnancy	Section was updated as per standard language.	Program updates.
[redacted]		
Section 9.2.7, Adverse Events of Special Interest (AESI/AEOSI)	New section added.	Program updates.
Section 9.2.9, Potential Drug Induced Liver Injury	Definitions of DILI were updated as per standard program language.	Program updates.
Section 9.3, Overdose	Added a sentence that all instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record eCRF.	Template language updates.
Section 9.4.3, Echocardiogram	It was clarified that abnormalities on echocardiogram should be discussed with medical monitor prior to randomization.	Additional guidance.
Section 9.4.4, Pregnancy Tests	It was clarified that a serum or urine pregnancy test could be done and a negative pregnancy test result must be obtained within 24 hours prior to the administration of the study drug. Correct section number (Section 9.2.6) was referred to for guidelines to be followed in case of pregnancy.	Program updates.
Section 9.4.5, Clinical Safety Laboratory Assessments, Table 9.4.5-1	Added “Creatinine clearance (at Screening only)” to ‘Chemistry’. Added “Urine or serum” for pregnancy test. Added the statement “Urine dipstick can be done and if abnormal perform microanalysis” to ‘Urinalysis’.	Additional guidance for lab collection.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.6, Pharmacodynamics	Added a sentence that selected biomarkers may be explored with the data permitted.	Added new information about testing.
Section 9.8, Biomarkers	Removed language that "samples may be used to expand the translational R&D capability at BMS." Other minor updates to the text for clarity.	Adding clarification.
Section 9.8.2, Biomarker Sampling Schedule	In Tables [redacted] 9.8.2-2 updates and sampling changes were made and the footnotes were updated.	Provide additional guidance and clarity.
Section 9.8.3, Tumor Tissue Specimens	Removed the requirement of a "fresh" tumor biopsy sample to be provided at Screening. Added language that "Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission" Lesion criteria were added. It was recommended that on occurrence of a Grade 3 drug-related AE that resulted in dose delay, if a biopsy of the affected organ was performed, a specimen for biomarker analysis also be collected.	A new biopsy is not required. Provide additional guidance and clarity.
Section 9.8.4, Tumor Gene Expression and Mutation Analyses	Section heading modified. Added language to explore the potential association of tumor mutation burden with clinical outcomes.	Added new information about testing.
Section 9.8.7, Exploratory Serum and Plasma Biomarkers	Added text for additional factors for which serum and plasma may be assessed.	Added new information about testing.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8.8, Plasma cfDNA/ctDNA	New section added.	Added new information about testing.
Section 9.8.9, Serum MicroRNA (miRNA)	New section added.	Added new information about testing.
Section 10.1, Sample Size Determination	Approach used to test ORR, PFS, and OS was added. Table 10.1-1 (Summary of Sample Size Parameters and Schedule of Analyses) was added. Updated projection of analysis times based on updated enrollment projection.	Provide additional guidance and clarity on the fallback testing strategy of primary endpoints and schedule of analyses. Provide update of analysis time projections
Section 10.1.1, Sample Size Justification for ORR Estimate	New section heading added. Updates to text for clarification.	To provide more clarity.
Section 10.1.2, Sample Size Justification for PFS Comparison	Minor clarifications were made to the text.	Provide editorial clarification.
Section 10.1.3, Sample Size Justification for OS Comparison	Section was reworded to include changes in sample size justification for OS comparison	Provide additional guidance and clarity of the fallback testing procedure on OS. In addition, [redacted] a formal OS interim analysis is added at the time of final PFS analysis.
Section 10.2, Populations for Analyses	Table in this section was updated.	Provide additional guidance and clarification on populations for analyses.
Section 10.3.1, Efficacy Analyses	Table in this section was updated: • 95% confidence interval was corrected to 97% CI for primary endpoint of PFS • Mention of DoCR was removed from secondary endpoints Language that participants who do not have sufficient baseline or on-study tumor assessments to evaluate response status will be counted as failures and ORR by Investigator assessment, was removed	Provide editorial clarification. DoCR was removed to simplify the list of endpoints, given the presence of the endpoint "Duration of Response (DoR)". To provide clarifications of ORR and to consolidate ORR secondary analyses by Investigator-assessed ORR to the secondary endpoint section.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3.4, Interim Analyses	Section was updated to include the interim analyses for this study. Table 10.3.4-1 (Interim Analyses Schedule) was also added.	Provide clarity on schedules of analyses.
Appendix 1	Abbreviation list was updated	Abbreviations no longer used were deleted and new abbreviations used were added.
Appendix 2	Appendix was modified to include the latest updates	Template language updates.
Appendix 3	Appendix was modified to include the latest updates	Template language updates.
Appendix 4	Appendix was modified to include latest updates	Template language updates.
Appendix 6	Appendix was modified to include the latest updates	Template language updates.
Appendix 7	New appendix with Cerebrovascular Accident Adverse Event Management Algorithm was added. As a result following appendices were renumbered.	Program updates.
Appendix 8	Mucosal Melanoma of the Head and Neck TNM definitions were added to the appendix.	Information added as per AJCC 7th Edition.
Appendix 10	Italy was removed from the countries' list. Ireland-specific amendment was added.	Not applicable for Italy. Hypertension Precautions were modified to reinforce blood pressure medication guidance for Ireland sites.