Official Title of Study:

A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus Bempegaldesleukin (NKTR-214), Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible

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CLINICAL PROTOCOL CA045009/18-214-13

A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus Bempegaldesleukin (NKTR-214), Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible

Protocol Amendment 04

Incorporates Administrative Letter 04

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	10-Jun-2022	• Participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy on protocol for the remainder of their treatment duration. New enrollment in this study has been stopped. • Imaging will be performed per local standard of care; blinded independent central review is discontinued. All study treatment decisions including progression and recurrence will be based on the investigator's assessment of tumor images. • The efficacy endpoints of pathologic complete response, event-free survival, and overall survival, as well as safety and tolerability for each treatment arm, will be summarized descriptively in all randomized participants. Secondary [redacted] objectives except for safety [redacted] parameters will not be required. No further efficacy data will be collected/analyzed. • For each randomized participant, the maximum duration of the study is 62 weeks plus 100 days of safety follow-up. • Participants currently in survival follow-up will discontinue from the study following one recurrence update and survival status update.
Administrative Letter 04	06-Apr-2022	The purpose of this letter is to clarify and align the Schedule of Activities for collection and submission of tumor tissue samples for participants assigned to Arm C in the CA045009 trial following radical cystectomy with the protocol text, Section 5.1.2.2 Surgery (Radical Cystectomy). To clarify, tissue samples for all participants, irrespective of study assignment, must be submitted to central lab for pathologic confirmation after radical cystectomy.
Protocol Amendment 03	26-Aug-2021	• Revised to include participants with high-risk urothelial carcinoma (UC) of the bladder with N1 disease and muscle-invasive bladder cancer (MIBC), addition of nivolumab + bempegaldesleukin vs nivolumab secondary endpoint comparisons, and the updated alpha allocation for the pathologic complete response (pCR) and event free survival (EFS) primary endpoints • Modifications made to align with Bempegaldesleukin and Nivolumab program standards • Align with changes to safety assessments including safety management algorithms, guidance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status, and coronavirus disease 2019 (COVID-19) vaccine
Administrative Letter 03	06-Jun-2020	This letter is to correct inconsistency in the protocol: • The note referring to AE biopsy was inadvertently not removed in treatment section 7.4.1 of the protocol. [redacted]

Document	Date of Issue	Summary of Change
		[redacted]
Revised Protocol 02	05-Mar-2020	• Revised to align with most recent language for BMS program updates • Modifications made to align with NKTR-214 program and IB updates • Appendix 2 updated (Study Governance Considerations) • Appendix 6 updated (Management Algorithms) • Appendix 7 added (CVA Management Algorithm)
Revised Protocol 01	21-Jan-2019	• Modifications made to align with BMS policy updates • Added nivolumab and NKTR-214 program updates • Correction to Section 5.1.4: added missing paragraph regarding adjudicated events • Appendix 3 updated (Adverse Events) • Appendix 4 updated (WOCBP) • Appendix 9 added (Country Specific Requirements)
Original Protocol	05-Oct-2018	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04

Three recent studies from the bempegaldesleukin and nivolumab development program, Study CA045-001/17-214-08, a Phase 3 study in metastatic melanoma, Study 17-214-09/PIVOT-09, a Phase 3 study in metastatic renal cell carcinoma, and Study 18-214-10/PIVOT-10, a Phase 2 study in cisplatin ineligible metastatic urothelial carcinoma have demonstrated that there was no additional benefit of combining bempegaldesleukin with nivolumab. On 14-Apr-2022, Nektar Therapeutics and Bristol-Myers Squibb (BMS) announced a joint decision to end the clinical development program for bempegaldesleukin in combination with nivolumab. Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A of CA045009 are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy. The purpose of this amendment is to allow participants who are deriving benefit to continue on study treatment while minimizing participant burden.

All new enrollment to CA045009 has been stopped, and study procedures that no longer apply due to the discontinuation of bempegaldesleukin are indicated throughout the protocol and are specified below.

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 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated synopsis to align with protocol revisions.	To align the Synopsis with updates made to the full protocol.
Title page	The [redacted] for this study has changed..	Updated to reflect current study personnel.
Table 2-1 Screening Procedural Outline (CA045009)	Note added to the table title indicating that all new enrollment has been stopped.	Enrollment has been stopped per the joint decision of Nektar Therapeutics and BMS to end the clinical development program of bempegaldesleukin in combination with nivolumab.
Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A + Arm B)	Note to the table titles to specify text related to bempegaldesleukin is not applicable, but criteria for nivolumab remain unchanged.	Bempegaldesleukin will no longer be administered.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)	Update of Administer Study Drug: Arm A: Bempegaldesleukin (0.006 mg/kg) and Nivolumab (360 mg) **(Arm A)**: Text added to indicate that bempegaldesleukin dose is not applicable. Note has also been updated.	Bempegaldesleukin will no longer be administered.
Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A + Arm B)	Added text to indicate that the procedures listed below and corresponding notes are not applicable per Protocol Amendment 04: • Administer Intravenous (IV) Fluids, **(Arm A ONLY)** • Review Hydration Guidelines with Participants **(Arm A ONLY)** • Oral Hydration Follow-up **(Arm A ONLY)** • [redacted] • Submission of Tissue for [redacted] Analysis (Table 2-3) • Submission of Tissue for pCR (Table 2-3) • Severe Acute Respiratory Syndrome Coronavirus 2; (SARS-CoV-2) Serology (Table 2-2) • [redacted] • [redacted] • [redacted] • [redacted]	Bempegaldesleukin will no longer be administered.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A + Arm B)	Laboratory Tests, Clinical - Laboratory Testing - Deletion of bempegaldesleukin from instruction for pre-dose testing of renal function.	No longer applicable as bempegaldesleukin will no longer be administered.
Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A + Arm B)	Efficacy: Body Imaging: Text added to indicate that per Protocol Amendment 04, imaging will be performed per local standard of care (SOC) and images will no longer be submitted for blinded independent central review (BICR)	Since further efficacy will not be assessed, imaging will be performed per local SOC and tumor assessments will be evaluated by investigator assessment.
Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A + Arm B)	Cystoscopy - Text added within Table 2-3 and to Footnote c to indicate that per Protocol Amendment 04, cystoscopy will be performed per local SOC.	No further efficacy assessments.
Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)	Text has been added to indicate that participants will have a final follow-up for recurrence status and overall survival and then will discontinue from the study. Added text to indicate that the sections listed below as well as corresponding notes are not applicable per Protocol Amendment 04: [redacted] • Subsequent Anti-cancer Therapy • Survival Status • Footnote c.	Per Protocol Amendment 04, survival follow-up every 3 months is no longer applicable. Indicated assessments are no longer applicable; the. program is being discontinued.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Efficacy: Body Imaging: Text added to indicate that per Protocol Amendment 04, imaging will be performed per local SOC and images will no longer be submitted for BICR.	Aligned with change to investigator assessment of imaging.
	Cystoscopy - Text added to indicate that per Protocol Amendment 04, cystoscopy will be performed per local SOC.	No further efficacy assessments.
Table 2-5: Study Assessment - Arm C	Text has been added to indicate that participants will have a final follow-up for recurrence status and overall survival and then will discontinue from the study.	Per Protocol Amendment 04, survival follow-up every 3 months is no longer applicable.
	Subsequent Anti-cancer Therapy: note added to indicate that per Protocol Amendment 04, the details of subsequent anti-cancer therapy will no longer be collected after 100 days of safety follow-up.	
	Efficacy: Body Imaging: Text added to indicate that per Protocol Amendment 04, imaging will be performed per local SOC, and images will no longer be submitted for BICR.	Aligned with change to investigator assessment of imaging.
	Cystoscopy - Text added to indicate that per Protocol Amendment 04, cystoscopy will be performed per SOC.	No further efficacy assessments.
	Added text to indicate that the sections listed below as well as corresponding notes are not applicable per Protocol Amendment 04: [redacted]	Indicated assessments are no longer applicable; the. program is being discontinued.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted] • Subsequent Anti-cancer Therapy • Submission of Tissue for Pathologic Complete Response • Footnote b	
Section 3: Introduction Section 3.1.1 Research Hypothesis Section 3.2.1: Epidemiology/Indication	Added text that sections are not applicable per Protocol Amendment 04 and if required by the content of the specific section, that participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.	No longer applicable as bempegaldesleukin is no longer administered in the study. .
Section 3.2.4.2: Study 16-214-02 (PIVOT-02; Bempegaldesleukin and Nivolumab Combination Therapy) Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information Section 9.2.7: Adverse Events of Special Interest (AEOSI)	Text added to indicate that the Cerebrovascular Accident Adverse Event Management Algorithm ([(CVA-AE] Appendix 7) is no longer applicable per Protocol Amendment 04.	Bempegaldesleukin will no longer be administered.
Section 3.2.4.3: Study 18-214-10 (PIVOT-10); Bempegaldesleukin and Nivolumab Combination Therapy	New section added that summarizes the results of Study 18-214-10 (PIVOT-10).	Addition of summary background that supported the joint decision of Nektar Therapeutics and BMS to discontinue clinical development.
Section 3.3 3: Bempegaldesleukin and Nivolumab Benefit and Risk Assessment	Added statement on the joint decision by Nektar Therapeutics and BMS to stop the global clinical development of the bempegaldesleukin and nivolumab combination program.	Benefit/Risk section adjusted per changes of Protocol Amendment 04.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4: Objectives and Endpoints	• Added that secondary [redacted] endpoints except for safety [redacted] are not applicable per Protocol Amendment 04. • Efficacy endpoints of pathologic complete response (pCR), event free survival (EFS) and overall survival (OS), as well as safety and tolerability, will be summarized descriptively in all randomized participants.	Additional data for secondary [redacted] objectives, [redacted] will not be captured.
Section 5.1: Overall Design	• The updates in this section describe the end of the global clinical program and indicate text that is not applicable per Protocol Amendment 04 and that participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy. • In addition, the disposition of participants who are receiving treatment on the study or in safety follow-up or long term follow-up is specified.	Section is now aligned with changes of Protocol Amendment 04 and includes instructions for disposition of participants who remain on the study.
Section 5.1.1: Screening Period Section 5.1.2.1: Neoadjuvant (Pre-surgical Treatment) Randomized Participants Section 5.1.2.3: Adjuvant (Post-surgical Treatment) Section 5.1.4: Data monitoring Committee and Other External Committees	Added that these sections are not applicable per Protocol Amendment 04 and, if required by the content of the specific section, that participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.	No longer applicable as bempegaldesleukin will no longer be administered.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2.2: Surgery (Radical Cystectomy)	Per Protocol Amendment 04, radical cystectomy will be performed per local SOC. In addition, text referring to pathology slides are designated as no longer applicable per Protocol Amendment 04 as is text with procedures for participants who do not undergo radical cystectomy (RC).	No further efficacy assessments.
Section 5.1.3: Long-term Follow-up	Per Protocol Amendment 04, participants will have a final follow-up for recurrence status and overall survival and then will discontinue from the study. For each randomized participant, the total maximum duration of the study is up to 62 weeks + 100 days of safety follow up.	Per Protocol Amendment 04, survival follow-up every 3 months is no longer applicable. Descriptive analyses will now be performed in the study, the maximum duration of the study for each participant was shortened to the study treatment period plus 100 days safety follow-up.
Section 5.1.4.1: Blinded Pathology and Radiology Review	Text added to indicate that this section is no longer applicable but descriptive analysis of pathologic complete response (pCR) will be conducted on samples collected prior to Protocol Amendment 04. Radiology Review is no longer applicable per Protocol Amendment 04.	The program is being discontinued and no further efficacy data is being collected. Descriptive analyses on pathology samples collected prior to Protocol Amendment 04 will be conducted.
Section 5.2: Number of Participants	Updated to specify that all new enrollment in CA045009 has stopped.	Aligned with the Nektar Therapeutics and BMS joint decision to stop clinical development of bempegaldesleukin and nivolumab combination.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.3: End of Study Definition	Paragraph that previously defined end of the study in terms of accrual events is no longer applicable per Protocol Amendment 04.	No longer applicable as study will stop once last participant completes the treatment period plus safety follow-up or earlier on the Sponsor's decision.
Section 5.4.4: Rationale for Open-label Design Section 5.5.1: Justification for Dose of Bempegaldesleukin	Added that sections are not applicable per Protocol Amendment 04.	No longer applicable as bempegaldesleukin will no longer be administered.
Section 5.5.3: Rationale for Bempegaldesleukin/Nivolumab Combination Dose Table 5.5.3-1: Patient Exposure Supporting Combination Dose	Added text to the section and to the table title to specify not applicable per Protocol Amendment 04.	
Section 6: Study Population Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria	Text added to indicate no longer applicable per Protocol Amendment 04 as enrollment has stopped.	New enrollment in the study has stopped.
Section 6.3: Lifestyle Restrictions	Added that section is not applicable per Protocol Amendment 04.	No longer applicable as bempegaldesleukin will no longer be administered.
Section 7: Treatment Table 7-1: Study Treatment for CA045009/18-214-13 Section 7.1: Treatments Administered Table 7.1-1: Selection and Timing of Dose Section 7.1.1: Bempegaldesleukin Dosing	• Added to the section text and in the study tables text to specify that bempegaldesleukin is not applicable per Protocol Amendment 04. • Updated text states that participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy 360 mg IV Q3W for the remainder of the study treatment period.	
Section 7.1.1.1: Hydration Guidelines	Added that section is not applicable per Protocol Amendment 04.	Bempegaldesleukin will no longer be administered.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4: Dosage Modification Section 7.4.1: Nivolumab and Bempegaldesleukin Dose Delay, Resume, and Discontinuation Criteria	Added text that section is not applicable per Protocol Amendment 04, but criteria remain unchanged for nivolumab.	Bempegaldesleukin will no longer be administered, and participants may receive nivolumab monotherapy.
Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed)	• Added to the table title that text related to bempegaldesleukin is not applicable per Protocol Amendment 04 but criteria remain unchanged for nivolumab. • Note added to table title that participants must discontinue bempegaldesleukin.	Bempegaldesleukin will no longer be administered, and the participants may receive nivolumab monotherapy.
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)	• Added to the table title that text related to bempegaldesleukin is not applicable per Protocol Amendment 04 but criteria remain unchanged for nivolumab. • Note added after the table to specify that bempegaldesleukin must be discontinued for participants receiving bempegaldesleukin plus nivolumab and that participants may continue on nivolumab monotherapy. • In addition, note states participants with CVA must be managed by Advanced Cardiac Life Support (ACLS) and institutional guidelines and Appendix 7 no longer applies for the management of participants with CVA/TIA.	Bempegaldesleukin will no longer be administered, and the participants may continue to receive nivolumab monotherapy.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.1.1: Dose Modification Criteria for Bempegaldesleukin and Nivolumab for Cycle 1 AST/ALT Elevations Section 7.4.2: Monitoring and Management of Elevated Hepatic Transaminases Section 7.4.3: Monitoring and Management of Bempegaldesleukin-induced Eosinophilia	Added that sections are not applicable per Protocol Amendment 04.	No longer applicable as bempegaldesleukin will no longer be administered.
Section 7.4.5: Management Algorithms for Immuno-oncology Agents	Added that text related to bempegaldesleukin is not applicable per Protocol Amendment 04 but criteria remain unchanged for nivolumab. Advanced Cardiac Life Support (ACLS) and institutional guidelines should be followed for all CVA cases. Text added to indicate that the Cerebrovascular Accident Adverse Event Management Algorithm ([(CVA-AE] Appendix 7) is no longer applicable per Protocol Amendment 04.	Bempegaldesleukin will no longer be administered, and the participants may continue to receive nivolumab monotherapy.
Section 7.4.5.1: Management Algorithm for Cytokine-release Syndrome	Added that the algorithm for the management of Cytokine - Release Syndrome (CRS), provided in Appendix 8, is not applicable per Protocol Amendment 04.	No longer applicable as bempegaldesleukin will no longer be administered.
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 04, but criteria remain unchanged for nivolumab.	Bempegaldesleukin will no longer be administered, and the participants may receive nivolumab monotherapy.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7: Concomitant Therapy	Added text to indicate that Per Protocol Amendment 04, bempegaldesleukin will no longer be administered.	Bempegaldesleukin will no longer be administered.
Section 7.6: Treatment Compliance Section 7.7.1.1: Effect of Bempegaldesleukin on PK of Concomitant Medications Section 7.7.2.3: Blood Pressure Precautions	Added that section is not applicable per Protocol Amendment 04.	Bempegaldesleukin will no longer be administered, and the participants may receive nivolumab monotherapy.
Section 7.7.2.1: Restricted Treatments	Added first paragraph on ischemic cerebrovascular events and anticoagulation therapy no longer being mandated for the study.	Participants are required to discontinue bempegaldesleukin.
Section 7.7.3: Permitted Therapy	Added that text related to bempegaldesleukin is not applicable per Protocol Amendment 04, but criteria remain unchanged for nivolumab.	Bempegaldesleukin will no longer be administered, and the participants may continue to receive nivolumab monotherapy.
Section 7.8: Treatment After the End of the Study	Text added to specify how treatment will be available to participants if the study is terminated.	The Sponsor will determine access to care if the study is terminated.
Section 8.1.1: Nivolumab and Bempegaldesleukin Discontinuation Criteria	Text added to specify that Per Protocol Amendment 04 participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy and that per Protocol Amendment 04 bempegaldesleukin is not applicable but criteria remain unchanged for nivolumab.	Bempegaldesleukin will no longer be administered, and participants may continue to receive nivolumab monotherapy.
Section 8.1.2: Post-study Treatment Study Follow-up	For each randomized participant, the maximum total duration of	For each randomized participant, the maximum duration of the study was

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the study is 62 weeks plus 100 days of safety follow-up. No longer applicable per Protocol Amendment 04 is the collection of subsequent cancer therapy details.	shortened to the study treatment period plus 100 days for safety follow-up.
Section 8.2: Discontinuation from the Study	Updated to specify that participants who wish to discontinue study treatment will remain in the study and will be followed for up to 100 days of safety follow-up and will be documented for last overall survival.	Recommended duration of safety follow-up for nivolumab.
Section 9.1: Efficacy Assessments Section 9.1.2 Imaging Assessment for the Study Section 9.1.2.2: BICR Confirmation of Progression or Recurrence Section 9.1.2.3: Confirmation and Date of Progression or Recurrence	• Per Protocol Amendment 04, tumor assessments will be determined by investigator. • Updated to reflect that per Protocol Amendment 04, images will no longer be submitted for central review. • Per Protocol Amendment 04, BICR will be discontinued, and all study treatment decisions will be based on the investigator's assessment of tumor images.	As there are no further efficacy assessments, BICR will not be conducted, and images will be assessed by the investigator.
[redacted]		
Section 9.2.6, Immune-mediated Adverse Events	Per Protocol Amendment 04, text related to collection of additional information on select AEs related to bempegaldesleukin is not applicable.	No longer applicable as bempegaldesleukin will no longer be administered.
Section 9.4.7 Clinical Safety Laboratory Assessments	Per Protocol Amendment 04, all clinical safety laboratory	Submission to the central laboratory is no longer

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	assessments will be performed locally.	required; the program is being discontinued.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1: Sample Size Determination Table 10.1-1: Sample Size Calculations per Comparison for Primary Endpoints	Updated to indicate that section is not applicable per Protocol Amendment 04.	The underlying assumptions for efficacy comparisons between Arm A and Arm C in sample size determinization are no longer applicable.
Section 10.3: Statistical Analyses	Text added in alignment with the termination of the global development of bempegaldesleukin, the study will be unblinded and there will be no hypothesis testing. The efficacy endpoints of pCR, EFS, and OS will be summarized descriptively.	No hypothesis testing for any efficacy endpoints will be performed between the treatment arms.
Table 10.3-1: Efficacy Analyses Figure 10.3-1: Graphical Representation of the Statistical Testing Approach	Text added to indicate Not Applicable per Protocol Amendment 04. Text below study table not applicable per Protocol Amendment 04.	
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.3: Interim Analyses Table 10.3.3-1: Interim Analyses Schedule Section 10.3.4: Interim Analyses for EFS Section 10.3.5: Interim Analyses for OS	Text added to indicate Not Applicable per Protocol Amendment 04.	No hypothesis testing for any efficacy endpoints will be performed between the treatment arms.
Section 11: References	Reference to joint decision of Nektar Therapeutics and BMS on the decision to discontinue development program of the combination of bempegaldesleukin and nivolumab has been added.	Support of new text in Section, 3.2.4.3, Study 18-214-10 (PIVOT-10); Bempegaldesleukin and Nivolumab Combination Therapy
Appendix 7: Cerebrovascular Accident Adverse Event Management Algorithm	Added that Appendix 7 is not applicable per Protocol Amendment 04.	Participants are required to discontinue bempegaldesleukin.
Appendix 8: Cytokine Release Syndrome (CRS) Management Algorithm	Added that Appendix 8 is not applicable per Protocol Amendment 04.	Participants are required to discontinue bempegaldesleukin.

TABLE OF CONTENTS

1 SYNOPSIS

A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus Bempegaldesleukin (NKTR-214), Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible

Study Phase: Phase 3

Rationale:

On 14-April-2022, Nektar Therapeutics and BMS jointly decided to end the global clinical development program for bempegaldesleukin in combination with nivolumab. All new enrollment to CA045009 has been stopped. Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

The study of neoadjuvant nivolumab and bempegaldesleukin followed by continued adjuvant nivolumab and bempegaldesleukin after radical cystectomy (RC), aims to demonstrate that perisurgical treatment with nivolumab combined with bempegaldesleukin will significantly increase the rate of pathologic complete response (pCR) and prolong event-free survival (EFS) in cisplatin-ineligible participants with high-risk urothelial carcinoma (UC) of the bladder, including MIBC who undergo RC.

Study Population:

Male or female participants, aged 18 years or local age of majority, inclusive, with previously untreated high-risk UC, including MIBC, who are candidates for RC and cisplatin-ineligible.

Key Eligibility Criteria: *No longer applicable as all new enrollment has stopped.

Inclusion

- Participants with UC of the bladder clinical stage T2-T4a, N0 (< 15 mm in short axis on CT or MRI), M0 or T1-T4aN1 (≥ 15 mm in short axis on computed tomography [CT] or magnetic resonance imaging [MRI]), M0, diagnosed at transurethral resection of bladder tumor (TURBT) within 12 weeks of randomization. Variant histology is acceptable if there is a predominant urothelial component.

  Note: Stained slides from the initial TURBT used to make the UC of the bladder/MIBC diagnosis and associated pathology report must be submitted to the vendor for confirmation of UC of the bladder/MIBC prior to randomization.
- Participant must be deemed eligible for RC by his/her urologist, and must agree to undergo RC. For arms A and B, participants must agree to undergo RC after completion of neoadjuvant therapy.
- Documentation of programmed cell death ligand-1 (PD-L1) status by immunohistochemistry (IHC) performed by the central laboratory during the screening period; the tumor should be classified as PD-L1 ≥ 1% or PD-L1 < 1% as determined by a central laboratory during the screening period and the results must be submitted to interactive response technology (IRT)

prior to randomization. Indeterminate participants are allowed in the study. Either a formalin-fixed paraffin-embedded (FFPE) tissue block or 20 unstained tumor tissue sections with an associated pathology report, must be submitted for [redacted] evaluation prior to randomization. The bladder tumor sample submitted should be from the initial TURBT (obtained within 12 weeks of randomization) in which the UC of the bladder/MIBC diagnosis was made. Submitted tissue sample must not be previously irradiated and systemic therapy must not be given after samples are obtained prior to enrollment.

Note: If despite best efforts, a minimum of 20 unstained slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with the Medical Monitor.

- A documented left ventricular ejection fraction (LVEF) > 45% within 60 days prior to randomization, using standard echocardiogram or multigated acquisition (MUGA) scan test
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Cisplatin-ineligible participants will be defined by any one of the following criteria:
  - Impaired renal function (glomerular filtration rate [GFR] ≥ 30 but < 60 mL/min)
  - GFR should be assessed by direct measurement (ie, creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
  - Common Terminology Criteria for Adverse Events (CTCAE) version 5, ≥ Grade 2 hearing loss (assessed per local standard of care[SOC])
  - CTCAE version 5, ≥ Grade 2 peripheral neuropathy

Exclusion

- Clinical evidence of ≥ N2 or metastatic bladder cancer
- Prior systemic therapy, radiation therapy, or surgery for bladder cancer other than TURBT or biopsies is not permitted. Prior Bacillus Calmette-Guerin (BCG) or other intravesicular treatment of non-muscle invasive bladder cancer (NMIBC) is permitted if completed at least 6 weeks prior to initiating study treatment
- Evidence of UC in upper urinary tracts (ureters or renal pelvis) or history of previous MIBC

Objectives and Endpoints:

Per Protocol Amendment 04, the secondary [redacted] objectives except for safety [redacted] parameters are no longer applicable. [redacted]

Per Protocol Amendment 04, Nektar Therapeutics and Bristol Myers Squibb (BMS) are terminating the development of bempegaldesleukin in combination with nivolumab. The efficacy endpoints of pCR, EFS by investigator assessment and overall survival (OS), as well as safety and tolerability for each treatment arm, will be summarized descriptively in all randomized participants. Details will be included in the Statistical Analysis Plan (SAP).

Table 1-1: Objectives and Endpoints

Objective	Endpoint
Primary	
To compare the pCR rate of neoadjuvant nivolumab + bempegaldesleukin to Standard of Care (SOC, no neoadjuvant therapy) in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To compare the EFS of neoadjuvant nivolumab + bempegaldesleukin followed by adjuvant nivolumab + bempegaldesleukin after radical cystectomy (RC) versus SOC (no neoadjuvant or adjuvant therapy) in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause
Secondary	
To compare the pCR rate of neoadjuvant nivolumab monotherapy to SOC (no neoadjuvant therapy) in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To compare the EFS of neoadjuvant nivolumab followed by adjuvant nivolumab versus SOC in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause
To compare the overall survival (OS) of each experimental arm versus SOC in all randomized participants	OS, defined as the time between the date of randomization and the date of death from any cause. OS will be censored on the last date a participant was known to be alive
To assess safety and tolerability for each treatment arm in all treated participants	Worst grade AEs, SAEs, AEs leading to discontinuation, immune-mediation AEs and worst grade clinical laboratory values
To evaluate (descriptively) the pCR rate of neoadjuvant nivolumab + bempegaldesleukin to neoadjuvant nivolumab monotherapy in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To evaluate (descriptively) the EFS of neoadjuvant nivolumab + bempegaldesleukin followed by adjuvant nivolumab + bempegaldesleukin after radical cystectomy (RC) versus neoadjuvant nivolumab followed by adjuvant nivolumab after RC in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause

Overall Design:

Per Protocol Amendment 04, this section is no longer applicable.

This is a multicenter, randomized, Phase 3, study of neoadjuvant and adjuvant nivolumab plus bempegaldesleukin, versus nivolumab alone versus standard of care in participants with high-risk UC of the bladder, including MIBC, who are candidates for RC and cisplatin-ineligible.

Participants must have pathologically proven UC of the bladder, clinical stage T2-T4aN0M0 or T1-T4aN1M0, that has not been previously treated (except for TURBT or prior intravesicular treatment of NMIBC). Participants must be deemed potentially curable, medically fit for RC, and be willing to undergo RC as part of the study treatment.

The study is divided into screening period, treatment period and long-term follow-up period.

Randomization will be stratified by the following:

- Clinical stage (T2N0 vs T3-T4aN0 vs T1-T4aN1)
- PD-L1 status (≥ 1% vs < 1%/indeterminate)

Number of Participants:

All new enrollment to CA045009 has been stopped.

It is anticipated that approximately 720 participants will be screened for approximately 540 participants to be randomized overall to the 3 arms in a 1:1:1 ratio, assuming a screen failure rate of approximately 25%.

Treatment Arms and Duration:

Participants were randomized (1:1:1) to one of the following 3 treatment arms:

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

- **Arm A**: Bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed by bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
- **Arm B**: Nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed by nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
- **Arm C**: SOC (cystectomy alone, without neoadjuvant or adjuvant therapy)

Per Protocol Amendment 04:

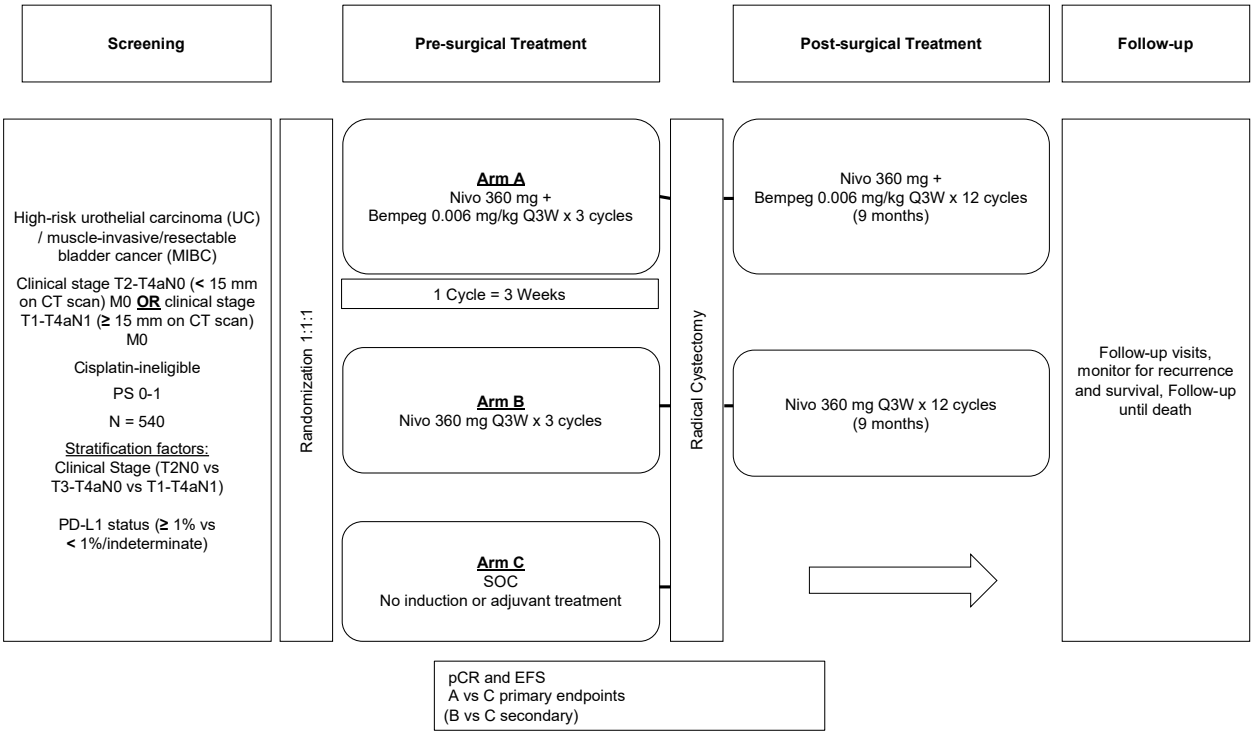
- Participants in Arm A are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy.
- Participants on adjuvant nivolumab monotherapy can receive up to a maximum of 12 cycles.
- All participants in Arm A and Arm B who have completed therapy or are currently within the 100 days safety follow-up should discontinue from the study once they complete the safety follow-up 100 days, if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of recurrence status and last overall survival should occur upon discontinuation.

- All participants in Arm C who have completed radical cystectomy or are currently within the 100 days safety follow-up after radical cystectomy, should discontinue from the study once they complete the safety follow-up 100 days, if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of recurrence status and last overall survival should occur upon discontinuation.
- Participants who have completed therapy, including 100 days safety follow-up, and are currently in survival follow-up should discontinue from the study if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.

For each randomized participant, the total maximum duration of the study is up to 62 weeks + 100 days of safety follow-up.

Study Design Schematic

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.



Abbreviations: Bempeg, bempegaldesleukin; CT, computed tomography; EFS, event-free survival; Nivo, nivolumab; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PS, performance score; Q3W, every 3 weeks; SOC, standard of care.

Study Treatment:

Study Drug for CA045009		
Medication	**Potency**	**IP/Non-IP**
***Not applicable per Protocol Amendment** 04 Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.3 mg, 0.5 mg, or 1 mg of rhIL-2 per vial[a]	IP
Nivolumab Solution for Injection[b]	100 mg (10 mg/mL)	IP

[a] ***Not applicable per Protocol Amendment 04** Note: For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.

[b] May be labeled as either "BMS-936558-01" or "nivolumab."

Data Monitoring Committee: Yes**. Per Protocol Amendment 04, this section is no longer applicable.**

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA045009)

***All new enrollment to CA045009 has been stopped.**

Procedure[a]	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. Register in the Interactive Response Technology (IRT) to obtain participant number. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study, including the following: any serious organ system dysfunction; prior cancer therapy; Tumor; Node and Metastasis (TNM) stage (T1, T2/T3 or T4a, N0, N1, or M0); smoking history (including electronic cigarettes); and alcohol history.
Urothelial Carcinoma (UC) of the Bladder/Muscle-invasive Bladder Cancer (MIBC) Confirmation	X	Diagnostic hematoxylin and eosin (H&E) and, if applicable, immunohistochemistry (IHC) stained slides from the initial transurethral resection of bladder tumor (TURBT) (conducted within 12 weeks of randomization) in which the UC of the bladder/MIBC diagnosis was made, along with associated pathology report must be submitted to the vendor for confirmation of UC of the bladder/MIBC prior to randomization. Submitted tissue must not be previously irradiated and systemic therapy must not be given after samples are obtained prior to enrollment. Vendor must provide IRT with UC of the bladder/MIBC confirmation prior to randomization. See Section 5.1.4.1 for further details.
Tumor Sample Submission	X	All participants must have bladder tumor tissue submitted for [redacted] analysis prior to randomization. To be randomized, a participant must have quantifiable programmed death ligand 1 (PD-L1) expression (≥ 1% [positive] or < 1% [negative] tumor cell membrane staining) or be classified as PD-L1 indeterminate. PD-L1 non-evaluable participants are not eligible for randomization.

Table 2-1: Screening Procedural Outline (CA045009)

***All new enrollment to CA045009 has been stopped.**

Procedure[a]	Screening Visit	Notes
		Pre-randomization bladder tumor tissue submitted must be from the initial TURBT (ie, obtained within 12 weeks of randomization) in which the UC of the bladder/MIBC diagnosis was made. One (1) formalin-fixed paraffin-embedded (FFPE) tumor tissue block or 20 unstained tumor tissue sections with an associated pathology report are acceptable. Submitted tissue must not be previously irradiated and systemic therapy must not be given after samples are obtained prior to enrollment. 1) Note: If despite best efforts, a minimum of 20 unstained slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with the Medical Monitor. See [redacted] the Study Laboratory Manual for additional information.
PD-L1 Analysis	X	The analytical laboratory must provide IRT with confirmation of the PD-L1 results prior to randomization. [redacted]
Safety Assessments		
Prior and Concomitant Medication Review/Use	X	Within 14 days prior to randomization. Document vaccine use within 30 days prior to first study treatment.
Physical Examination, Measurements, Vital Signs, and Performance Status	X	Must be collected within 14 days prior to randomization Vital signs including the following: Blood Pressure (BP), Heart Rate, Temperature Height, Weight Pulse oximetry ECOG performance status (Appendix 5)
Serious Adverse Events (SAEs) Assessment	X	SAEs collected and reported from time of consent. All adverse events (AEs [SAEs or non-serious AEs]) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection collected from time of consent.
Clinical Complaints/Signs and Symptoms	X	Collected within 14 days from randomization.

Table 2-1: Screening Procedural Outline (CA045009)

***All new enrollment to CA045009 has been stopped.**

Procedure[a]	Screening Visit	Notes
ECG	X	Within 14 days of randomization. See Section 9.4.3.
Echocardiogram (ECHO) or MUGA	X	Left Ventricular Ejection fraction > 45% within 60 days is required 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 judgement. See Section 9.4.4.
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. See Table 9.4.7-1 for a list of laboratory tests to conduct.
Pregnancy Test	X	WOCBP only: Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study therapy in women of childbearing potential (WOCBP).
[redacted]		
Tumor Assessments		
Body Imaging	X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis (including excretory imaging), and all other known and/or suspected sites of disease to be completed within 35 days prior to randomization. See Section 9.1.2 for further details.
Other Imaging for Staging	See note[a]	As clinically indicated per local standards. See Section 9.1.2.3.
[redacted]		

[a] NOTE: Some of the assessments referred to in this table may not be captured as data in the eCRF. 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.

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
Study Treatment							
Randomize	X						First dose must occur within 3 calendar days of randomization.
Administer Study Drug							
***The text below related to bempegaldesleukin is not applicable.** Bempegaldesleukin (0.006 mg/kg) and Nivolumab (360 mg) **(ARM A)**	X			X			**Not applicable per Protocol Amendment 04.** See Section 7.1 for complete details.
Nivolumab (360 mg) **(ARM B)**	X			X			See Section 7.1 for complete details.
***Not applicable per Protocol Amendment 04.** Administer Intravenous (IV) Fluids **(Arm A ONLY)**	X			X			**Not applicable per Protocol Amendment 04**. May be withheld if deemed in the best interest of the participant by the investigator. See Section 7.1.1.1 for additional information.

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
***Not applicable per Protocol Amendment 04.** Review Hydration Guidelines with Participant **(Arm A ONLY)**	X			X			**Not applicable per Protocol Amendment 04.** Applicable only to Study Arm A treated with bempegaldesleukin. See Section 7.1.1.1.
***Not applicable per Protocol Amendment 04.** Oral Hydration Follow-up **(Arm A ONLY)**		X (Day 3-5)			X		**Not applicable per Protocol Amendment 04.** For the first two doses of bempegaldesleukin, between Days 3 and 5, following infusion (inclusive), 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. For subsequent administrations of bempegaldesleukin, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin. See Section 7.1.1.1for details.

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
Safety Assessments							
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X		X Vital Signs only	X			Vital Signs: BP, Heart Rate, and Temperature Weight ECOG performance status (Appendix 5). Monitor and record vital signs at predose and within 30 minutes after administration of nivolumab in Arms A and B.
Adverse Event and Serious Adverse Event Assessments	Continuously						All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Concomitant Medication Use	Continuously						Record at each visit.
Laboratory Tests							
Clinical Laboratory Testing	X		X	X			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 treatment, including renal function (ie, serum creatinine) must be assessed within 24 hours prior to dosing or as soon as locally feasible. For the first treatment visit, labs, except pregnancy test, may not need to be repeated if they were performed within

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
							72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.7 Clinical Safety Laboratory Assessments for list of laboratory tests to be conducted.
Pregnancy Test	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 WOCBP.
[redacted]							

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
[redacted]							

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
Efficacy Assessment							
Body Imaging	**Per Protocol Amendment 04, imaging will be performed per local SOC, and images will no longer be submitted for blinded independent central review (BICR).** FIRST post-baseline tumor assessment should be performed after completion of last dose of neoadjuvant therapy (3 cycles or fewer). Participants who undergo RC, should have the first post-baseline tumor assessment within 4 weeks prior to RC. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis (including excretory imaging), and all other known and/or suspected sites of disease. See Section 9.1.2.1 for details.						
[redacted]							

Table 2-2: Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Procedure[a]	Cycle 1 Only[b] 1 cycle = 3 weeks			Cycle 2 and 3[b] 1 cycle = 3 weeks		Pre-surgery (Within 14 Days Before Surgery)	Notes
	Day 1	Day 5 (± 1 day)	Day 8 (-1 day)	Day 1 (± 3 days)	Day 3-5		
[redacted]							

[a] Some assessments referred to in this section may not be captured as data in the eCRF. 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.

[b] 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: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
Administer Study Drug				
***Not applicable per Protocol Amendment 04.** Bempegaldesleukin (0.006 mg/kg) and nivolumab (360 mg) **(Arm A)**		X	X	
Nivolumab (360 mg) **(Arm B)**		X	X	
***Not applicable per Protocol Amendment 04.** Administer IV Fluids **(Arm A only)**		X	X	**Not applicable per Protocol Amendment 04.** Applicable only to Arm A with bempegaldesleukin May be withheld if deemed in the best interest of the participant by the investigator. See Section 7.1.1.1 for additional information.
***Not applicable per Protocol Amendment 04.** Review Hydration Guidelines with Participants **(Arm A only)**		X	X	**Not applicable per Protocol Amendment 04.** Applicable only to Arm A with bempegaldesleukin. See Section 7.1.1.1.

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
***Not applicable per Protocol Amendment 04.** Oral Hydration Follow-up (**Arm A only)**		X (Day 3-5)	X (Day 3-5)	**Not applicable per Protocol Amendment 04.** For the first two doses of bempegaldesleukin, between Days 3 and 5, inclusive, following infusion, 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. 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				
Adverse Event and Serious Adverse Event Assessments	Continuously			All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Concomitant Medication Use	Continuously. Record at each visit.			

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
ECG	X			
ECHO/MUGA		Pre- dose, only if clinically indicated		
Cystoscopy	**Per Protocol Amendment 04, cystoscopy will be performed per local SOC.** Participants who do not undergo RC, for reasons other than progression, will be monitored for disease recurrence/progression by cystoscopy, every 12 weeks (± 7 days) for the next 2 years, and then every 24 weeks (± 14 days) for 3 additional years. For these participants maximal TURBT of all visible tumor should be performed at the time of the first cystoscopic examination.			For participants who do not undergo RC at the time of the decision made, a cystoscopy with maximum TURBT for visible tumor should be performed instead. Monitoring will begin from the first cystoscopic examination.
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X	X	X	Vital Signs: BP, Heart Rate, and Temperature Weight ECOG performance status (Appendix 5). Monitor and record vital signs at predose and within 30 minutes after administration of nivolumab.

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
Laboratory Tests				
Clinical Laboratory Testing	X	X	X	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 treatment, including renal function (ie, serum creatinine) must be assessed within 24 hours prior to dosing or as soon as locally feasible. Refer to Section 9.4.7 Clinical Safety Laboratory Assessments for list of laboratory tests to be conducted.
Pregnancy Test		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 WOCBP.
[redacted]				

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
Efficacy Assessments				
***Not applicable per Protocol Amendment 04.** Submission of Tissue for Pathologic Complete Response (pCR)	**Not applicable per Protocol Amendment 04.** Please review details for specimen collection and submission in the Laboratory Manual.			

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days)** **1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days)** **1 cycle = 3 weeks**	**Notes**
Body Imaging	**Per Protocol Amendment 04, for any participant remaining on study treatment, imaging will be performed per schedule of local SOC and images will no longer be submitted for BICR.** Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis (including excretory imaging), and all other known and/or suspected sites of disease. Participants having RC should undergo tumor assessments 60 to 90 days after RC and within 2 weeks prior to beginning adjuvant therapy. Tumor assessments should continue to be performed every 12 weeks (± 1 week) for up to 2 years from randomization date. Then every 24 weeks (± 2 weeks) up to a maximum of 5 years from the date of randomization, or until investigator-assessed disease progression that precludes surgery, until blinded independent central review (BICR) confirmed disease progression or recurrence (whichever occurs later). Participants who do not undergo RC (for reasons other than disease progression) should be aligned with continuing tumor assessments schedule including cystoscopy assessments. See Section 9.1.2.1 for details on methodology.			All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.2.2.

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days) 1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days) 1 cycle = 3 weeks**	**Notes**
[redacted]				

Table 2-3: Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable: however, the criteria remain unchanged for nivolumab, unless specifically designated.**

Participants who have not completed radical cystectomy, may continue onto cycles 1-12 once consent has been obtained and follow the post-surgery on study assessments[a]				
Procedure	**Post-surgery Visit**[b,d] **60 to 90 Days Post-surgery**[d,e]	**Cycle 1**[c,d] **(started within 60 to 120 days) 1 cycle = 3 weeks**	**C2-C12**[c,d] **Day 1 (± 3 days) 1 cycle = 3 weeks**	**Notes**
[redacted]				

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

[b] All participants are required to have a visit at 60-90 days after RC or cystoscopy to collect data related to RC/cystoscopy and imaging is required at this visit. Participants who do not undergo RC for reasons other than disease progression, must have cystoscopy prior to their planned post-surgical treatment following the first post-baseline tumor assessment (see Section 5.1.2.2 for further details).

[c] **Per Protocol Amendment 04, cystoscopy will be performed per local SOC**. Participants who do not have RC, but continue on study, will require cystoscopy every 12 weeks (± 7 days) for the next 2 years, and then every 24 weeks (± 14 days) for 3 additional years, then once per year for subsequent years.

[d] 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.

[e] If participant does not have RC, participant needs to have post-surgery procedures before starting adjuvant therapy (eg, cystoscopy with tumor removal and imaging).

Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Follow-up Visit 1[a,b]	Follow-up Visit 2[a,b]	*Not applicable per Protocol Amendment 04. Survival Follow-up Every 3 Months (± 14 Days)[c,b]	Notes
Safety Assessments				
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X	X		Vital Signs: BP, Heart Rate, and Temperature Weight ECOG Performance Status
Adverse Events Assessment (Including SAEs)	X	X	See Notes	SAEs to be collected after the 100-day safety visit if the SAE is deemed to be related or residual toxicities are persisting. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment for adjuvant therapy and 100 days following RC in participants who do not have adjuvant therapy. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.8), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Review of Concomitant/Subsequent Medications	X	X		Record at each visit.

Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Follow-up Visit 1[a,b]	Follow-up Visit 2[a,b]	*Not applicable per Protocol Amendment 04. Survival Follow-up Every 3 Months (± 14 Days)[c,b]	Notes
Subsequent Anti-cancer Therapy	X	X	X	**Per Protocol Amendment 04, the following will no longer be collected after 100 days of follow- up:** Collect every 3 months at Survival Visits until death, lost to follow-up, withdrawal of study consent, or up to 5 years. May be performed by phone contact or office visit. Include documentation of additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, and best response to the regimen and date of progression to subsequent anti-cancer therapies will be collected.
Laboratory Tests				
Clinical Laboratory Testing	X	Follow-up Visit 2 *(if toxicities are present)*		Hematology and Chemistry: See Table 9.4.7-1.
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.
[redacted]				

Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Follow-up Visit 1[a,b]	Follow-up Visit 2[a,b]	*Not applicable per Protocol Amendment 04. Survival Follow-up Every 3 Months (± 14 Days)[c,b]	Notes
[redacted]				
Efficacy Assessments				
Survival Status	**Per Protocol Amendment 04, during follow-up: after 100 days from last dose, participants will be discontinued. For participants already in survival follow-up, recurrence and overall survival should be documented and participant will then come off study**. During Safety Follow-up (Follow-up Visits 1 and 2) and every 3 months (clinic visit or by telephone) during Survival Follow-up. Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).			
Body Imaging	**Per Protocol Amendment 04, imaging will be performed per local SOC and images will no longer be submitted for BICR.** Only for participants **without** BICR-confirmed progression or recurrence and without investigator-assessed progression precluding surgery. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis (including excretory imaging), and all other known and/or suspected sites of disease. See Section 9.1.2.1 for details on methodology. Every 12 weeks (± 1 week) for up to 2 years from the date of randomization. Then every 24 weeks (± 2 weeks) up to a maximum of 5 years from the date of randomization, or until investigator-assessed disease progression that precludes surgery, until BICR confirmed disease progression or recurrence, whichever occurs later.			

Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Follow-up Visit 1[a,b]	Follow-up Visit 2[a,b]	*Not applicable per Protocol Amendment 04. Survival Follow-up Every 3 Months (± 14 Days)[c,b]	Notes
	Participants who do not have RC (for reasons other than disease progression) should be aligned with continuing tumor assessments schedule including cystoscopy assessments.			
Cystoscopy	**Per Protocol Amendment 04, cystoscopy will be performed per local SOC.** Participants who do not undergo RC for reasons other than progression, will be monitored for disease recurrence/progression by cystoscopy, every 12 weeks (± 7 days) for the next 2 years, and then every 24 weeks (± 14 days) for 3 additional years, then once per year for subsequent years. For these participants, maximal TURBT of all visible tumor should be performed at the time of the first cystoscopic examination.			Monitoring will begin from the first cystoscopic examination.
[redacted]				

Table 2-4: Long-term Follow-up Assessments (Arm A and Arm B)

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Follow-up Visit 1[a,b]	Follow-up Visit 2[a,b]	*Not applicable per Protocol Amendment 04. Survival Follow-up Every 3 Months (± 14 Days)[c,b]	Notes
[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] Some assessments referred to in this section may not be captured as data in the eCRF. These assessments are intended to be used as safety monitor by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[c] ***Not Applicable per Protocol Amendment 04.** 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. Bristol-Myers Squibb 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 his or her survival status unless the participant has withdrawn consent for all contact.

Table 2-5: Study Assessments - Arm C

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Pre-surgery	Pre-surgery	Post-surgery	Follow-up[a]		Notes
		Within 14 Days Before Surgery	60-90 Days Post- surgery	Follow-up Visits 1 and 2	*Not applicable per Protocol Amendment 04. Survival Follow-up Visits[b]	
Study Treatment[c]						
Randomize	X					Radical Cystectomy must occur within 6 weeks from randomization.
Safety Assessments						
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status		X	X	X		Vital Signs: BP, Heart Rate, and Temperature Weight ECOG Performance Status
Concomitant Medication Use	Continuously					Record at each visit.
Subsequent Anti-cancer Therapy[d]				X	X	**Per protocol amendment 04, the following will no longer be collected after 100 days of follow-up**: Collect every 3 months at Survival Visits until death, lost to follow-up, withdrawal of study consent, or up to 5 years. May be performed by phone contact or office visit. Include documentation of additional subsequent cancer therapy details

Table 2-5: Study Assessments - Arm C

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Pre-surgery	Pre-surgery	Post-surgery	Follow-up[a]		Notes
		Within 14 Days Before Surgery	60-90 Days Post- surgery	Follow-up Visits 1 and 2	*Not applicable per Protocol Amendment 04. Survival Follow-up Visits[b]	
						such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, and date of progression to subsequent anti-cancer therapies will be collected.
SAE/AE Assessment	Continuously until 100 days from RC. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.8), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.					
Efficacy Assessments						
***Not applicable per Protocol Amendment 04.** Submission of Tissue for Pathologic Complete Response (pCR)	***Not applicable per Protocol Amendment 04.** Please review details for specimen collection and submission in the Laboratory Manual.					
Body Imaging	**Per Protocol Amendment 04, Imaging will be performed per SOC and images will no longer be submitted for BIC**R. Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis (including excretory imaging), and all other known and/or suspected sites of disease. • Participants that have RC should undergo tumor assessments 60-90 days after RC					

Table 2-5: Study Assessments - Arm C

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Pre-surgery	Pre-surgery	Post-surgery	Follow-up[a]		Notes
		Within 14 Days Before Surgery	60-90 Days Post- surgery	Follow-up Visits 1 and 2	*Not applicable per Protocol Amendment 04. Survival Follow-up Visits[b]	
	• Tumor assessment should continue to be performed every 12 weeks (± 1 week) for up to 2 years from randomization date, then every 24 weeks (± 2 weeks) up to a maximum of 5 years from the date of randomization until investigator-assessed disease progression that precludes surgery, or until BICR confirmed disease progression or recurrence, whichever occurs later. • Participants who do not have RC (for reasons other than disease progression) should be aligned with continuing tumor assessments schedule including cystoscopy assessments • See Section 9.1.2.1 for details on methodology.					
Cystoscopy	**Per Protocol Amendment 04, cystoscopy will be performed per local SOC.** Participants who do not undergo RC for reasons other than progression, will be monitored for disease recurrence/progression by cystoscopy, every 12 weeks (± 7 days) for the next 2 years and then every 24 weeks (± 14 days) for 3 additional years, then once per year for subsequent years. For these participants, maximal TURBT of all visible tumor should be performed at the time of the first cystoscopic examination.					Monitoring will begin from the first cystoscopic examination.
[redacted]						

Table 2-5: Study Assessments - Arm C

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Pre-surgery	Pre-surgery	Post-surgery	Follow-up[a]		Notes
		Within 14 Days Before Surgery	60-90 Days Post- surgery	Follow-up Visits 1 and 2	*Not applicable per Protocol Amendment 04. Survival Follow-up Visits[b]	
[redacted]						

Table 2-5: Study Assessments - Arm C

***Per Protocol Amendment 04, participants will discontinue from the study following one recurrence update and survival status update.**

Procedure	Pre-surgery	Pre-surgery	Post-surgery	Follow-up[a]		Notes
		Within 14 Days Before Surgery	60-90 Days Post- surgery	Follow-up Visits 1 and 2	*Not applicable per Protocol Amendment 04. Survival Follow-up Visits[b]	
[redacted]						

[a] Follow-up Visit 1 should occur 30 days from post-surgery visit (± 7 days). Follow-up Visit 2 should occur approximately 100 days (± 7 days) from post-surgery visit. Both follow up visits should be conducted in person.

[b] **Not applicable per Protocol Amendment 04**. Survival visits: every 3 months from Follow-up Visit 2 (± 14 days). Survival visit may be conducted in person or by telephone. Bristol-Myers Squibb (BMS) 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 his or her 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 eCRF. These assessments are intended to be used as safety monitor by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[d] Including details on subsequent therapy such as start and stop dates, best response, date of progression.

3 INTRODUCTION

CA045009 is a Phase 3, randomized study of neoadjuvant nivolumab plus NKTR-214 (bempegaldesleukin) or nivolumab alone followed by radical cystectomy (RC) and further post-surgery immuno-oncology (IO) therapy, versus standard of care (SOC) treatment with RC alone in participants with previously untreated high-risk urothelial carcinoma (UC) of the bladder, including muscle-invasive bladder cancer (MIBC) who are candidates for RC and are cisplatin-ineligible.

About 20%-25% of patients diagnosed with UC of the bladder present with MIBC, defined as stage T2-T4a, N0, M0, or prognostic stage II or IIIA per the American Joint Committee on Cancer (AJCC) staging manual.[1] Primary tumor assessment includes multiple factors and examinations to properly stage a patient's cancer. The tumor, node, and metastasis (TNM) categories are assigned by using the information and with that, the prognostic stage groups are assigned for these cancers. For UC, regional lymph node staging is of significant prognostic importance given the negative impact on recurrence after treatment and long-term survival. Clinical staging of regional lymph node involvement by imaging often is inaccurate and does not necessarily provide information on the extent of disease within the nodes.

The 8th edition of the AJCC staging manual, included changes to the staging of urinary bladder carcinoma, including the AJCC prognostic stage groups, stages III and IV disease (stage III into stage IIIA and stage IIIB; stage IV into stage IVA and stage IVB).[1] Notably, the new staging system groups T1-T4aN1M0 within stage IIIA and similar prognostic category as the T3-T4aN0M0. And based on the new staging, the National Comprehensive Cancer Network (NCCN) guidelines includes the T1-T4aN1M0 within the same treatment as the T3-T4aN0M0 in the same prognostic category.[2]

For patients who are ineligible to receive cisplatin-based chemotherapy, the primary treatment for these patients is RC, without any neoadjuvant therapy. Although this can be curative for some, up to 50% of patients ultimately develop recurrent, metastatic disease.

This Phase 3 study in the neoadjuvant and adjuvant treatment of participants with clinical stage T2-T4aN0M0 or T1-T4aN1M0 UC of the bladder ineligible for cisplatin will allow for direct comparison of nivolumab plus bempegaldesleukin versus SOC treatment with RC alone. The study is designed with an analysis of the rate of pathologic complete response (pCR) and will continue follow-up for an analysis of event free survival (EFS).

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

3.1 Study Rationale

The study of neoadjuvant nivolumab and bempegaldesleukin followed by continued adjuvant nivolumab and bempegaldesleukin after RC, aims to demonstrate that perisurgical treatment with nivolumab combined with bempegaldesleukin will significantly increase the rate of pCR and

prolong EFS in cisplatin-ineligible participants with high-risk UC of the bladder, including MIBC who undergo RC.

3.1.1 Research Hypothesis

This section is not applicable per Protocol Amendment 04.

The combination of nivolumab and bempegaldesleukin as neoadjuvant and adjuvant therapy will significantly increase the pCR and prolong EFS following RC in participants with high-risk UC, including MIBC who are ineligible for cisplatin therapy.

3.2 Background

3.2.1 Epidemiology/Indication

Urothelial cancer of the bladder is the ninth most common cancer in the world[3] and the fifth most common malignancy in the United States.[4] In 2020, an estimated 81,400 patients were newly diagnosed with bladder cancer in the United States and approximately 17,980 patients will succumb to the disease.[5] Bladder cancer is more common in men with nearly a 3:1 incidence.

Nonmuscle-invasive tumors account for 75%–85% of bladder neoplasms, whereas the remaining 15% to 25% are muscle-invasive or metastatic tumors at the time of initial presentation.[6] Once invasive into the muscularis propria, urothelial cancer of the bladder is an aggressive disease that requires multimodal treatment with surgery or radiation therapy with or without chemotherapy. Despite multimodality treatment, more than 50% of patients will develop metastatic disease. Median survival of patients with metastatic urothelial cancer of the bladder is 12 to 14 months.[7]

Management of UC of the Bladder, Including MIBC

Patients with UC of the bladder, including clinical stage T2-T4aN0M0, and clinical stage T1-T4aN1M0, are at a high risk for developing metastatic disease, even after receiving SOC treatment RC.[8,9,10] For patients with MIBC who are eligible to receive cisplatin-based chemotherapy, level 1 evidence demonstrates a significant increase in overall survival (OS) with the use of neoadjuvant chemotherapy. The SWOG 8710 Phase 3 study, which compared neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) plus RC to RC alone, showed a 66% increased risk of death from bladder cancer (hazard ratio [HR] = 1.66; 95% confidence interval [CI] = 1.22-2.45) and a 33% increased risk of death from all causes (HR = 1.33; 95% CI = 1.00-1.76) in patients who received RC alone compared to combination treatment.[11] A meta-analysis of 3005 patients found a 5% absolute improvement in OS at 5 years (HR = 0.86, 95% CI 0.77-0.95, P = 0.003) and a 9% absolute disease free survival (DFS) improvement at 5 years (HR = 0.78 95% CI 0.71-0.86, P < 0.0001) in the chemotherapy group.[12] The combination of gemcitabine and cisplatin (GC) is considered an acceptable community standard as neoadjuvant therapy based on large retrospective analyses demonstrating similar pCR rates compared to MVAC.[13,14]

The OS benefit from neoadjuvant chemotherapy is closely associated with achieving a pCR.[11,15,16,17,18] The pCR rate associated with 3 to 4 cycles of approved chemotherapy regimens

(GC or MVAC) is 25 to 30%.[17,18] Patients who attain a pCR after neoadjuvant chemotherapy have 5-year EFS and OS rates of greater than 80%.[11,19]

However in clinical practice, cisplatin-ineligible patients account for 40% to 50% of the total population with MIBC. Patients with MIBC who are ineligible for cisplatin-based chemotherapy due to poor renal function (usually defined as a creatinine clearance of < 60 mL/minute), advanced age, hearing loss, peripheral neuropathy, or poor performance status represent a population with a high unmet medical need because there is currently no recommended neoadjuvant therapy (or adjuvant therapy) for this group. SOC therapy is to proceed directly to RC, which is associated with a 50% recurrence rate at 2 years. The majority of patients will die from metastatic UC within 1 year.[8]

Equally, there are no definitive randomized trials that demonstrate unequivocal support for the use of adjuvant chemotherapy for MIBC in patients who are cisplatin-ineligible. However, meta-analyses and retrospective studies for patients that were able to receive cisplatin chemotherapy suggest there may be a benefit from adjuvant chemotherapy after cystectomy in select patients.[10,20,21] A meta-analysis of available studies published in 2005 showed a HR for survival of 0.75 for adjuvant chemotherapy (95% CI = 0.60–0.96); however, this meta-analysis included only 491 patients from 6 trials and was thus underpowered.[21,22] Since then, several larger randomized trials have been performed, but results of individual studies have been conflicting. An updated meta-analysis in 2014 found a similar benefit of adjuvant chemotherapy (HR = 0.77, 95% CI = 0.59-0.99) in pooled data from 9 clinical trials.[22,23] The majority of these trials included patients with high-risk disease defined as extravesical extension and/or positive lymph nodes.

A Spanish Oncology Genitourinary Group (SOGUG) 99/01 study enrolled high-risk patients with MIBC after cystectomy and randomized them to 4 cycles of paclitaxel, gemcitabine, and cisplatin (PGC) or observation. This study suffered from poor recruitment, and 142 patients were enrolled. However, those who received adjuvant chemotherapy had a significantly improved 5-year survival compared to those who did not (60% vs 31%, $P < 0.0009$).[22,24]

The adjuvant Phase 3 trial of EORTC 30994, recruited 284 of a planned 660 patients, once again limited in power due to under accrual. Patients with high-risk MIBC (pT3-pT4 or node positive) were randomized to 4 cycles of adjuvant chemotherapy (GC or MVAC or high-dose MVAC [HD-MVAC]) or deferred chemotherapy at relapse. Adjuvant therapy improved progression-free survival (PFS) compared to deferred treatment with a median PFS of 3.11 years (95% CI = 1.84-7.77) in the immediate treatment group compared with 0.99 years (95% CI = 0.63-1.49) in the deferred treatment group (HR = 0.54, 95% CI = 0.4-0.73, P < 0.0001) with no statistically significant improvement in OS (HR = 0.78, 95% CI = 0.56-1.08).[10,22]

Galsky et al. presented an abstract of the comparative effectiveness of adjuvant chemotherapy using the National Cancer Data Base (NCDB).[22,25] This study compared those who received adjuvant chemotherapy with a propensity-score matched control group that received cystectomy alone. Adjuvant chemotherapy was associated with improved survival with an adjusted HR of 0.72 (95% CI = 0.71-0.86) compared to observation.

Recently at the American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium 2021, data from the largest adjuvant trial to date was presented for CheckMate-274 (NCT02632409), a Phase 3, randomized, double-blind study, comparing nivolumab and placebo in a 1:1 randomized fashion among participants with high-risk muscle-invasive UC (with primary tumor sites including bladder, ureter, or renal pelvis) after radical surgery.

In total, 709 participants were randomized to the following:

- 353 participants to nivolumab 240 mg every 2 weeks
- 356 participants to placebo

All participants had to have underwent radical surgery (cystectomy or nephroureterectomy) within 120 days of randomization and received adjuvant therapy for up to 1 year. The primary endpoints of the trial were DFS in all randomized participants (ie, the intention-to-treat [ITT] population) and in the subset of participants whose tumors express PD-L1 ≥ 1%. Key secondary endpoints included OS, non-urothelial tract recurrence-free survival, and disease-specific survival.

Over a median follow-up of approximately 20 months, median DFS was significantly longer for participants receiving nivolumab (21 months) compared to placebo (11 months; HR = 0.70, 95% CI = 0.54-0.89). The improvement in DFS was generally consistent across subgroups. Additionally, non-urothelial tract recurrence-free survival and distant metastasis-free survival were improved with the administration of nivolumab in both the ITT and PD-L1 ≥ 1% populations. The safety profile of nivolumab was consistent with previously reported studies in participants with solid tumors. Treatment-related adverse events (TRAEs) occurred in 77.5% of participants who received nivolumab vs 55.5% of participants who received placebo, while Grade 3 or 4 TRAEs were observed in 17.9% vs 7.2% of participants, respectively.[26]

Since there is currently no neoadjuvant or adjuvant SOC for patients who are eligible for RC, but not eligible for cisplatin-based chemotherapy, defining an unmet medical need, novel therapies are needed to increase the number of patients who qualify to receive neoadjuvant and adjuvant therapy and subsequently achieve a pCR and improved EFS. Data from 2 ongoing clinical studies demonstrate the safety and potential activity of programmed cell death protein-1 (PD-1) inhibitors as neoadjuvant therapy for MIBC.[27,28] A Phase 2 Study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS) enrolled cisplatin-ineligible patients with operable bladder cancer. After receiving only 2 cycles of neoadjuvant atezolizumab, pCR occurred in 31% (95% CI = 21%-41%) (37% [95% CI = 21%-55%] of programmed death ligand 1 [PD-L1]–positive patients and 24% [95% CI = 13%-39%] of PD-L1–negative patients).[27] TRAEs were relatively infrequent and study medication was well tolerated. In an ongoing Phase 2, open-label study of neoadjuvant pembrolizumab before RC for MIBC, regardless of cisplatin eligibility, neoadjuvant treatment with a PD-L1 agent was also well tolerated and was associated with pCR in about 37% of patients (95% CI: 28%-46%).[28]

***Per Protocol Amendment 04, this paragraph is not applicable.** This current Phase 3 study examining the neoadjuvant and adjuvant treatment of high-risk UC including MIBC participants,

ineligible for cisplatin, will allow for direct comparison of nivolumab plus bempegaldesleukin versus SOC treatment with RC alone. The study is designed with an analysis of the rate of pCR and will continue follow-up for an analysis of EFS.

3.2.2 Nivolumab

3.2.2.1 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.[29,30,31] 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 and negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[32] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD-28 family of T-cell co-stimulatory receptors that also includes CD-28, CTLA4, ICOS, and B and T lymphocyte associated (BTLA).[33] 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 the 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.[34] 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 = ± 1nM). 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 mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cell (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/NPAN02).[35]

3.2.2.2 Clinical Experience with Nivolumab

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), SCLC, gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). Please refer to the Investigator's Brochure (IB) for additional details.[36]

Nivolumab monotherapy has demonstrated clinical benefit in participants with UC who have progressed during or following platinum-containing chemotherapy or progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, and has been approved for use in the United States and European Union.

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of patients with locally advanced or metastatic UC was evaluated in a Phase 2, multicenter, open-label, single-arm study (CA209275).[37] The study included patients (18 years or older) who had disease progression during or following platinum-containing chemotherapy for advanced or metastatic disease or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and were enrolled regardless of their tumor PD-L1 status. Patients with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients who received more than 2 prior lines of chemotherapy with liver metastases were excluded. A total of 270 patients who received nivolumab 3 mg/kg administered intravenously over 60 minutes every 2 weeks with a minimum follow-up of 8.3 months were evaluable for efficacy. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The primary efficacy outcome measure was objective response rate (ORR) as determined by blinded independent central review (BICR). Additional efficacy measures included duration of response (DOR), PFS, and OS. Median age was 66 years (range: 38 to 90 years) with 55% of patients aged ≥ 65 years and 14% aged ≥ 75 years. The majority of patients were White (86%) and male (78%). Baseline ECOG performance score was 0 (54%) or 1 (46%). Median time to response was 1.9 months (range: 1.6-7.2 months). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI = 14.5%-34.4%).

Median treatment duration was 3.3 months (range: 0 to 13.4+ months). Forty-six percent of patients had a drug delay for an adverse reaction. Fourteen (5.2%) patients died from causes other than disease progression. This includes 4 (1.5%) patients who died from pneumonitis or cardiovascular failure that was attributed to treatment with nivolumab. Nivolumab was discontinued for adverse reactions in 17% of patients. Serious adverse reactions occurred in 54% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

3.2.3 Bempegaldesleukin

3.2.3.1 Mechanism of Action

Bempegaldesleukin 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 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 regulatory T cells (Tregs) that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ).[38,39] 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.[40,41] 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.[42]

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 Bempegaldesleukin

3.2.4.1 Study 15-214-01 (EXCEL; Bempegaldesleukin Monotherapy)

The bempegaldesleukin clinical development program started with the monotherapy study EXCEL (Study 15-214-01; A Phase 1/2, Open-label, Multicenter, Dose-Escalation and Dose Expansion Study of bempegaldesleukin in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies). The first part of the study was a dose escalation phase, designed to evaluate the

safety and tolerability, and define the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of bempegaldesleukin.

The second part of the study was an expansion phase following identification of the RP2D, designed to evaluate the safety and tolerability, as well as the efficacy of bempegaldesleukin in specific tumor types. Bempegaldesleukin at a dose of 0.009 mg/kg administered once every 3 weeks (q3w) was deemed the MTD by pre-defined dose-limiting toxicity (DLT) criteria. The RP2D was determined to be 0.006 mg/kg q3w. Enrollment was closed after 28 patients were exposed to bempegaldesleukin in the dose-escalation phase and the dose expansion phase was not initiated.

The safety of single-agent bempegaldesleukin has been assessed in 28 patients across 5 dose cohorts administered bempegaldesleukin q3w at doses ranging from 0.003 mg/kg to 0.012 mg/kg and a dosing frequency of every 2 weeks (q2w) was explored at 0.006 mg/kg. For the q3w dosing frequency, doses up to 0.009 mg/kg were well tolerated. One patient dosed at 0.012 mg/kg experienced cytokine release syndrome and the DLTs of hypotension and syncope; this patient received 2 additional cycles of bempegaldesleukin at a lower dose of 0.006 mg/kg and tolerated treatment well. The bempegaldesleukin dose of 0.009 mg/kg was determined to be the MTD.

As of the data cutoff date of 29-Mar-2018, 593 treatment-emergent adverse events (TRAEs) were reported among the 28 patients who received single-agent bempegaldesleukin. Overall, the most common TRAEs fatigue (82.1%), flu-like symptoms (consisting of influenza-like illness, influenza, pyrexia, and chills, 71.4%), pruritus (67.9%), hypotension (64.3%), rash (also consisting of erythema, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, rash generalized, and rash macular, 53.6%), decreased appetite (53.6%), and arthralgia or cough (42.9% each).[43]

The most common AEs considered by the investigator to be related to bempegaldesleukin were fatigue (71.4%), flu-like symptoms (67.9%), pruritus (64.3%), hypotension (57.1%), rash (50.0%), decreased appetite (46.4%), and arthralgia or cough (32.1% each). Such TRAEs as flu-like symptoms, rash and pruritus were generally mild or moderate in severity, predictable, manageable, and short-lived. These cytokine-related AEs generally occurred 3 to 4 days after dosing and corresponded to the time of peak plasma concentration of the active cytokines. The flu-like symptoms were managed with acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) and the cases of rash/pruritus were either self-limiting or treated with anti-histamines (steroids were administered for occasional patients who had severe rash/pruritus).

Six of 28 patients reported Grade 3 TRAEs, which included hypotension, abdominal pain, infusion-related reaction, headache, and syncope. The cases of Grade 3 hypotension were rapidly reversed with intravenous fluids, and a hydration management guideline was implemented during the study which mitigated the hypotension severity. One patient, who had a prior history of an infusion reaction to a previously administered immunotherapy, discontinued treatment due to an infusion-related reaction following the first dose of bempegaldesleukin 0.009 mg/kg. With the exception of one event of hypothyroidism, no other immune mediated AEs consistent with

checkpoint inhibitors were reported. No patient experienced capillary leak syndrome and no Grade 4 TRAEs or treatment-related deaths were reported on the study.

Fifteen patients (53.6%) reported 31 SAEs in monotherapy Study 15-214-01. Eleven SAEs reported among 7 (25.0%) patients were considered related to treatment. The only treatment-related SAE reported for more than 1 patient was hypotension (5 patients, 17.9%, 4 of 5 were Grade 3 in severity).

In the 28 patients evaluable for efficacy in Study 15-214-01, best overall response included stable disease (SD) in 14 patients (50%), progressive disease (PD) in 12 patients (42.9%), and not evaluable (NE) for 2 patients (7.1%). While no objective responses were observed in Study 15-214-01, 9 patients experienced tumor shrinkage between 1% and 30% and two patients, after progressing on multiple prior therapies, had durable stable disease over 1 year. One patient with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of bempegaldesleukin and had durable stable disease for 18 months. A second patient with metastatic renal cell carcinoma (RCC), who had progressed on high-dose IL-2 and was refractory to single-agent OX40 (ie, an antibody targeting the tumor necrosis factor receptor superfamily member 4) and nivolumab, was treated with 19 cycles of bempegaldesleukin and had durable stable disease for 14 months. Given the biological properties of bempegaldesleukin and nivolumab these observations further supported the rationale for combining these two agents.

In Study 15-214-01, hypotension was identified as a principal toxicity. Hypotension is a known AE associated with both IL-2 and engineered cytokines. Instances of hypotension most commonly appeared 2-4 days following the infusion of bempegaldesleukin. Participants for whom intravenous (IV) fluid administration was clinically indicated responded rapidly (in less than 24 hours) to IV hydration. To mitigate the risk of hypotension, management guidelines were implemented during the conduct of the study.

3.2.4.2 Study 16-214-02 (PIVOT-02; Bempegaldesleukin and Nivolumab Combination Therapy)

The PIVOT-02 trial (NCT02983045) is an ongoing Phase 1/2 open-label, multicenter, dose escalation, and dose expansion study of bempegaldesleukin in combination with nivolumab and other anti-cancer therapies in patients with locally advanced or metastatic solid tumors. Part 1 of the study was a dose escalation phase to evaluate the safety and tolerability, and define the MTD or RP2D of bempegaldesleukin in combination with nivolumab. Following determination of the RP2D (0.006 mg/kg bempegaldesleukin q3w plus 360 mg nivolumab q3w), Part 2 of the study is evaluating the safety and tolerability as well as the efficacy of the combination by assessing the objective response rate (ORR) at the RP2D. The indications studied in Part 2 include melanoma, RCC, non-small cell lung cancer (NSCLC), UC, breast cancer, gastric cancer, colorectal carcinoma (CRC), and small cell lung cancer (SCLC). Parts 3 and 4 are schedule-finding and dose expansion for the triplet, studying the safety and tolerability of bempegaldesleukin in combination with nivolumab and ipilimumab in patients with metastatic RCC, UC, melanoma, or NSCLC who are treatment-naïve.

The bempegaldesleukin + nivolumab dose escalation portion of PIVOT-02 has been completed, with the safety results of bempegaldesleukin at 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks indicating no DLTs and no Grade ≥ 3 TRAEs at the time of completion. Bempegaldesleukin 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks was the recommended dose regimen to be taken forward into expansion cohorts in Part 2.

As of 28-Oct-2020, a total of 557 patients had been treated with bempegaldesleukin in combination with nivolumab (503 patients with doublet [bempegaldesleukin and nivolumab]; 43 patients with triplet [bempegaldesleukin, nivolumab, and ipilimumab]; and 11 patients with doublet [bempegaldesleukin and nivolumab] plus other anti-cancer study drug). Of the 557 patients, most have NSCLC (184 patients [33%]), RCC (139 [25%]), or melanoma (102 [18%]), followed by UC (61 [11%]), breast cancer (47 [8%]), and CRC (22 [4%]), and gastric cancer (2 [< 1%]). The median duration of exposure was 106.0 days (doublet, 101.0; triplet, 179.0; doublet plus other anti-cancer drug, 113.0) (range: 1 to 817 days).

As of 28-Oct-2020, among the 503 patients who received the doublet:

- 94.6% (476 of 503) of patients reported TRAEs; the most frequent were fatigue (47.1%), pyrexia (44.7%), pruritus (36.0%), nausea (31.4%), influenza-like illness (26.8%), decreased appetite (26.6%), rash (26.0%), and chills (25.8%).
- 24.9% (125 of 503) of patients reported treatment-related, Grade ≥ 3 AEs; the most frequent (> 2%) were syncope (2.8%), hypotension (2.6%), and lipase increased (2.2%).
- 16.3% (82 of 503) of patients reported treatment-related SAEs; the most frequent were pyrexia (3.0%), hypotension (2.0%), and pneumonitis (1.0%).

Therefore, the generally non-overlapping toxicities observed with nivolumab and bempegaldesleukin are expected to result in a reasonably well-tolerated IO combination therapy.

Serious events of cerebrovascular accident (CVA) have been observed in patients who have received bempegaldesleukin in the triplet combination with nivolumab and ipilimumab and in the doublet combination with nivolumab. A total of 3 of 43 patients (7.0%) who received bempegaldesleukin, nivolumab, and ipilimumab (triplet immunotherapy) and 8 of 478 patients (1.7%) who received bempegaldesleukin and nivolumab (doublet immunotherapy) in Study 16-214-02 were determined to have CVA events that were confirmed by the independent neurology consultants. No confirmed CVA events occurred in any patients in any other studies of bempegaldesleukin. The incidence of CVA, combining all clinical trials in which the doublet of bempegaldesleukin plus nivolumab was administered was 8 out of 593 patients (1.3% or 3.52 per 100 person-years [P-Y]). By comparison, incidence rates of ischemic CVA among patients treated with nivolumab monotherapy was 1.4 per 100 (P-Y). Rates of CVA in metastatic cancer patients, based on Pharmetrics and MarketScan data, are 4.17 and 5.35 per 100 P-Y, respectively. The incidence rate in the patients receiving doublet immunotherapy is likely within the incidence rate of CVA in patients with advanced malignancies. The relationship of these events to the triplet and doublet combinations is unclear. As more information is needed to better understand and characterize these events, CVA events will be monitored as adverse events of special interest,

which will involve additional monitoring and expedited reporting for any new events. The CVA AE Management Algorithm, which was added to the protocol as Appendix 7, is no longer applicable per Protocol Amendment 04.

Tumor response data are available for 37 of the dose escalation patients, including 11 with metastatic melanoma, 21 with RCC, and 5 with NSCLC. Of these 37 response-evaluable patients, 25 were treated at 0.006 mg/kg bempegaldesleukin combined with nivolumab 360 mg flat dose every 3 weeks. As of 18-Jan-2019, 22 of 37 response evaluable patients (59.5%) achieved an investigator-assessed response (complete or partial response) by RECIST v1.1.[44]

For select tumors, additional efficacy data have been presented. PIVOT-02 has a 2-stage design and data for either the Stage 1 (N1) population alone or in combination with the Stage 2 (N2; expansion) population were presented depending on data maturity. Data presented for the efficacy evaluable population (defined as having received one dose of study treatment and having undergone at least one scan) were as follows:

- In first-line RCC patients, a 46% (12 of 26 patients) ORR was observed (N = 48 enrolled; N = 26 in the N1 + N2 population; 29-May-2018 cutoff).[45]
- In first-line melanoma patients, a 53% (20 of 38 patients) ORR via blinded independent central review (BICR) was observed (N = 41 enrolled; N = 38 included in the N1 + N2 population; 01-Sep-2020 data cutoff).[46]
- In first-line metastatic UC patients, a 48% (13 of 27 patients) ORR was observed (N = 41 enrolled; N = 27 in the efficacy evaluable population; 03-Dec-2018 data cutoff).[47]
- In metastatic triple-negative breast cancer (TNBC) patients, a 13% (5 of 38 patients) ORR was observed (N = 43 enrolled; N = 38 in the efficacy evaluable population; 01-Jul-2019 data cutoff).[48]

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

3.2.4.3 Study 18-214-10 (PIVOT-10); Bempegaldesleukin and Nivolumab Combination Therapy

On 14-Apr-2022, Nektar Therapeutics and Bristol Myers Squibb (BMS) announced updates on results from a late-stage clinical study of bempegaldesleukin in combination with nivolumab in bladder cancer (PIVOT-10).[49]

PIVOT-10 is a global Phase 2 single-arm study evaluating bempegaldesleukin combined with nivolumab in patients deemed ineligible for cisplatin therapy including those whose baseline tumor cells express low levels of PD-L1. A total of 192 patients were enrolled and patients were treated until disease recurrence, unacceptable toxicity or withdrawal of consent for up to 24 months. A final ORR analysis assessed by BICR showed that bempegaldesleukin in combination with nivolumab did not reach an efficacy threshold to support continuing the program in urothelial carcinoma.

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

3.2.4.4 Pooled Safety Analysis of Participants with Bempegaldesleukin and Nivolumab Exposure

A pooled safety analysis (28-Oct-2020 data cutoff) is available of participants who received the bempegaldesleukin and nivolumab doublet from the ongoing combination Phase 1/2 studies (16214-02 and 16-214-05), the ongoing combination Phase 2 study (18-214-10), and the completed Phase 1 study in Japan (CA045010). Of the 696 participants who received the bempegaldesleukin and nivolumab doublet:

- 93.0% (647 of 696) of participants reported TRAEs; the most frequent were pyrexia (42.1%), fatigue (39.9%), pruritis (37.6%), nausea (27.9%), rash (24.6%), decrease appetite (23.7%), influenza-like illness (22.4%), and chills (22.1%).
- 24.6% (171 of 696) of participants reported treatment-related, Grade ≥ 3 AEs; the most frequent were hypotension (2.6%), fatigue (2.0%), arthralgia (1.1%), diarrhea (0.9%), and pyrexia (1.1%).
- 15.8% (110 of 696) of participants reported treatment-related SAEs; the most frequent were pyrexia (2.6%), hypotension (1.7%), dehydration (0.9%), pneumonitis (0.7%), acute kidney injury, atrial fibrillation, myocarditis (0.6% each).

3.2.4.5 Observed Events of Cerebrovascular Accident

3.2.4.5.1 Initial Analysis of Cerebrovascular Accident Events in PIVOT-02 (16-214-02) Study

Serious events of CVA, including one fatal event, have been observed in participants who have received bempegaldesleukin in the triplet combination with nivolumab and ipilimumab, and in the combination of bempegaldesleukin, nivolumab, and other anti-cancer therapy. As of 28-Oct-2019, 3 of 43 participants (7.0%) who received triplet therapy in Study 16-214-02 (PIVOT-02) were reported to have CVA events, including one fatal event, all of which were considered by the investigator to be related to treatment with bempegaldesleukin, nivolumab, and ipilimumab. Additionally, 9 of 488 participants (1.8%) who received doublet therapy (bempegaldesleukin and nivolumab) had 10 CVA events, which were considered by the investigator to be related to at least one of the study treatments in 4 participants (3 related to the doublet therapy and 1 related to nivolumab only); and one of 10 (10.0%) participants who received combined bempegaldesleukin, nivolumab, and other anti-cancer therapy (platinum-based chemotherapy) had a CVA event, which was considered by the Investigator to be unrelated to study treatment.

Updated Analysis of CVA Events Observed with Bempegaldesleukin

A cumulative search of the bempegaldesleukin global safety database was conducted on 28-Oct-2020, which included 1,345 participants who received bempegaldesleukin in triplet combinations with nivolumab plus ipilimumab or with nivolumab plus NKTR-262 (a toll-like receptor agonist 7/8); in doublet combinations with checkpoint inhibitors; in a doublet combination with nivolumab

plus chemotherapy, and in combination with NKTR-262 from the following Studies: 15-214-01, 16-214-02, 16-214-05, 17-214-09, 18-214-10, 20-214-29, CA045001 (17-214-08), CA045009 (18-214-13), CA045010 (18-214-14), SP-IND, and 17-262-01.

Overall, 1.9% (26 of 1,345) of participants exposed to bempegaldesleukin reported CVA events. Of the 26 participants, 13 participants experienced Grade 3 or 4 events and 4 participants had a fatal outcome. The mean time to first CVA event was 218.7 days (range 4 to 727 days; median 158 days). Twenty of the 26 participants with CVA events received a doublet combination with a checkpoint inhibitor, which included 1.7% (19 of 1,116) of participants who received nivolumab, 1.3% (1 of 76) who received pembrolizumab, and 0% (0 of 23) who received atezolizumab.

Based on these events, CVA was escalated to an AEOSI and mitigations were put in place to reduce the risk of CVA. These mitigations include implementation of a CVA adverse event management algorithm (Appendix 7) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria. Additional information on the clinical safety and risk of CVA is found in the bempegaldesleukin Investigator's Brochure.

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, cytokine-related toxicities (eg, flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and serum creatinine elevations), infusion-related reactions/hypersensitivity reactions, thyroid dysfunction, eosinophilic disorder (including cases of hypereosinophilic syndrome), 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 IB and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy 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 AEs 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 cytokine-related toxicities (eg, flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations and serum creatinine elevation), infusion related reactions, thyroid dysfunction, eosinophilic disorder, 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; however, there is no evidence that bempegaldesleukin increases the frequency or severity of immune-mediated AEs associated with nivolumab with the limitation of small sample size and relatively shorter treatment duration for bempegaldesleukin-treated patients.

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 coronavirus disease 2019 (COVID-19) during the trial, then the benefit and risk considerations remain the responsibility of the investigator. Non-live COVID-19 vaccination is considered a standard concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving nivolumab and bempegaldesleukin is not fully known.

Given there was no additional clinical benefit with the addition of bempegaldesleukin to nivolumab in the PIVOT-10 study, Nektar Therapeutics and BMS have jointly decided to end the clinical development program for bempegaldesleukin in combination with nivolumab and new enrollment to all studies has been discontinued.

4 OBJECTIVES AND ENDPOINTS

The secondary [redacted] objectives except safety [redacted] parameters are no longer applicable. [redacted]

Per Protocol Amendment 04, Nektar Therapeutics and BMS are terminating the development of bempegaldesleukin in combination with nivolumab. The efficacy endpoints of pCR, EFS, and OS, as well as safety and tolerability for each treatment arm will be summarized descriptively in all randomized participants. Details will be included in SAP.

Table 4-1: Objectives and Endpoints

Objective	Endpoint
Primary	
To compare the pCR rate of neoadjuvant nivolumab + bempegaldesleukin to Standard of Care (SOC, no neoadjuvant therapy) in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To compare the EFS of neoadjuvant nivolumab + bempegaldesleukin followed by adjuvant nivolumab + bempegaldesleukin after radical cystectomy (RC) versus SOC (no neoadjuvant or adjuvant therapy) in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause
Secondary	
To compare the pCR rate of neoadjuvant nivolumab monotherapy to SOC (no neoadjuvant therapy) in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To compare the EFS of neoadjuvant nivolumab followed by adjuvant nivolumab versus SOC in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause
To compare the overall survival (OS) of each experimental arm versus SOC in all randomized participants	OS, defined as the time between the date of randomization and the date of death from any cause. OS will be censored on the last date a participant was known to be alive
To assess safety and tolerability for each treatment arm in all treated participants	Worst grade AEs, SAEs, AEs leading to discontinuation, immune-mediation AEs and worst grade clinical laboratory values

Table 4-1: Objectives and Endpoints

Objective	Endpoint
To evaluate (descriptively) the pCR rate of neoadjuvant nivolumab + bempegaldesleukin to neoadjuvant nivolumab monotherapy in all randomized participants	pCR rate, defined by the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, based on blinded independent pathology review
To evaluate (descriptively) the EFS of neoadjuvant nivolumab + bempegaldesleukin followed by adjuvant nivolumab + bempegaldesleukin after RC versus neoadjuvant nivolumab followed by adjuvant nivolumab after RC in all randomized participants	EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause
[redacted]	

Table 4-1: Objectives and Endpoints

Objective	Endpoint
[redacted]	

5 STUDY DESIGN

5.1 Overall Design

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A of CA045009 are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy. Three recent studies from the bempegaldesleukin and nivolumab development program, Study CA045-001/17-214-08, a Phase 3 study in metastatic melanoma, Study 17-214-09/PIVOT-09, a Phase 3 study in metastatic renal cell carcinoma, and Study 18-214-10/PIVOT-10, a Phase 2 Study in cisplatin-ineligible metastatic urothelial carcinoma have demonstrated that there was no additional benefit of combining bempegaldesleukin with nivolumab. On 14-Apr-2022, Nektar Therapeutics and BMS announced a joint decision to end the clinical development program for bempegaldesleukin in combination with nivolumab. All new enrollment to CA045009 has been stopped.

CA045009 is a multicenter, randomized, Phase 3, study of neoadjuvant and adjuvant nivolumab plus bempegaldesleukin, versus nivolumab alone versus SOC in participants with high-risk UC of the bladder, including MIBC, who are candidates for RC and cisplatin-ineligible. Participants must

have pathologically proven UC of the bladder, clinical stage T2-T4aN0M0 or T1-T4aN1M0, that has not been previously treated (except for Transurethral Resection of Bladder Tumor [TURBT] or prior intravesicular treatment of non-muscle invasive bladder cancer [NMIBC]). Participants must be deemed potentially curable, medically fit for RC, and be willing to undergo RC as part of the study treatment.

The study is divided into screening period, treatment period and long-term follow-up period.

Participants were randomized (1:1:1) to one of the following 3 treatment arms: **Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.**

- **Arm A**: Bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed by bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy)
- **Arm B**: Nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy)
- **Arm C**: SOC (cystectomy alone, without neoadjuvant or adjuvant therapy)

Randomization will be stratified by the following:

- Clinical stage (T2N0 vs T3-T4aN0 vs T1-T4aN1)
- PD-L1 status (≥ 1% vs < 1%/indeterminate)

Per Protocol Amendment 04:

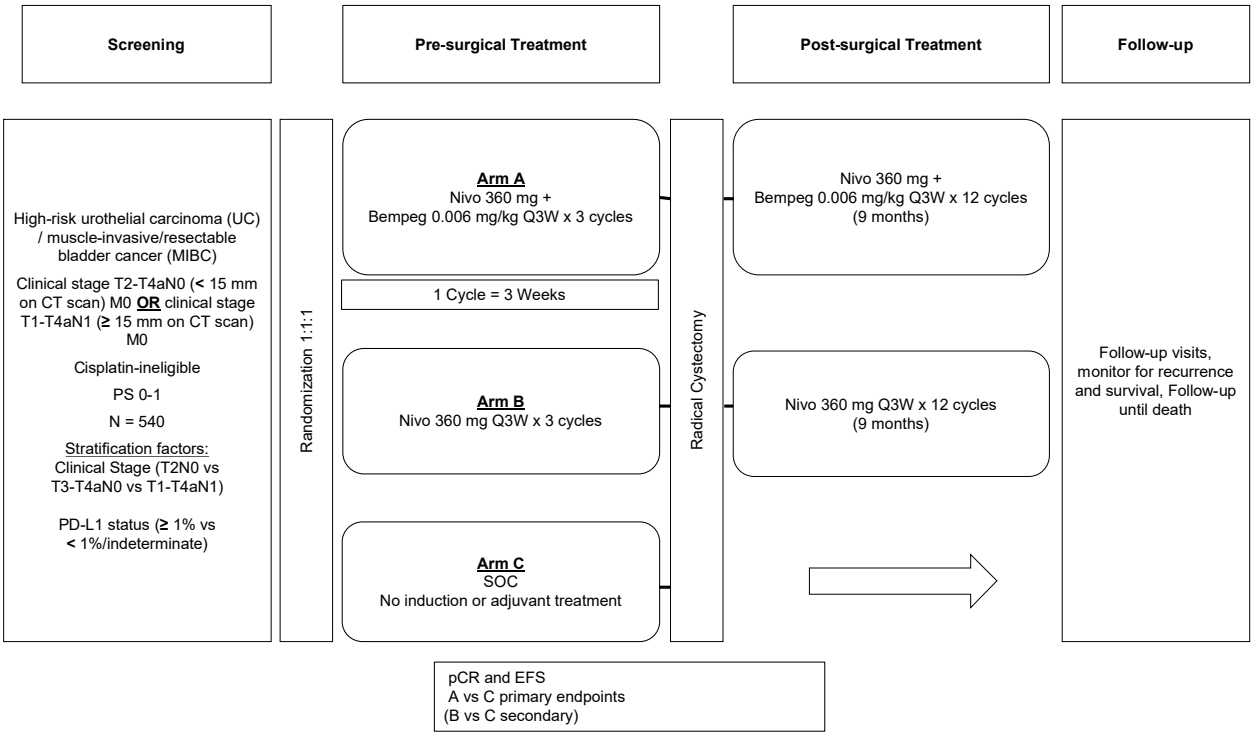
- Participants in Arm A are required to discontinue bempegaldesleukin and may continue nivolumab monotherapy.
- Participants on adjuvant nivolumab monotherapy can receive up to a maximum of 12 cycles.
- All participants, in Arm A and Arm B, who have completed therapy or are currently within the 100 days safety follow-up should discontinue from the study once they complete the safety follow-up 100 days, if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of recurrence status and last overall survival should occur upon discontinuation.
- All participants, in Arm C, who have completed radical cystectomy or are currently within the 100 days safety follow-up after radical cystectomy, should discontinue from the study once they complete the safety follow-up 100 days, if AE reporting requirements have been fulfilled as per Section 9.2.3. Documentation of recurrence status and last overall survival should occur upon discontinuation.

- Participants who have completed therapy, including 100 days safety follow-up, and are currently in survival follow-up should discontinue from the study if AE reporting requirements have been fullfilled as per Section 9.2.3. Documentation of last overall survival should occur upon discontinuation.

The study design schematic is presented in Figure 5.1-1.

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

Figure 5.1-1: Study Design Schematic



Abbreviations: Bempeg, bempegaldesleukin; CT, computed tomography; EFS, event-free survival; Nivo, nivolumab; pCR, pathologic complete response; PD-L1, programmed death ligand 1; PS, performance score; Q3W, every 3 weeks; SOC, standard of care.

5.1.1 Screening Period

Not applicable per Protocol Amendment 04 as all new enrollment to CA045009 has been stopped.

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 informed consent form (ICF), participants will be evaluated for entry criteria during the Screening period before randomization. Rescreening after screen failure will be allowed.

Diagnostic hematoxylin and eosin (H&E) and, if applicable, immunohistochemistry (IHC) stained slides from the initial TURBT (conducted within 12 weeks of randomization) confirming UC of the bladder/MIBC diagnosis along with pathology report must be submitted to the vendor for confirmation of UC of the bladder/MIBC prior to randomization.

The central laboratory must provide IRT with UC of the bladder/MIBC confirmation prior to randomization (refer to the Laboratory Manual for detailed instructions on required sample submission of UC of the bladder diagnosis and MIBC confirmation).

Sufficient (ie, one [1] formalin-fixed paraffin-embedded [FFPE] block or 20 unstained slides), recent bladder tumor tissue obtained within 12 weeks prior to randomization from the initial TURBT confirming UC of the bladder/MIBC diagnosis will be submitted to the central laboratory. Submitted tissue must not be previously irradiated and systemic therapy must not be given after samples are obtained prior to enrollment. PD-L1 results must be determined by central testing prior to study randomization.

The central laboratory must provide IRT with PD-L1 results from tumor tissue sample prior to randomization (Section 5.1.4.1). All research sites will be blinded to the results of [redacted] PD-L1 testing.

Screening images should be performed and submitted to the central imaging vendor per study inclusion criteria (Section 6.1). Any relevant historical scans should be submitted as well. At the discretion of the Sponsor, additional historical scans may be requested.

5.1.2 Treatment Period

5.1.2.1 Neoadjuvant (Pre-surgical Treatment) Randomized Participants

Per Protocol Amendment 04, participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

- Arm A: Bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W up to 3 cycles
- Arm B: Nivolumab 360 mg Q3W up to 3 cycles
- Arm C: SOC (no therapy), participants will go to RC within 6 weeks after randomization

Dose reduction will not be allowed for nivolumab. Some participants may not receive all 3 cycles of planned pre-surgical therapy (eg, toxicity, refusal to receive further therapy). However, participants should receive as much of the planned pre-surgical therapy as possible, with a minimum of at least one cycle. If one of the components of the treatment is not tolerated after the first cycle(s) of therapy, then the other component may be continued to complete 3 cycles. Thus, a participant may receive all 3 cycles of bempegaldesleukin even though nivolumab was discontinued sooner, or may complete all 3 cycles of nivolumab even though bempegaldesleukin was previously discontinued. Such treatment decisions will be at the discretion of the Investigator and participant (in case it is being proposed to continue treatment as monotherapy and permanently discontinue one of the agents).

5.1.2.2 Surgery (Radical Cystectomy)

Per Protocol Amendment 04, radical cystectomy will be performed per local SOC.

Participants should receive RC within 6 weeks of the last neoadjuvant treatment administration (Arm A and Arm B), after recovery from any immunotherapy-related toxicities or within 6 weeks of randomization (Arm C).

In specific cases, when RC does not occur within 6 weeks of the last neoadjuvant treatment administration, RC may be permitted at a later date after consultation with Medical Monitor.

Analysis of data from the SWOG-8710 Phase 3, randomized, neoadjuvant study for patients undergoing RC showed that negative surgical margins (P = 0.0007) and removal of > 10 lymph nodes (LN) (P = 0.0001) were associated with longer survival and decreased local recurrence.[50] Positive surgical margins are associated with a poor prognosis, and in experienced hands, the positive soft-tissue margin rate should be ≤ 5%.[51] Lymph node numbers vary among patients, making it difficult to judge the quality of the pelvic lymph node dissection (PLND) by LN numbers alone. Rather the PLND surgical template is the key, and if followed, should yield adequate numbers of pelvic LN from critical sites that drain the bladder.[52,53] For RC, the following is recommended as the surgical SOC:

- When performing RC, the surgeon should remove the bladder, prostate and seminal vesicles in males, and the bladder, uterus, fallopian tubes, ovaries and anterior vaginal wall in females. All efforts should be made to obtain grossly negative surgical margins.[54]
- Bilateral pelvic lymphadenectomy, should include at a minimum the region below the bifurcation of the common iliac artery, which involves removal of the external and internal iliac and obturator LNs (standard lymphadenectomy). Dissection along the common iliac artery to at least the crossing of the ureter, but most commonly the aortic bifurcation, and sometimes the inferior mesenteric artery is recommended when the surgeon is experienced in performing this extent of surgery termed an extended lymph node dissection.[55]

If this template is followed, > 10 LN should be obtained in most cases.

Pathologists must examine the RC specimen according to SOC practices. To the extent feasible, all excised lymph nodes should be identified, processed, and examined microscopically for the presence or absence of metastatic bladder cancer.

Not applicable per Protocol Amendment 04. Pathology slides, which includes all H&E from every specimen sampled from the entire RC specimen (involved and uninvolved tissue), and if applicable, any diagnostically relevant IHC that was used in addition to H&E (comprehensive guidelines for bladder specimen handling and identification of the tumor bed are described in the Laboratory Manual) from the RC specimen should be submitted to pathology review to confirm whether a pCR [redacted] was achieved.

Not applicable per Protocol Amendment 04. Participants must agree to submit all diagnostic stained slides including H&E and, if applicable, all diagnostically relevant IHCs from the RC

specimen for pCR assessment, as well as unstained tissue from the RC specimen for use in [redacted] studies. Stained slides from the RC specimen will be used for pathology review and an additional 2 FFPE tumor blocks or a minimum of 25 unstained slides obtained from a single block that meet acceptable criteria, as defined in the Laboratory Manual, will be used for [redacted] analysis.

It is planned that all participants will undergo RC following recovery from pre-surgical therapy. Participants with PD that precludes RC will be discontinued from treatment. Participants in Arm A or B who have completed pre-surgical treatment, but are no longer considered medically fit for RC (due to treatment-related toxicity or other medical issues) or refuse, will be eligible to receive follow-up immunotherapy (see Section 5.1.2.3), provided that the participant's physician considers the treatment to be safe and appropriate and that the participant has not experienced PD.

Prior to surgery, participants with disease progression that precludes surgery (as judged by the investigator, see Section 9.1.1.2) must be discontinued from study treatment and tumor assessments. Participants who do not undergo RC for reasons other than disease progression that precludes surgery may continue on protocol-defined treatment once consent has been obtained.

Not applicable per Protocol Amendment 04. Participants who do not undergo RC but continue on study (eg, do not have disease progression) will be surveyed for disease recurrence/progression by cystoscopy every 12 weeks (± 7 days) for the next 2 years, then every 24 weeks (± 14 days) for 3 additional years, and then once per year for subsequent years. Monitoring will begin from the first cystoscopic examination. For these participants, maximal TURBT of all visible tumor should be performed at the time of the first cystoscopic examination.

5.1.2.3 Adjuvant (Post-surgical Treatment)

Per Protocol Amendment 04 , participants who are currently receiving bempegaldesleukin plus nivolumab in Arm A are required to discontinue bempegaldesleukin and may continue to receive nivolumab monotherapy.

- Arm A: Bempegaldesleukin 0.006 mg/kg Q3W + nivolumab 360 mg Q3W for 12 cycles (approximately 9 months)
- Arm B: Nivolumab 360 mg Q3W for 12 cycles (approximately 9 months)
- Arm C: SOC (no therapy) observation

For participants in Arms A and B, post-surgical treatment must begin within 60 to 120 days from the date of RC. All participants must have restaging imaging at the post-surgery visit after RC and prior to beginning post-surgical immunotherapy to rule-out recurrence of UC. See Section 2 for details.

Some participants in Arm A or B who have completed neoadjuvant therapy (3 or fewer cycles), may develop medical conditions either due to neoadjuvant therapy, refusal, or other causes that, in the opinion of the participant's physician, precludes them from safely undergoing RC. The reasons for not proceeding with RC should be clearly documented in the medical record and the

CRF. Despite not having undergone this protocol-specified surgery, these participants (Arms A and B only) will be eligible to receive the planned post-surgery immunotherapy once consent has been obtained (see Section 5.1.2.2). This therapy (bempegaldesleukin + nivolumab or nivolumab alone), can begin no sooner than 3 weeks after completion of the last dose of neoadjuvant therapy. An imaging assessment must be done prior to continuation of this therapy, when all significant toxicities associated with neoadjuvant therapy have recovered.

Participants will complete 12 cycles of adjuvant therapy except in the event of disease progression, death, unacceptable toxicity, symptomatic deterioration, investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant being lost to follow-up, or BMS and Nektar Therapeutics' decision to terminate the study.

5.1.3 Long-term Follow-up

Per Protocol Amendment 04, participants will be followed one final time for recurrence status and overall survival and will be discontinued from study.

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. For each randomized participant, the total maximum duration of the study is up to 62 weeks + 100 days of safety follow-up.

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

- Assessments should continue as described in Table 2-4
- Participants in Arms A and B must be followed for safety 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
- Participants in Arm C will be followed as described in Table 2-5
- **Per Protocol Amendment 04 this is not applicable:** 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
- In cases where clinically significant AEs deemed related to the study drug present at any time during the follow-up phase, 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

Per Protocol Amendment 04, this section will not be applicable.

A Data Monitoring Committee will be established to provide oversight of safety and efficacy considerations 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.

5.1.4.1 Blinded Pathology and Radiology Review

Per Protocol Amendment 04, this section is not applicable. However, descriptive analysis of pCR by central review will be conducted based on samples collected before Protocol Amendment 04 and reviewed by the independent pathology review committee.

Independent radiology review will be performed by BICR and will assess for the confirmation of endpoints. Images and pathology sample acquisition guidelines and submission process will be outlined in the study Imaging/Laboratory Manuals to be provided by the vendors.

Pathology Review

UC of the bladder/MIBC will be clinically diagnosed by pathological examination of stained slides from tumor tissue obtained at initial TURBT establishing diagnosis of UC of the bladder/MIBC (obtained within 12 weeks of randomization); central pathology review and confirmation are required prior to randomization (refer to the Laboratory Manual for detailed instructions on required sample submission). Details of the above process will be specified in the pathology review charter.

For RC surgical specimens, the Laboratory Manual will provide detailed instructions for the collection and handling of specimens.

Blinded central review by an independent pathology review committee with extensive prior experience interpreting post-neoadjuvant bladder specimens will be performed on all RC specimens to determine the pathology stage and whether the participant achieved pCR [redacted]. All pathologists will be blinded to participant treatment arm.

The pCR is defined as pT0N0[redacted]

Radiology Review

Per Protocol Amendment 04, this section will not be applicable. Radiologic tumor assessments outlined in Section 2 should be submitted to the third-party central imaging vendor. The site should submit screening tumor assessments as well as any relevant historical scans. In addition, the site will also inform the central imaging vendor when the investigator assessment indicates either (i) unequivocal disease progression per RECIST v 1.1 (for participants without RC), or (ii) unequivocal evidence of disease recurrence (see Section 9.1.1.2 for further details). Details of the BICR responsibilities and procedures will be specified in the BICR charter with the vendor.

5.2 Number of Participants

Not applicable per Protocol Amendment 04 as all new enrollment to CA045009 has been stopped.

It is anticipated that approximately 720 participants will be screened for approximately 540 participants to be randomized overall to the 3 arms in a 1:1:1 ratio, assuming a screen failure rate of approximately 25%. See Section 10.1 for sample size determination.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last participant's last visit in the Schedule of Activities (Section 2). Study completion is defined as a maximum of 12 cycles of adjuvant therapy + 100 days safety follow-up (Arm A and Arm B) or 100 days safety follow-up from radical cystectomy (Arm C) from last participant randomized or earlier on sponsor decision.

This paragraph is not applicable per Protocol Amendment 04. The total duration of the study for the primary endpoints will be determined by accrual events. Final analysis for the primary endpoint examining pCR rate will occur approximately 47 months after the date of the first participant randomized (approximately 4 months after the end of last participant randomized). Final analysis for the primary endpoint EFS will occur approximately 65 months after the date of the first participant to be randomized and is also determined by accrual of events (Section 10.3). Additional follow-up for OS may be conducted up to approximately 5 years after the randomization of the last participant.

5.4 Scientific Rationale for Study Design

About 20-25% of patients diagnosed with bladder cancer present with MIBC, defined as stage T2-T4a, N0-N1, M0. The primary treatment for these patients is RC, which can be curative for some but up to 50% ultimately develop recurrent, metastatic disease. Neoadjuvant chemotherapy has been shown in randomized trials to prolong OS in cisplatin-eligible patients and is the current SOC for this patient population. However, in clinical practice, cisplatin-ineligible patients account for 40% to 50% of the total population with MIBC. Standard of care for these patients is to proceed directly to RC, which is associated with a 50% recurrence rate at 2 years, with most of these patients who recur, dying from metastatic urothelial cancer within 1 year.[8]

Data presented at ASCO 2018 demonstrate the safety and potential activity of PD-1 inhibitors as neoadjuvant therapy for MIBC. Since there is currently no neoadjuvant SOC for patients who are not eligible to receive cisplatin-based chemotherapy, defining an unmet medical need, novel therapies are needed to increase the number of patients who qualify to receive neoadjuvant therapy and subsequently achieve a pCR and improved EFS. See Section 3.2.1 for additional details on study design rationale.

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 previously untreated, advanced or metastatic UC. Updated data from that cohort

with a cutoff date of 03-Dec-2018 were presented at the ASCO GU Symposium 2019. The cohort included 41 patients who were cisplatin-eligible (n=25) or ineligible (n=16). PD-L1 status, as determined using tumor staining with the DAKO PD-L1 IHC 28-8 pharmDx assay, was ≥ 1% (positive) in 32%, <1% (negative) in 32%, and unknown or not evaluable in 37%. Twenty-seven patients were efficacy evaluable, defined as having at least one post-treatment scan to evaluate response; one patient was not evaluable (no target lesions), 3 patients discontinued prior to the first scan, and 10 patients were still pending a first scan. Among the efficacy evaluable population, the ORR was 44.4%, including 5 (18.5%) CRs and 7 (25.9%) PRs. The response rate was similar in PD-L1 positive (5/11, 45.5%) and PD-L1 negative (6/12, 50%) subgroups. The safety profile was consistent with previously published bempegaldesleukin + nivolumab data, with the most common TRAEs being flu-like symptoms and fatigue.

5.4.2 Rationale for Study Comparator and Study Population

Patients with high-risk UC of the bladder (T1-T4a, N1M0), including MIBC (stage T2-T4a, N0, M0), are at high-risk for the development of metastatic disease, even after receiving SOC treatment RC. Currently, there are no neoadjuvant or adjuvant approved therapies for this patient population with cisplatin-ineligible MIBC.[56] Study comparators are not available.

5.4.2.1 Rationale for Including Participants with Clinical Stage T2 Bladder Cancer

For participants with MIBC confined to the bladder (clinical stage T2N0), it has been suggested that outcomes with RC are good, and further neoadjuvant therapy is not needed.[57] However, data from SWOG 8710 demonstrate that MVAC neoadjuvant chemotherapy increased median survival in patients with clinical stage T2 (cT2) disease by 2.5 years.[58] One of the reasons for this is that many patients diagnosed with cT2 bladder cancer are upstaged at RC; clinical staging of early stage bladder cancer is notoriously inaccurate. Data from MD Anderson Cancer Center showed that 43% of 174 patients with low-risk disease who underwent RC without neoadjuvant chemotherapy (NAC) were upstaged to more advanced disease.[59] Of 212 patients with cT2 disease who underwent RC at Fox Chase Cancer Center, 153 (73.2%) patients had either pT3-T4 or pN+ tumors at RC.[60] Therefore, because of the inaccuracy of clinical staging of bladder cancer, it is imperative that patients with clinical stage T2N0 are not excluded from this trial.

5.4.2.2 Rationale for Including Participants with N1 in Bladder Cancer

Regional lymph node involvement is an important prognostic factor in invasive bladder cancer. The 5-year survival in N1-N3 patients in contemporary series is from 13%-29%.[61,62] Per the new AJCC criteria, N1 patients have been added to the prognostic stage category IIIA and per NCCN treatment guidelines, are treated similarly and have similar outcomes as patients with clinical stage T3-T4aN0 disease, therefore participants with N1 bladder cancer have been included in this protocol.[1,2]

5.4.3 Rationale for Choice of Endpoints

EFS is a primary endpoint that captures on-treatment clinical benefit. This is the optimal endpoint to capture events that could occur both during the neoadjuvant and adjuvant phases of treatment.

The pCR as one of the primary endpoints will be used to capture the benefit in the neoadjuvant part of the treatment.

5.4.3.1 Rationale for pCR as One of the Primary Endpoints

Extensive clinical data demonstrate that achieving a pCR after NAC is associated with increased OS in cisplatin eligible patients. In a meta-analysis of 886 patients who received NAC and RC, the 28.5% of patients who attained a pCR had a relative risk for OS of 0.45 (95% CI = 0.36-0.56; P < 0.00001) compared with those who did not achieve a pCR. The relative risk for relapse-free survival (RFS) was 0.19 (95% CI = 0.09-0.39; P < 0.00001). There was a 26% and 51% lower absolute risk of mortality and recurrence, respectively, when pCR was achieved.[63]

A multicenter assessment of NAC demonstrated pCR rates of approximately 23% irrespective of the type of chemotherapy (MVAC vs GC). A Cox regression analysis assessing factors associated with OS identified patients achieving ≤ pT1N0 status compared with those with residual MIBC (≥ pT2), HR = 0.25 (95% CI = 0.16-0.40; P < 0.001).[18]

In a combined analysis of the Nordic Cystectomy Trials 1 and 2, 449 patients who achieved pCR with NAC (22.7%) exhibited an 88.2% 5-year OS.[64]

The SWOG 8710 Phase 3 study of NAC in 317 patients showed an 85% OS at 5 years associated with pCR. Median survival was 77 months for patients receiving NAC and RC compared with 46 months for RC alone; OS at 5 years was 57% vs 43%, respectively (P = 0.06).[11] A retrospective analysis of the SWOG data demonstrated that OS was significantly worse for patients with residual MIBC after RC.[21]

Achieving pCR after NAC for MIBC is clearly associated with prolonged OS. The CA045009 study is designed to target a doubling of pCR in the experimental arm.

5.4.3.2 Rationale for Event-free Survival as One of the Primary Endpoints

In the FDA Guidance for Industry/Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval (2014), EFS is described as an important endpoint for neoadjuvant studies and includes the time from randomization to progression of disease that precludes surgery, recurrence, or all-cause death. EFS may also be a realistic endpoint if a large percentage of participants achieve complete responses and where prolonged survival makes an OS endpoint impractical. While the FDA guidance is explicitly written only for breast cancer, the principles outlined within provide a scientific basis for extension to UC.

5.4.4 Rationale for Open-label Design

This section is not applicable per Protocol Amendment 04. Due to the hydration program and the special restrictions for withholding anti-hypertensive in the bempegaldesleukin arm, a placebo-controlled, double-blinded study is not appropriate for this study.

Participants must have UC of the bladder/MIBC that is deemed potentially curable by RC, and must be considered medically fit for RC and be willing to undergo RC as part of the study treatment.

For Arm C participants who do not have any neoadjuvant therapy, delaying surgery is not acceptable.

5.4.5 Rationale for Stratification by Disease State and PD-L1

Stratification by clinical stage (T2N0 vs T3-T4aN0 vs T1-T4aN1) will help account for any potential prognostic outcome differences.

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

5.4.6 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 immunotherapy development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment.

This protocol includes 3 cycles of neoadjuvant therapy and 12 cycles of adjuvant therapy, which comprises approximately 1 year in total treatment duration. The decision to use 3 cycles of neoadjuvant therapy was intended to optimize the chance of achieving pCR, and was based, in part, on recent data from other neoadjuvant studies with PD-1/PD-L1 inhibitors as discussed in the background (Section 3.2).

5.5 Justification for Dose

5.5.1 Justification for Dose of Bempegaldesleukin

This section is not applicable per Protocol Amendment 04. The dose for bempegaldesleukin is 0.006 mg/kg Q3W taking in consideration the clinical safety profile associated with the robust immune system activation observed in the PIVOT-02 study. See Section 3.2.4.2 for additional details on PIVOT-02.

5.5.2 Justification for Dose of Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, and UC, 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 UC, using one of the following regimens: nivolumab 240 mg Q2W, nivolumab 3 mg/kg Q2W, or 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 expected 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.

[redacted]

5.5.3 Rationale for Bempegaldesleukin/Nivolumab Combination Dose

This section is not applicable per Protocol Amendment 04. 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 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 04. Patient Exposure Supporting Combination Dose

	Bempegaldesleukin Dosing Frequency	Nivolumab (Flat Dose[a]) Dosing Frequency	Bempegaldesleukin Dose (mg/kg)	No. Patients Examined for Safety
Bempegaldesleukin Monotherapy	Q3W	n/a	0.003, 0.006, 0.009, 0.012	22
	Q2W	n/a	0.006	6
Bempegaldesleukin+ Nivolumab	Q3W	Q2W	0.006	4
	Q2W		0.006	3
	Q3W		0.006	25
	Q2W		0.003	3
	Q3W		0.009	3

[a] Nivolumab Q2W = 240 mg, Q3W = 360 mg.

6 STUDY POPULATION

Not applicable per Protocol Amendment 04, as new enrollment in study has been stopped.

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

6.1 Inclusion Criteria

Not applicable per Protocol Amendment 04, as new enrollment in study has been stopped.

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB/IEC approved written informed consent form (ICF) 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 patient 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

2) Type of Participant and Target Disease Characteristics

a) ***Not applicable per Protocol Amendment 03 (see new criterion g) below):*** Participants with MIBC, clinical stage T2-T4a, N0 (<10 mm on CT or MRI), M0, diagnosed at TURBT within 12 weeks of randomization. Variant histology is acceptable if there is a predominant urothelial component.

Note: Stained slides from the TURBT or tumor biopsy must be submitted to the vendor for confirmation of MIBC prior to randomization.

b) Participant must be deemed eligible for RC by his/her urologist, and must agree to undergo RC. For arms A and B, participants must agree to undergo RC after completion of neoadjuvant therapy.

c) ***Not applicable per Protocol Amendment 03 (see new criterion h) below):*** Documentation of PD-L1 status by immunohistochemistry (IHC) performed by the central lab during the screening period; the tumor should be classified as PD-L1 ≥1% or PD-L1 < 1% as determined by a central laboratory during the screening period and the results must be submitted to IRT prior to randomization. Indeterminate participants are allowed in the study. Either a FFPE tissue block or 20 unstained tumor tissue sections with an associated pathology report, must be submitted for [redacted] evaluation prior to randomization. The tumor tissue sample may be a fresh or recent sample (within 12 weeks) and should be from the TURBT or tumor biopsy. No systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) should be given after the sample was obtained.

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

e) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

f) Cisplatin-ineligible participants will be defined by any one of the following criteria:
   i) Impaired renal function (glomerular filtration rate [GFR] ≥ 30 but < 60 mL/min)
   ii) GFR should be assessed by direct measurement (ie, creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
   iii) Common Terminology Criteria for Adverse Events (CTCAE) version 5, ≥ Grade 2 hearing loss (assessed per local SOC)
   iv) CTCAE version 5, ≥ Grade 2 peripheral neuropathy

g) Participants with UC of the bladder, clinical stage T2-T4aN0 (< 15 mm in short axis on CT or MRI), M0 or T1-T4aN1 (≥ 15 mm in short axis on CT or MRI), M0, diagnosed at TURBT within 12 weeks of randomization. Variant histology is acceptable if there is a predominant urothelial component.
   Note: Stained slides from the initial TURBT used to make the UC of the bladder/MIBC diagnosis and associated pathology report must be submitted to the vendor for confirmation of UC of the bladder/MIBC prior to randomization.

h) Documentation of PD-L1 status by IHC performed by the central laboratory during the screening period; the tumor should be classified as PD-L1 ≥ 1% or PD-L1 < 1% as determined by a central laboratory during the screening period and the results must be submitted to IRT prior to randomization. Indeterminate participants are allowed in the study. Either a FFPE tissue block or 20 unstained tumor tissue sections with an associated pathology report, must be submitted for [redacted] evaluation prior to randomization. The bladder tumor sample submitted should be from the initial TURBT (obtained within 12 weeks of randomization) in which the UC of the bladder/MIBC diagnosis was made. Submitted tissue sample must not be previously irradiated and systemic therapy must not be given after samples are obtained prior to enrollment.

   Note: If despite best efforts, a minimum of 20 unstained slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with the Medical Monitor.

3) Age and Reproductive Status

a) ***Not applicable per Revised Protocol 02 [see revised criteria in f i) and g i)]****:* Male or female participants, age 18 years or older at the time of signing the ICF

b) ***Not applicable per Revised Protocol 02 [see revised criteria in f iv)]***: 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

NOTE: WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in Section 2.

c) ***Not applicable per Revised Protocol 02 [see revised criteria in f ix)]***: Women must not be breastfeeding

d) ***Not applicable per Revised Protocol 02 [see revised criteria in f vii)]***: 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

e) ***Not applicable per Revised Protocol 02 [see revised criteria in g ii) and g iv) through g vii)]***: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (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.

- 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 and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

f) Female Participants

i) Females, ages 18 or local age of majority, inclusive

ii) Women who are not of childbearing potential are exempt from contraceptive requirements

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) WOCBP must have a negative highly sensitive urine or serum pregnancy test as required by local regulations pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive

- Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of assessments

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

v) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

vi) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4)

vii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months post study completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

g) Male Participants

i) Males, ages 18 or local age of majority, inclusive

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) Azoospermic males are not exempt from contraceptive requirements and 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 participant has undergone a successful vasectomy or if the partner is pregnant.

iv) ***Not applicable per Protocol Amendment 03 (see new criterion ix) below):*** 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. Males should continue to use a condom during the intervention period and for at least 7 months after the last dose of study intervention.

v) ***Not applicable per Protocol Amendment 03 (see new criterion x) below):*** Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 7 months after the last dose of study intervention in the male participant.

vi) ***Not applicable per Protocol Amendment 03 (see new criterion xi) below):*** Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the intervention period and for at least 7 months after the last dose of study intervention.

vii) ***Not applicable per Protocol Amendment 03 (see new criterion xii) below):*** Male participants must refrain from donating sperm during the intervention period and for at least 7 months after the last dose of study intervention.

viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms

ix) 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. Males should continue to use a condom during the intervention period and for at least 3 months after the last dose of study intervention.

x) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 3 months after the last dose of study intervention in the male participant.

xi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the intervention period and for at least 3 months after the last dose of study intervention.

xii) Male participants must refrain from donating sperm during the intervention period and for at least 3 months after the last dose of study intervention.

6.2 Exclusion Criteria

Not applicable per Protocol Amendment 04, as new enrollment in study has been stopped.

1) Target Disease Exceptions

a) ***Not applicable per Protocol Amendment 03 (see new criterion d) below):*** Clinical evidence of pathologic LN (≥ 10 mm in short axis) or metastatic bladder cancer

b) Prior systemic therapy, radiation therapy, or surgery for bladder cancer other than TURBT or biopsies is not permitted. Prior Bacillus Calmette-Guerin (BCG) or other intravesicular treatment of NMIBC is permitted if completed at least 6 weeks prior to initiating study treatment

c) Evidence of UC in upper urinary tracts (ureters or renal pelvis) or history of previous MIBC

d) Clinical evidence of ≥ N2 or metastatic bladder cancer.

2) Medical Conditions

a) Uncontrolled adrenal insufficiency

b) Major surgical procedure within 14 days prior to initiating study treatment or anticipation of the need for a major surgical procedure (other than RC) during the course of the study

c) Severe infection within 4 weeks prior to randomization

d) Prior malignancy active within the previous 3 years except for locally curable cancers that have been treated, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable prostate specific antigen (PSA), or carcinoma in situ of the prostate, cervix, or breast

e) 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)

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

g) Need for > 2 antihypertensive medications for management of hypertension (including diuretics)

h) Known cardiovascular history including unstable or deteriorating cardiac disease within the previous 12 months prior to screening including but not limited to the following:

   i) Unstable angina or myocardial infarction

   ii) Transient ischemic attack (TIA)/CVA

   iii) Congestive heart failure (New York Heart Association [NYHA] Class III or IV)

   iv) Uncontrolled clinically significant arrhythmias

i) 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

j) 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

k) 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 7.7.2.1 (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.

l) Participants with inadequately treated adrenal insufficiency.

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

3) Prior/Concomitant Therapy

a) 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 (See Section 7.7.1 for prohibited therapies)

b) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

c) Participants who have received a live / attenuated vaccine within 30 days before first treatment

d) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, agents that target IL-2 therapy or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

e) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

4) Physical and Laboratory Test Findings

a) White blood cells < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < $100x10^3$/μL

d) Hemoglobin < 9.0 g/dL

e) ***Not applicable per Protocol Amendment 03:*** Serum creatinine > 1.5x upper limit of normal (ULN), unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula)

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)

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

6) 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

***Not applicable per Protocol Amendment 04.** 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 who are not subsequently randomized in the study/included in the analysis population. 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, as applicable, 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 Period

Participant Re-enrollment: This study permits the re-enrollment of a participant who 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 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, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Testing for asymptomatic COVID-19 by RT-PCR or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic COVID-19, or be discovered to have asymptomatic COVID-19 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 COVID-19-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:

- Nivolumab Solution for Injection
- **Not applicable per Protocol Amendment 04**. Bempegaldesleukin (NKTR-214) Powder for Solution for Injection

An investigational product, also known as investigational medicinal product in some regions, is defined 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 SOC for a given diagnosis, may be considered as non-investigational products.

Per Protocol Amendment 04, 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 360 mg IV Q3W for the remainder of the study treatment period.

Table 7-1: Study Treatments for CA045009/18-214-13

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 04** Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.3 mg, 0.5 mg, or 1 mg of rhIL-2 per vial[a]	IP	Open-label	Vial (one or more vials per carton)	Refer to the label on container and/or pharmacy manual
Nivolumab Solution for Injection[b]	100 mg (10 mg/mL)	IP	Open-label	Vial (multiple vials/carton)	Store at 2°-8°C. Protect from light and freezing.

[a] ***Not applicable per Protocol Amendment 04.** Note: For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.

[b] May be labeled as either "BMS-936558-01" or "nivolumab."

7.1 Treatments Administered

Per Protocol Amendment 04, 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 360 mg IV Q3W for the remainder of the study treatment period.

Table 7.1-1: Selection and Timing of Dose

Study Treatment[a]	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
***Not applicable per Protocol Amendment 04.** Bempegaldesleukin (NKTR-214)[b]	0.006 mg/kg	q3w	IV
Nivolumab	360 mg	q3w	IV

[a] Study agent should be administered in an area with access to resuscitation equipment.

[b] ***Not applicable per Protocol Amendment 04.** Bempegaldesleukin (NKTR-214) dose is based on IL-2 content.

7.1.1 Bempegaldesleukin Dosing

This section is not applicable per Protocol Amendment 04. Per Protocol Amendment 04, participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and may continue nivolumab. 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 Cycle 1 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. Bempegaldesleukin will be administered as an IV infusion over 30 (± 5) minutes at a starting dose of 0.006 mg/kg every 3 weeks (± 3 days). 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 30 (± 5) minutes after the completion of bempegaldesleukin administration.

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 solutions 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 IB for details regarding preparation, storage, and administration.

7.1.1.1 Hydration Guidelines

This section is not applicable per Protocol Amendment 04. 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 and Table 2-3). 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 handout.

For those 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 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. Advise participants to refrain from activities 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 and Table 2-3). Following subsequent bempegaldesleukin administrations, 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 or adjust the recommendation for self-oral hydration

to a particular participant if this is deemed to be in the best interest of the participant (eg, evidence of fluid overload). Hydration guidelines should also be provided to the participant.

7.1.2 Nivolumab Dosing

Nivolumab administration should start 30 (± 5) minutes after the completion of bempegaldesleukin administration in Arm A. 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 12 cycles of adjuvant treatment or the study ends, whichever occurs first.

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 cycles. Premedications are not recommended for the first dose of nivolumab. In the event that bempegaldesleukin is permanently discontinued due to toxicities, see Section 8.1.1.

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 participants randomized to Arm A in the event that bempegaldesleukin is stopped due to toxicities.

Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or Pharmacy Manual.

7.2 Method of Treatment Assignment

The following information is required for participant randomization:

- Participant number
- Year of birth
- PD-L1 status (≥ 1% vs < 1%/ indeterminate)
- UC of the bladder/MIBC confirmation
- Clinical stage (T2N0 vs T3-T4aN0 vs T1-T4aN1) (see Appendix 9)

Stratified permuted block method will be used for randomization and randomized participants will be stratified by clinical T stage and PD-L1 status. Due to the importance of avoiding delays associated with obtaining a second tumor sample for evaluation, this study will allow up to 10% (total) of randomized participants to be included in the study with indeterminate PD-L1 status.

Participants with clinical stage T1-T4aN1M0 are eligible from Protocol Amendment 03. These participants will be randomized in the IRT using a new randomization schedule.

Tumor PD-L1 expression data will be transferred directly from the analyzing laboratory to the IRT vendor.

- PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells)

- PD-L1 negative/indeterminate (< 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells/tumor cell membrane scoring hampered by high cytoplasmic staining content).

Study treatment will be administered at the study visits as listed in the Schedule of Activities (Section 2).

7.3 Blinding

Not applicable as this is an open-label study; however, PD-L1 will be blinded to investigators but provided to the bioanalytical laboratory as appropriate.

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.

7.4 Dosage Modification

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab. If bempegaldesleukin or nivolumab meet the criteria for dose delay, then administration of both drugs must be delayed until the criteria to resume are met (see Table 7.4.1-1). Delay nivolumab and bempegaldesleukin dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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 Sections 7.4.1 and 8.1.1.

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

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab. The criteria to delay, resume, and discontinue nivolumab and bempegaldesleukin were initially developed using CTCAE v4.03 definitions of AE grading. In Oct-2020, the nivolumab AE grading criteria and algorithms were updated to CTCAE v5, which can be found in Table 7.4.1-1.

SARS-CoV-2 infection, either confirmed or suspected, requires delay of nivolumab and bempegaldesleukin study treatment. 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 patient's health or suitability for enrollment, as determined by the study team.

AE criteria for delaying, resuming, and discontinuing nivolumab and bempegaldesleukin are available in Table 7.4.1-1 and Section 8.1.1. Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent.

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 04. 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 04. 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 consultation is required for dose reduction.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must 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[a]	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 of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must 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 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 of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must 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 only 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 of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must 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 Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must be discontinued for participants receiving bempegdesleukin plus nivolumab			
Drug-related AE per CTCAE v5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
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	
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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must be discontinued for participants receiving bempegdesleukin plus nivolumab			
Drug-related AE per CTCAE v5	**Severity**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
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	
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 04**).	Grade 2 non-skin AE, except fatigue	Nivolumab: Delay dose[a]	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 of Nivolumab and Bempegaldesleukin (if One is Delayed, Both Delayed) *Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab

Note: Bempegaldesleukin must 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; BMS, Bristol Myers Squibb; CTCAE, Common Terminology Criteria for Adverse Events; CVA, cerebrovascular accident; DRESS, drug-reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre Syndrome; MS, myasthenia gravis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TIA, transient ischemic attach; ULN, upper limit of normal.

[a] ***Not applicable per Protocol Amendment 04**.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 of Nivolumab and Bempegaldesleukin (if one is delayed, both are delayed)

***Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab.**

Bempegaldesleukin-specific Criteria for Delay, Resumption, and Discontinuation			
Serum Creatinine Increased (transient, non-inflammatory)	Grade 2, 3, or 4	Delay dose[a]	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[a]	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 (eg, cryptogenic CVA) and for suspected TIA without clear alternative etiology. See Appendix 7.

Abbreviations: AE, adverse event; CVA, cerebrovascular accident; TIA, transient ischemic attack.

[a] If dosing of one drug is delayed, then dosing of both drugs is delayed.

***Per Protocol Amendment 04, 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 04.

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

This section is not applicable per Protocol Amendment 04. 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 alternative etiologies. Consider imaging if obstruction is suspected. If there is a non-inflammatory etiology, treat accordingly and continue bempegaldesleukin and nivolumab.

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

AST or ALT > 3.0 to ≤ 5 × ULN (within first cycle of bempegaldesleukin + nivolumab)

Increase frequency of liver function test (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.

ALT or AST > 5.0 to ≤ 8.0 × ULN (within first cycle of bempegaldesleukin + 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 [Appendix 6]);

- Discontinue bempegaldesleukin + 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

ALT or AST > 8.0 × ULN (follow Hepatic Adverse Event Management Algorithm [Appendix 6])

- Discontinue bempegaldesleukin + 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

Per Protocol Amendment 04, language for bempegaldesleukin is no longer applicable. 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 (Days 2-4), and are often accompanied by other cytokine-related toxicities such as flu-like symptoms, rash or pruritus. The transient elevations in hepatic transaminases are usually mild or moderate in severity, not associated with increased total bilirubin, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2. Grade 3 laboratory abnormalities with these characteristics have been observed in PIVOT-02 during Cycle 1, and participants were able to continue study treatment uninterrupted with close laboratory monitoring. 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).

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 Investigator's Brochure or product labeling for appropriate management.

7.4.3 Monitoring and Management of Bempegaldesleukin-induced Eosinophilia

This section is not applicable per Protocol Amendment 04. Frequent and significant eosinophilia has been observed in participants receiving both single agent bempegaldesleukin and bempegaldesleukin plus nivolumab, primarily starting at Cycle 2 or later, consistent with the known effect of IL-2 therapy. Clinical data analysis demonstrated that frequency of selected AEs (primarily Grade 1 or 2 in severity) such as rash, pruritus, edema, nausea, vomiting, diarrhea, and dizziness increased with level of eosinophilia. Isolated cases of suspected hypereosinophilic syndrome have been reported.

Absolute eosinophil count (AEC) should be closely monitored per protocol. If study participant is suspected to have hypereosinophilic syndrome (symptoms may involve skin, lungs, digestive tract, heart, blood and nervous system) with AEC at or above 5000/µL ($5x10^9$/L) level, bempegaldesleukin treatment may need to be withheld, and the participant should be treated as clinically indicated.

7.4.4 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

Adrenal insufficiency and hypophysitis have been observed in participants receiving nivolumab. Consider prompt evaluation when participants have signs or symptoms of hypophysitis or adrenal

insufficiency which includes levels of early-morning adrenocorticotropic hormone (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 Immuno-oncology Agents

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab. 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 immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms (see Appendix 6, Appendix 7, Appendix 8, and the nivolumab IB) have been developed to assist Investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis
- CVA
- Cytokine-release Syndrome (CRS)

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 experienced a CVA or TIA, the Investigator should discuss risk/ benefit of continuing nivolumab. A management algorithm for possible signs and symptoms of CVA or TIA for participants treated with bempegaldesleukin in combination with a checkpoint inhibitor is provided in Appendix 7 **(not applicable per Protocol Amendment 04)**.

7.4.5.1 Management Algorithm for Cytokine-release Syndrome

This section is not applicable per Protocol Amendment 04. 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. An algorithm for the management of CRS is provided in Appendix 8 **(not applicable per Protocol Amendment 04).**

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

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab. 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, hypotension, hypertension, bronchospasm, or other 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 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 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 (see Section 7.7.1 for corticosteroid dose equivalents). Subsequent infusions may be administered at a reduced rate (eg, 50% of the original infusion rate).

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 product is only administered to study participants. The investigational product must be administered 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 administered and BMS contacted 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).

Please refer to the current version of the Investigator's Brochures and/or pharmacy manual for complete preparation, storage, and handling information.

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 the 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 04 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 and Table 2-3). For subsequent doses, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment of the study in the appropriate section of the eCRF.

All medications (prescription and over-the-counter [OTC]), vitamin and mineral supplements, and/or herbs taken by the participant from Screening through End of Treatment phase 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.

Pre-medications should not be administered prior to the initial administration of bempegaldesleukin **(Per Protocol Amendment 04, bempegaldesleukin will no longer be administered).** or nivolumab, but if a participant reports symptoms (such as nausea and/or vomiting), prophylactic use of antiemetics may be used.

Any subsequent anti-cancer therapy will be recorded until end of study or death, in the appropriate section of the eCRF.

7.7.1 Prohibited and/or Restricted Treatments

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

- 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 7.7.2.1).
- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of disease under study).

- 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.
- 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 End of Treatment phase 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.
- Pre-medications should not be administered prior to the initial administration of bempegaldesleukin or nivolumab, but if a participant reports symptoms (such as nausea and/or vomiting), prophylactic use of antiemetics may be used.
- Administration of a live COVID-19 vaccine is prohibited within 30 days prior to randomization (or screening). Live COVID-19 vaccines should not be used during the study, including the treatment period and within 100 days following last dose of IP.

7.7.1.1 Effect of Bempegaldesleukin on PK of Concomitant Medications

This section is not applicable per Protocol Amendment 04. Bempegaldesleukin causes transient increases in circulating cytokines lasting for about one week after bempegaldesleukin dosing in the Q3W dosing schedule. Several of these cytokines (IFN-γ, IL-6, IL-10) have the potential to decrease the activity of multiple enzymes and drug transporters.[65,66] Consequently, treatment with bempegaldesleukin may lead to temporary decrease in clearance of drugs that are substrates of metabolizing enzymes or drug transporters. Where indicated based on decreased tolerability or the occurrence of adverse effects related to a concomitant drug, reduce the dosage of the concomitant drug during Days 3 to 8 of each cycle of bempegaldesleukin.

7.7.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to 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.

7.7.2.1 Restricted Treatments

The guidance for anticoagulation and anti-thrombotic 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 04 participants will receive nivolumab monotherapy only. Nivolumab monotherapy does not appear to be associated with an increased risk of ICE; anticoagulation therapy will no longer be mandated for patients 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 risk benefit for each individual patient.

Per protocol amendment 04, the remainder of this section is not applicable.

Participants with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation (LMWH or DOAC). Additionally:

- Use of warfarin (Coumadin) is permitted; however, therapeutic dosing should target a specific International Normalised Ratio (INR) stable for at least 4 weeks prior to enrollment. Bempegaldesleukin has the potential to down-regulate metabolizing enzymes for warfarin for approximately 1 week after administration of each dose of bempegaldesleukin. Due to the possibility of drug-drug interactions between warfarin and bempegaldesleukin, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the participant's participation on study.
- 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 the participant's time on study treatment.

7.7.2.2 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 per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose 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, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

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 standards set by the local Ethics Committee.

7.7.2.3 Blood Pressure Precautions

This section is not applicable per Protocol Amendment 04. Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha-blockers for benign prostatic hyperplasia, 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.

7.7.3 Permitted Therapy

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab.

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.

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 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.

7.8 Treatment After the End of the Study

At the end of the study/Period, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate SOC to treat the condition under study.

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 the 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 04, 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 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, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- EFS event as defined in Section 9.1.1

Refer to the Schedule of Activities (Section 2) 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. See 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 04, participants receiving bempegaldesleukin plus nivolumab are required to discontinue bempegaldesleukin and will receive nivolumab monotherapy.

Per Protocol Amendment 04, the text below related to bempegaldesleukin is not applicable; however, the criteria remain unchanged for nivolumab.

Nivolumab and bempegaldesleukin treatment must be permanently discontinued per criteria in Table 7.4.1-1. Discontinue nivolumab and bempegaldesleukin for 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 Post-study Treatment Study Follow-up

In this study, pCR, EFS, and OS are key endpoints of the study. 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 survival follow-up data as required and in line with Section 5 until death or the conclusion of the study. For each randomized participant, the maximum total duration of the study is up to 62 weeks + 100 days of safety follow-up.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol-defined window (see 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 04, this section is no longer 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.

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who 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 upon discontinuation. 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 (Section 2). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), 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 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 (Section 2).

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.

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, and fever) consistent with possible pulmonary AEs, 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 eCRF. 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 04, tumor assessments will be determined by investigator.

9.1.1 Definition of Events in EFS

EFS is defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause. Details on EFS events are provided below:

- Worsening of disease that precludes surgery (as determined by Investigator or Section 9.1.1.2)
- If surgery is possible, but not performed for other reasons (eg, participant refuses, AEs), and there has been RECIST v1.1 assessed progression in the neoadjuvant period, then it will be considered an EFS event (see Section 9.1.2.2).
- If surgery is possible but not performed for other reasons (participant refuses or worsening of medical condition), then the participant may continue on study treatment and will be considered to have an EFS event if and when:
  - There is RECIST v1.1 defined progression
  - If there is carcinoma in situ (CIS), high grade Ta, T1, or ≥ T2 disease at any time after neoadjuvant therapy is completed observed on cystoscopy and confirmed by pathologic review after TURBT and/or bladder biopsy (see schedule of cystoscopy in Section 2)
- If surgery is attempted but gross resection is abandoned, due to unresectable tumor or worsening of disease, then that will be considered an EFS event.
- If RC is completed with no or only microscopic residual disease (positive margins, not visible on imaging), then the participant will continue on study and will be considered to have an EFS event if and when radiographically (or by biopsy) visible recurrence occurs.

- If surgery is completed with unequivocal gross residual disease (visible on imaging or by biopsy), it will be considered as an EFS event. Equivocal residual disease should be confirmed by biopsy or confirmed by further progression (RECIST v1.1) at following scan (see Appendix 10).
- Local or distant recurrence or new upper tract tumor confirmed by imaging or biopsy
- Death due to any cause

9.1.1.1 Definition of Disease Recurrence

Bladder cancer recurrence will be defined as any unequivocal evidence of new bladder cancer lesions that are detected after RC. Biopsy should be employed where required to prove recurrence. In cases where recurrence is equivocal and biopsy cannot be performed or were not diagnostic, the participant may continue treatment and imaging of suspect lesions should be repeated in 4-8 weeks (Section 9.1.2.3).

The first post-surgery assessment will occur within 60 to 90 days after RC and prior to beginning post-surgery IO therapy for Arms A and B. Participants who have new LNs defined as short axis ≥ 10 mm with growth of ≥ 5 mm (eg, 9 mm LN grows to 14 mm) or have findings of other new, unequivocal non-nodal lesions will be considered as having recurrence. Confirmation of recurrence must be attempted as described in Section 9.1.2.2.

Tumor may recur in the following sites:

- Local, urothelial tract: Any new UC in ureter or renal pelvis, including lesions thought to be a second UC primary, will be considered recurrences, as well as new CIS, Ta high grade, T1 or muscle invasive lesion in participants who do not undergo RC.
- Local, non-urothelial tract: Any new UC in pelvic soft tissue or involving pelvic nodes below the aortic bifurcation.
- Distant: Any new non-local recurrence

Unequivocal recurrence of urothelial cancer at any of these sites will be considered an EFS event requiring that study treatment be discontinued.

9.1.1.2 Definition of Disease Progression

All participants including those who did not undergo RC due to reasons other than worsening of disease precluding surgery will be followed by imaging for disease progression according to RECIST v1.1 (see Appendix 10). For participants who are undergoing surveillance cystoscopies, see Section 9.1.1 above.

9.1.1.3 Definition of pCR

The pCR rate is defined as the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, as assessed by blinded pathology review.

9.1.2 Imaging Assessment for the Study

As per Protocol Amendment 04, images will no longer be submitted to central imaging vendor.

All images will be submitted to a central imaging vendor for BICR at any time during the study. Copies of additional scans conducted at the time of UC of the bladder/MIBC diagnosis should be stored at the sites for possible future analysis, at the Sponsor's discretion. Sponsor may also request additional historical scans to clarify baseline assessment. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA045009 Imaging Manual provided by the central imaging vendor. Screening and on study images should be acquired as outlined in Schedule of Activities (Section 2).

Tumor assessments at other time points may be performed if clinically indicated.

Tumor assessments for all participants should continue as per protocol even if dosing is delayed or discontinued. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible.

9.1.2.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis (including excretory imaging), 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 v1.1 criteria.

If a participant has a contraindication for CT IV contrast, then 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.

If a participant has a contraindication for both MRI and CT IV contrasts, then 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.

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

Use of CT component of a 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 v1.1 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 v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

9.1.2.2 BICR Confirmation of Progression or Recurrence

Per Protocol Amendment 04, BICR will be discontinued and all study treatment decisions will be based on the investigator's assessment of tumor images.

See comprehensive Definition of Events in EFS (Section 9.1.1). **Not applicable per Protocol Amendment 04.** All investigator-assessed events require BICR confirmation with the exception of events from preclusion of surgery due to disease worsening or abandoned surgery do not require BICR confirmation.

Not applicable per Protocol Amendment 04. Sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. The site will inform the central imaging vendor when the investigator assessment indicates either (i) unequivocal disease progression per RECIST v1.1 criteria (for participants without RC) or (ii) unequivocal evidence of disease recurrence after RC, in order for BICR assessment of progression/recurrence to be performed. The BICR will be completed and the results provided to the site as specified in the 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 04. Participants whose [progression or recurrence] is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule (Section 2) or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic [progression or recurrence], tumor assessments will continue according to the protocol-specified schedule, as noted in Schedule of Activities (Section 2) until progression has been confirmed by BICR (Section 9.1.2.2).

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2.3 Confirmation and Date of Progression or Recurrence

Per Protocol Amendment 04, BICR will be discontinued and all study treatment decisions including progression and recurrence will be based on the investigator's assessment of tumor images.

The first date when progression or recurrence was observed is taken into account regardless of the method of assessment. Therefore, recurrence will be declared for any lesion when:

- Progression or recurrence is unequivocal (eg, multiple new measurable lesions); confirmation with histology/cytology should be attempted but is not required.
- Progression or recurrence is equivocal; for example, LN only, solitary lesion, or disease in the urothelial tract, confirmation with histology/cytology should be considered if feasible. Confirmation of a defined lesion in the upper genitourinary tract may be obtained with a retrograde study and biopsy. If biopsy is not feasible, a follow-up CT or MRI scan may be used

to confirm recurrence. Follow-up (confirmatory) scan should occur 4 to 8 weeks after the initial scan. The date of the initial scan showing recurrence (or a suspect lesion, later shown to be a recurrence) will count as the date of recurrence.

- Any pathological evidence of new bladder cancer denotes recurrence.
- A suspicious urine cytology (eg, positive Urovision or similar urine assay) alone does not constitute the basis for recurrence of disease, but should prompt for further investigation, (eg, radiological confirmation). Tumor markers or auto-antibodies alone cannot be used to document recurrence. Biopsy and/or imaging is required to establish recurrence.
- If both pathology and imaging were done and recurrence or bladder cancer confirmed, the date of recurrence is the date of which ever examination came first.
- New NMIBC in participants who do not undergo RC would be progression.

[redacted]

[redacted]

9.2 Adverse Events

The definitions of an AE or SAE 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.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Serious Adverse Drug Reactions section in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

- The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment. All SAEs, and all AEs (SAEs and 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.
- 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.
- For participants randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. For participants in Arm C, SAEs should be collected for 100 days following RC.
- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- 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 or designee within 24 hours of updated information being available.
- CVA (any grade) is considered an AEOSI and should be assessed for seriousness using the standard seriousness definition. However, all CVAs are required to follow the timelines for SAE reporting (eg, 24 hours). CVA management guidelines, provided in Appendix 7, are no longer applicable per Protocol Amendment 04.

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 judgement in the context of known AEs, when appropriate for the program or protocol.

All nonserious AEs (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 adjuvant therapy for Arms A and B and 100 days from RC for Arm C. For participants who do not continue adjuvant therapy in Arms A and B, AEs and/or SAEs should be collected for a period of 100 days following RC.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 9.2), and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled-out.

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 9.2).

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 AEs 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 Suspected, Unexpected Serious Adverse Reaction (SUSAR) 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 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.

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.

9.2.6 Immune-mediated Adverse Events

Immune-mediated AEs (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

This paragraph is not applicable per Protocol Amendment 04. 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 (AEOSI)

CVA (any grade) is considered an AEOSI and should be assessed for seriousness using the standard seriousness definition. However, all CVAs are required to follow the timelines for SAE reporting (eg, 24 hours). CVA management guidelines, provided in Appendix 7, are no longer applicable per Protocol Amendment 04.

9.2.8 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious 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 (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential 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:

- Treatment-emergent ALT or AST > 3 times ULN (>2x baseline AND >3x ULN for participants with baseline elevation),
  AND
- Total bilirubin > 2 times ULN (>2x baseline AND >2x ULN for participants with baseline elevation) or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase),
  AND

- 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 nonserious 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 eCRF.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

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 and 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 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

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

9.4.4 Echocardiogram

Standard echocardiogram will be performed to assess cardiac function and LVEF according to the Schedule of Events. A MUGA scan can be performed to assess cardiac function and LVEF if a standard echocardiogram cannot be performed.

9.4.5 Pregnancy Tests

Serum or urine pregnancy tests will be performed on women of childbearing potential according to the Schedule of Activities (see Section 2). A negative pregnancy test result must be obtained within 24 hours prior to 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.

Guideline to be followed in case of pregnancy and reporting requirements are provided in Section 9.2.5.

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.

9.4.7 Clinical Safety Laboratory Assessments

As of Protocol Amendment 04, clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2) and will not be required to be submitted to central laboratory.

A list of the clinical laboratory analyses to be tested is provided in Table 9.4.7-1.

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

Investigators should document their review of each laboratory safety report.

The Investigator or a qualified Sub-Investigator will review all laboratory 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.

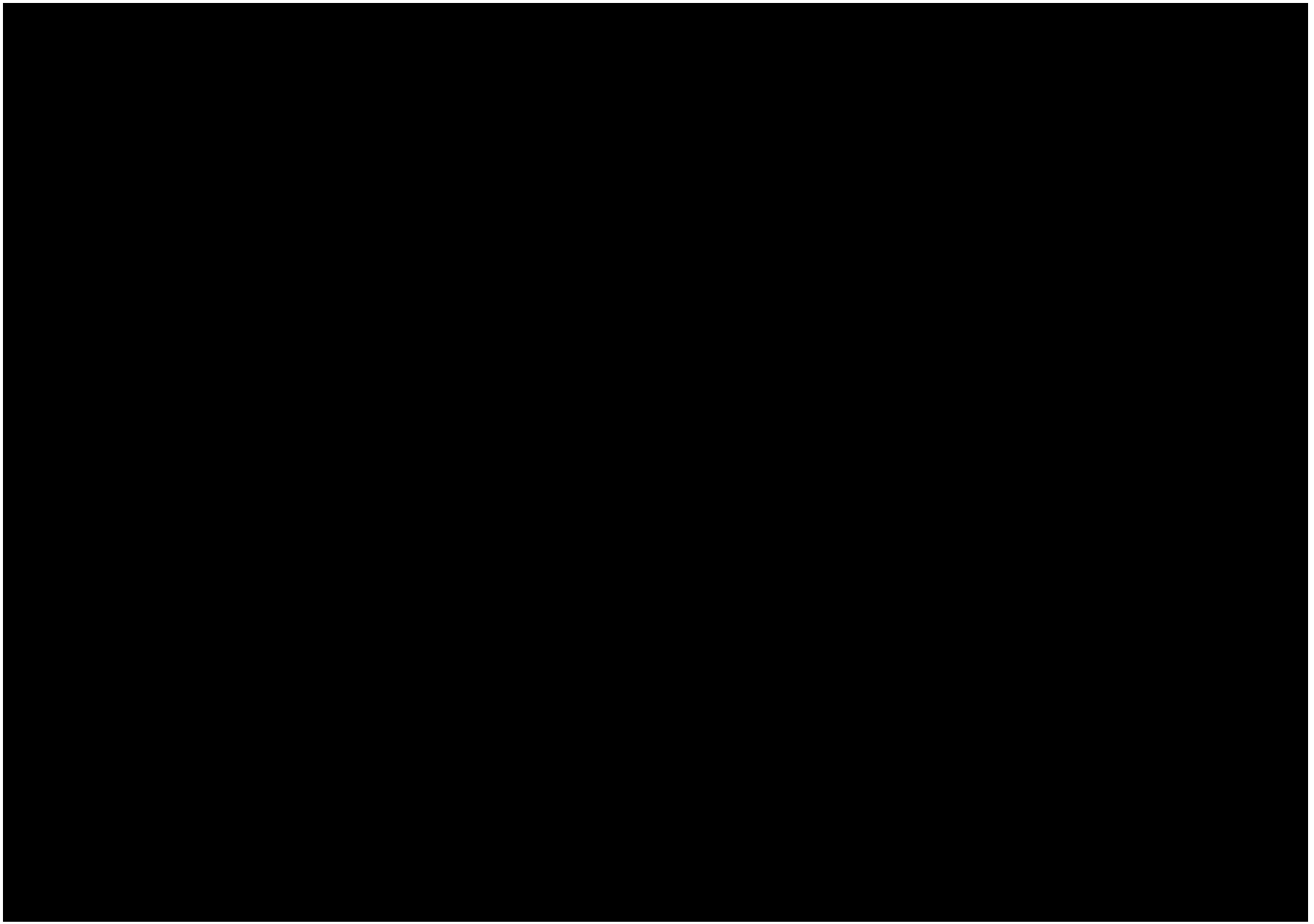
Table 9.4.7-1: Clinical Safety Laboratory Assessments

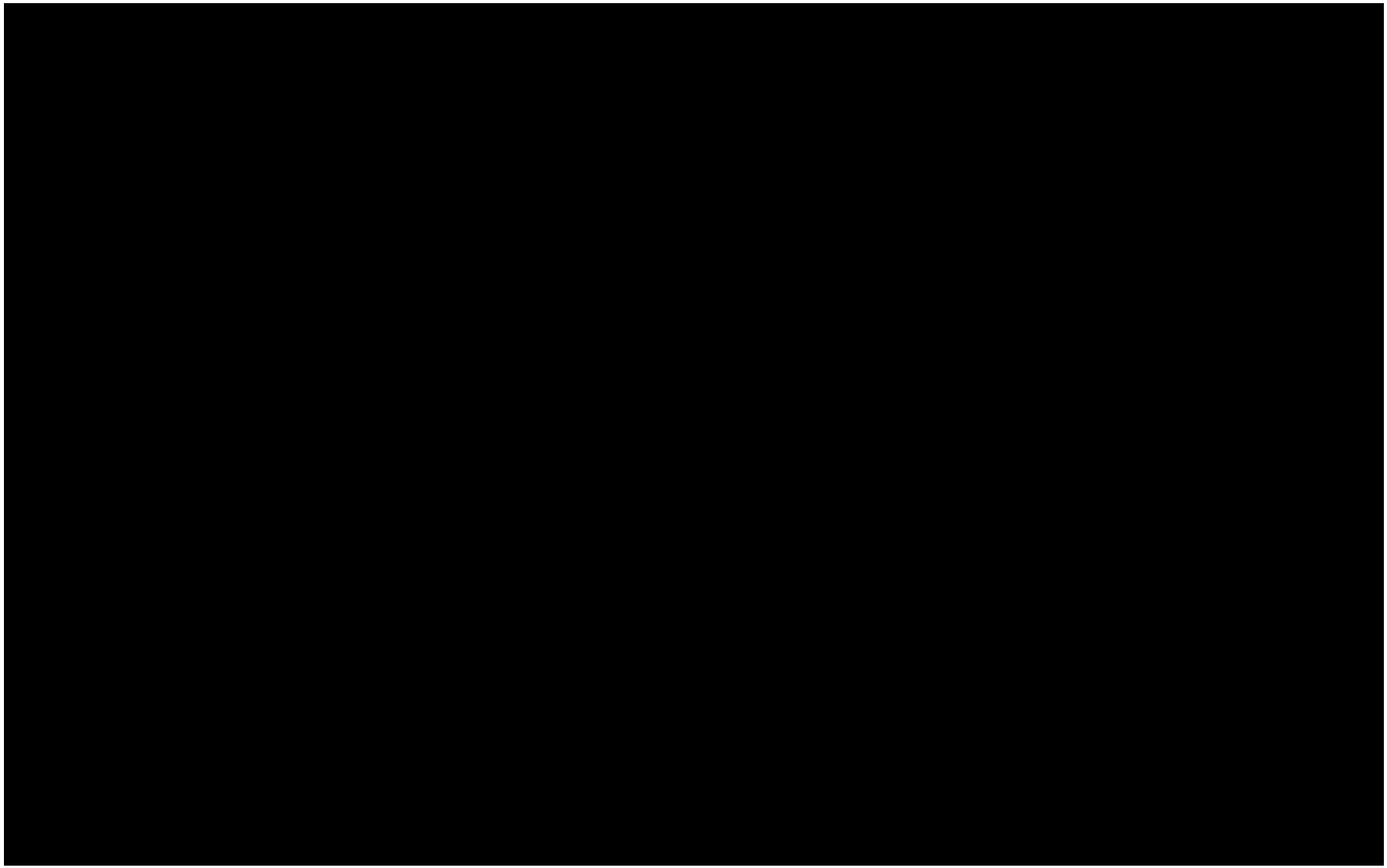
Hematology CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) or serum urea Uric acid	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Creatine kinase TSH, free T3 and free T4 - screening

Table 9.4.7-1: Clinical Safety Laboratory Assessments

Glucose	TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Creatinine clearance (CLcr)- screening only Lipase and /or amylase
Serology Serum for hepatitis C antibody, hepatitis B surface antigen, (screening only) HIV-1 and -2 antibody where mandated by local requirements (screening only) See Appendix 11 **Other Analyses**	
Urine or Serum Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG)	
Follicle stimulating hormone (FSH) (screening only; required to confirm menopause in women < age 55)	
Urinalysis - screening only and as clinically indicated.[a]	

[a] Urine dipstick can be done and if abnormal, perform microanalysis.





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9.7 Pharmacogenomics

Not applicable

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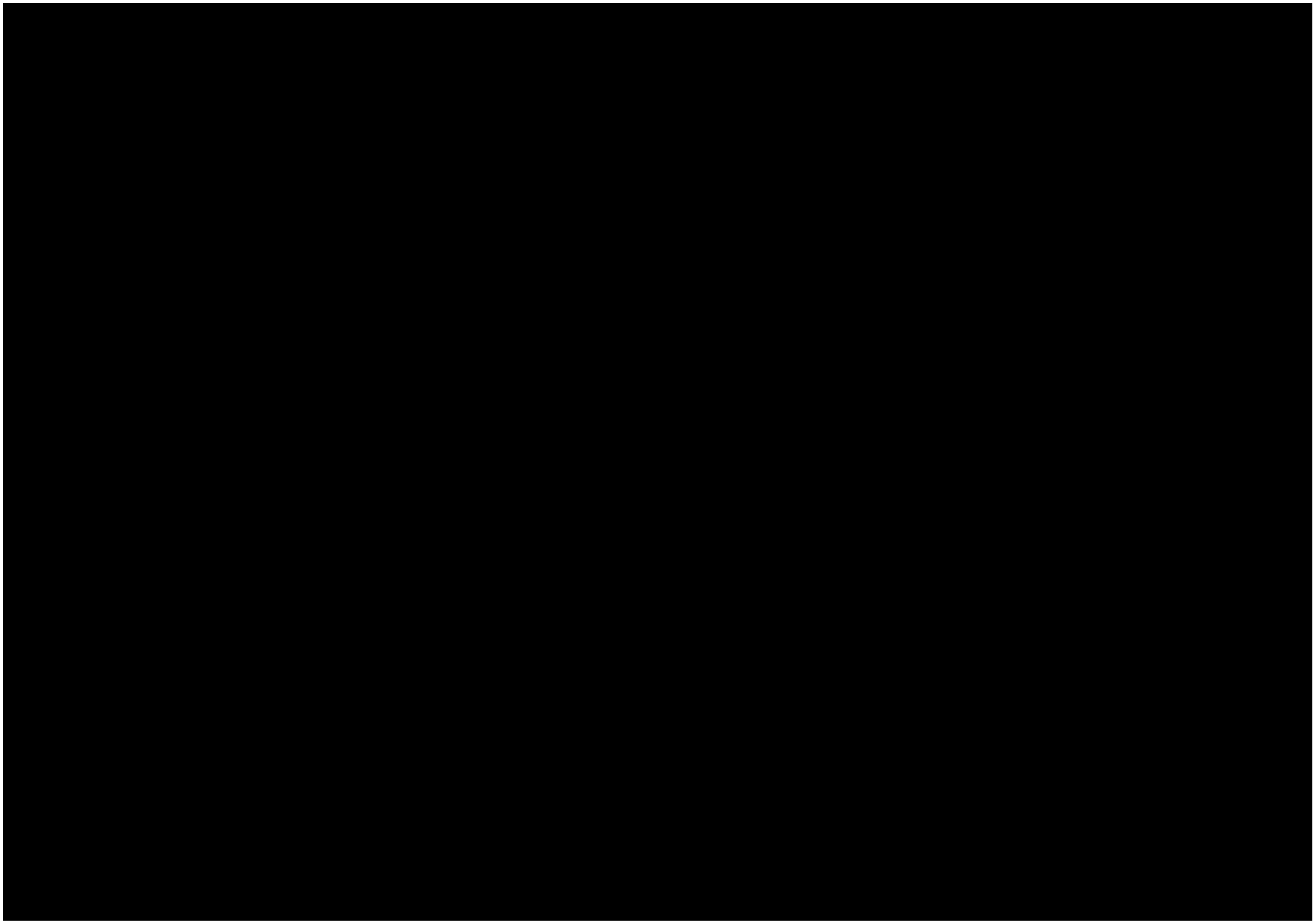

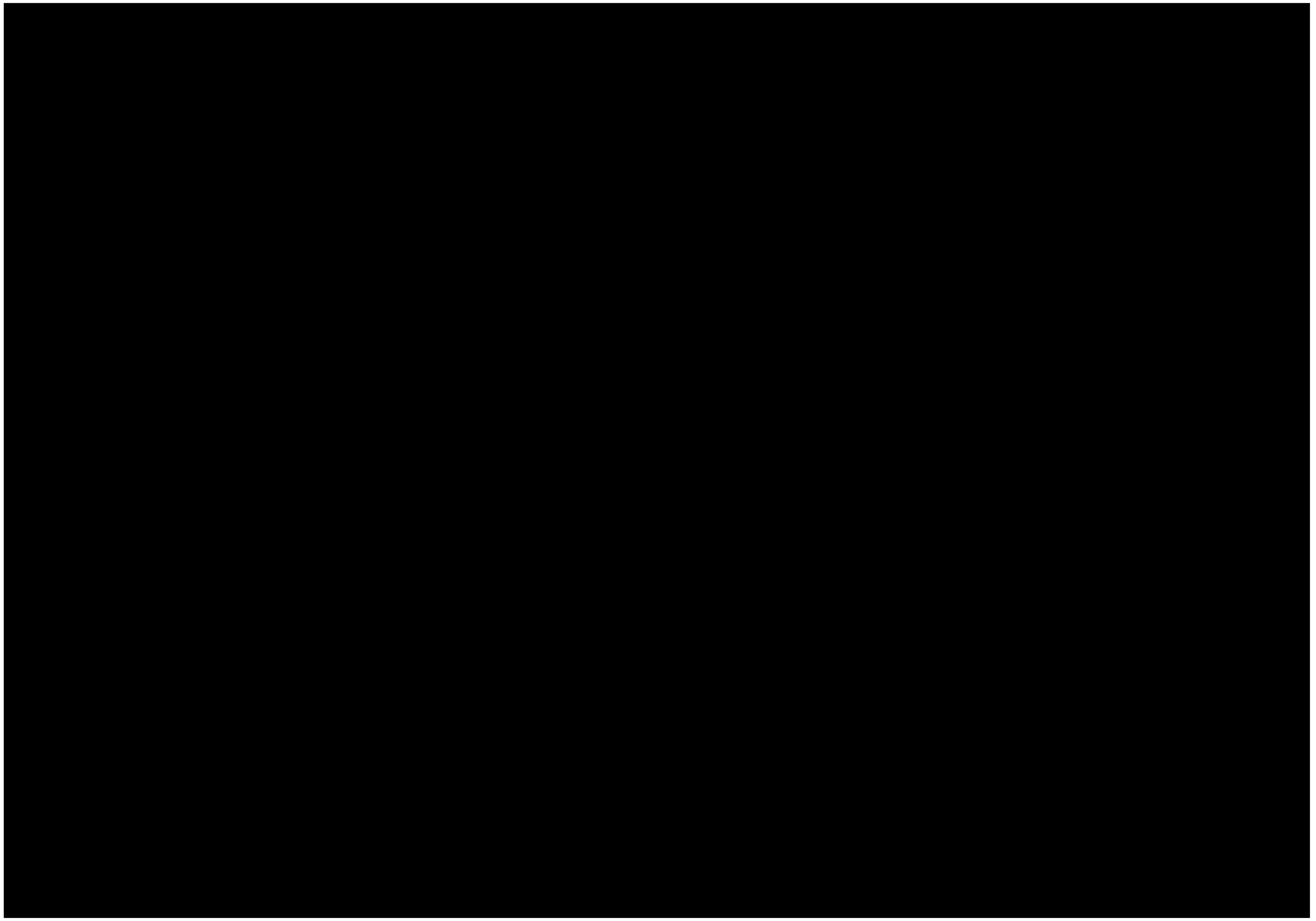

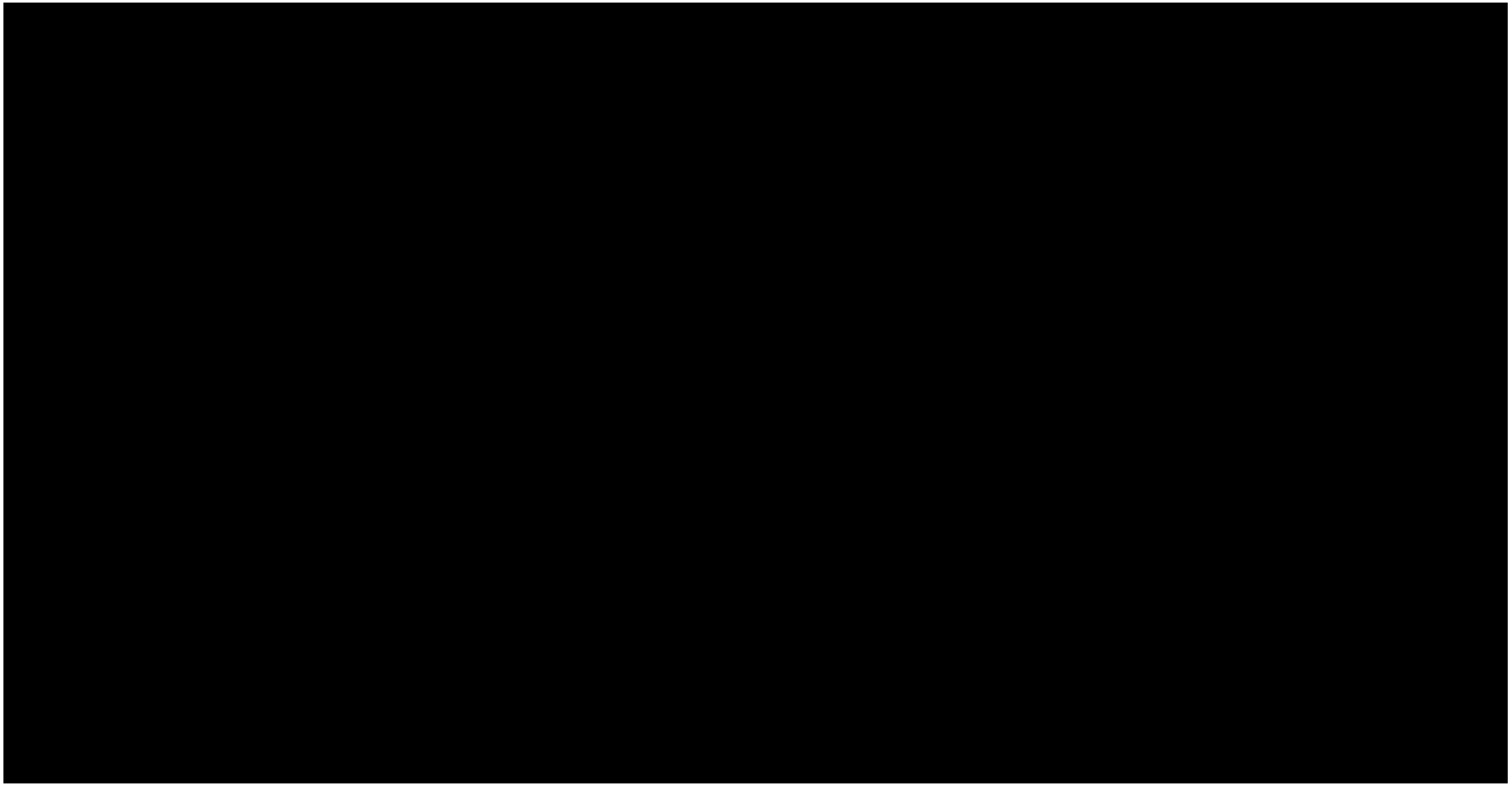

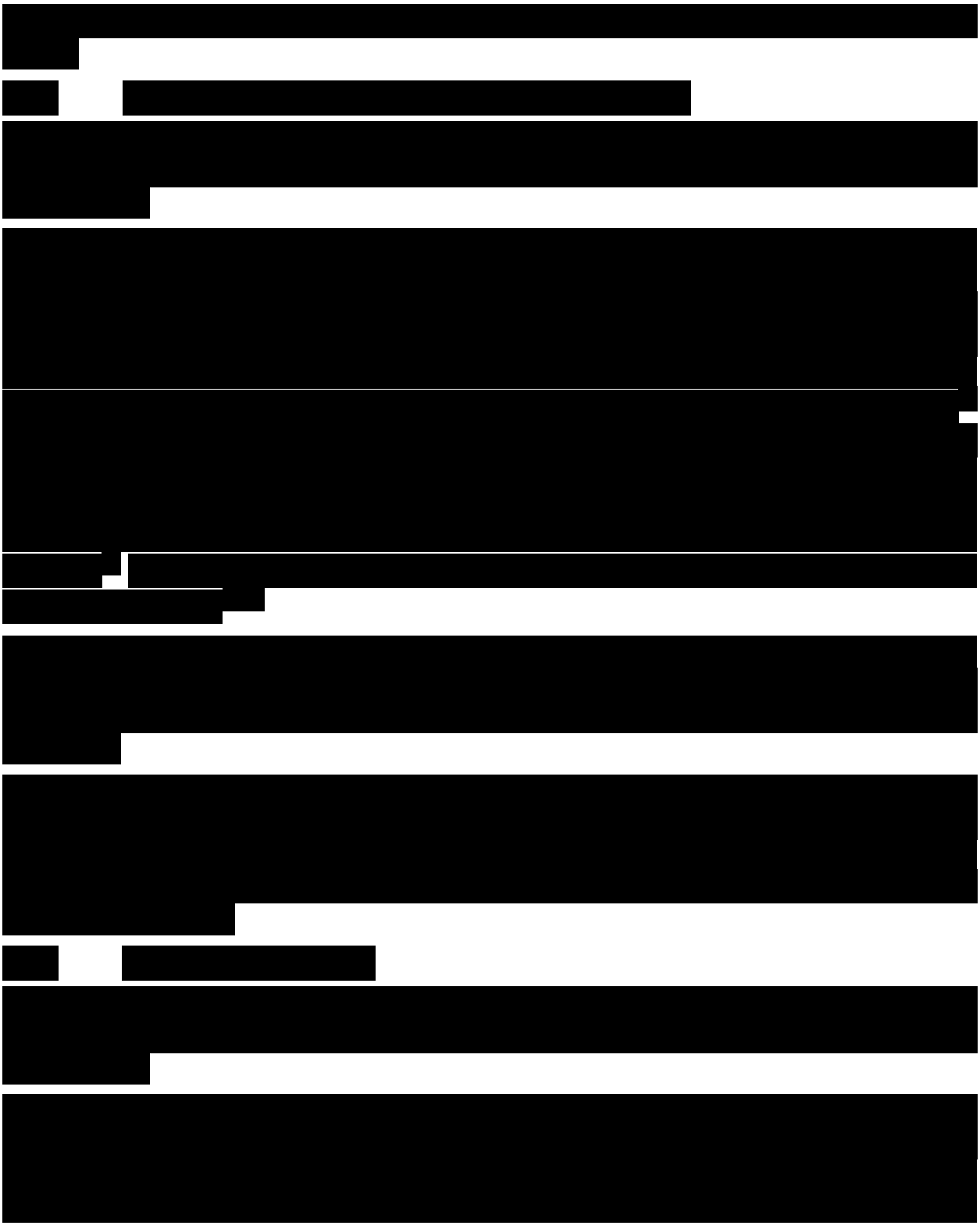

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10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Per Protocol Amendment 04 this section is not applicable.

The sample size (N = 540 across 3 arms) of the study accounts for the 2 primary efficacy comparisons:

- pCR comparison of Arm A vs Arm C in all randomized participants
- EFS comparison of Arm A vs Arm C in all randomized participants

The overall 2-sided alpha for this study is 0.05. For sample size determination this is split with 0.001 for the pCR comparison and 0.049 for the EFS comparison.

According to the original protocol assumption from 2019, the accrual rate of 17 participants per month estimated an accrual period of approximately 32 months for completion. Based on the revised accrual projection from April 2021 and the impact of COVID-19, the accrual period will take approximately 43 months to complete.

Sample size consideration for the pCR primary comparison of Arm A vs Arm C

Assuming the pCR rate for the experimental and the control arms are 36% and 15% respectively,[11] a total of 360 participants (180 per arm) will provide approximately 90% power for the 2-sided test at overall significance level of 0.001. The analysis will occur when all randomized participants will be eligible for pCR evaluation (approximately 4 months after the last participant is randomized).

Sample size consideration for the EFS primary comparisons of Arm A vs Arm C

Among the approximately 360 randomized participants (180 per arm), approximately 156 EFS events provide at least 88% power to detect a HR of 0.6 with an overall type 1 error of 0.049 (2-sided). The EFS distribution is assumed to be piecewise exponential with the following landmark values for the control group (Arm C): EFS rates of 43% at 36 months, 37% at 60 months and 25% at 120 months. These assumptions are based on the control arm (ie, local radical therapy alone without neoadjuvant therapy) of MRC/EORTC BA06 Phase 3 study[72] incremented by 5% to account for the fact that a subset of participants did not undergo RC as definitive treatment in that study. Proportional hazard is modeled for the treatment effect. The calculation accounts for approximately 11% drop out during study duration (exponential with 5% by 12 months).

Two interim analyses for EFS are planned and corresponding stopping boundaries will be based on an O'Brien and Fleming alpha spending function. The first will take place at the time of final pCR analysis (based on the assumptions, approximately 101 EFS events in Arms A and C will occur at this time). The second interim analysis will take place when approximately 85% of the total number of events have occurred (approximately133 EFS events in Arms A and C). If the first interim analysis is performed exactly at 101 events, the boundary in terms of statistical significance for declaring superiority would be 0.01. If the second interim analysis is performed exactly at 133 events, the boundary in terms of statistical significance for declaring superiority would be 0.026. The boundary for declaring superiority in terms of statistical significance for the final analysis after 156 events in Arms A and C would be 0.04. The final analysis of EFS is projected to occur approximately 65 months after the start of the study (approximately 43 months accrual and 22 months follow-up). Given the slowdown in events rate observed after 24 months in historical data, which could prevent the analysis to be performed in a reasonable time window, if

the 156th event in Arms A and C has not occurred 24 months after randomization of the last participant, then the final EFS analysis will take place at that time. In such a case, the final analysis boundary will be recalculated based on the actual updated final number of events.

Sample size calculations are summarized in Table 10.1-1.

Table 10.1-1: Sample Size Calculations per Comparison for Primary Endpoints

***Not applicable per Protocol Amendment 04.**

Endpoints	pCR (Arm A vs C)	EFS (Arm A vs C)
Accrual Duration	43 months	43 months
Power	90%	88%
Alpha	0.001 (2-sided)	0.049 (2-sided)
Hypothesized Rates Control vs Experimental	pCR: 15% vs 36%	EFS at 36 mo: 43% vs 60% EFS at 60 mo: 37% vs 55% EFS at120 mo: 25% vs 44%
Hypothesized Hazard Ratio	-	0.60
pCR Final/ EFS Interim Analysis 1	~47 months (accounts for 4 months to get pCR on all participants)	~47 months 101 events in Arms A and C (65% I)
EFS Interim Analysis 2		~56 months 133 events in Arms A and C (85% I)
EFS Final Analysis		~65 months 156 events in Arms A and C
Sample size for the comparison	~360 randomized participants in 2 treatment groups	
Total Sample Size	540 randomized participants (180/group)	

East version 6.4 was used for sample size/power computations

Assumptions of treatment effect for the overall survival comparison of Arm A vs Arm C

Among the approximately 360 randomized participants, approximately 156 OS events provide 88% power to detect a HR of 0.6 with an overall type 1 error of 0.049 (two-sided). The OS distribution is assumed to be piecewise exponential with the following landmark values for the control group: OS rates of 55% at 36 months, 48% at 60 months and 35% at 120 months. These assumptions are based on the control arm (ie, local radical therapy alone without neoadjuvant therapy) of MRC/EORTC BA06 Phase 3 study incremented by 5% to account for the fact that a subset of participants did not undergo RC as definitive treatment in that study.[72] Proportional hazard is modeled for the treatment effect without dropout.

Two interim analyses are planned and corresponding stopping boundaries will be based on an O'Brien and Fleming alpha spending function. The first will take place at the time of second EFS analysis (approximately after 133 EFS events in Arms A and C). At that time, approximately 109 OS events in Arms A and C are expected. The second interim analysis will take place at the time of final EFS analysis (approximately 156 EFS events in Arms A and C). At that time, approximately 84% of the total number of OS events will have occurred (approximately 131 OS events in Arms A and C). In case EFS reaches significance at an interim analysis, the subsequent OS analyses timing will be based on the OS number of events described above. The final analysis of OS will take place when 156 OS events in Arms A and C are observed, and it is projected to occur approximately 86 months after the start of the study (approximately 43 months accrual and 43 months follow-up). If the 156^{th} event in Arms A and C has not occurred 44 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 actual updated final number of events.

10.2 Populations for Analyses

For purposes of main analyses, the following populations are defined:

Table 10.2-1: Analysis Populations

Population	Description
All enrolled participants	All participants who signed an informed consent form and were registered into the IRT
All randomized participants	All participants who were randomized to any treatment arm in the study
All treated participants	All randomized participants who either received at least one dose of any study medication or underwent radical cystectomy

10.3 Statistical Analyses

Per Protocol Amendment 04, the Sponsor is terminating the development of bempegaldesleukin in combination with nivolumab. This trial will be unblinded and no hypothesis testing will be performed. The efficacy endpoints of pCR, EFS, and OS will be summarized descriptively in all randomized subjects. Details will be included in the SAP.

A description of the participant population will be included in a statistical output report.

Below is a summary of planned statistical analyses of the primary and secondary endpoints.

Table 10.3-1: Efficacy Analyses

***Not Applicable per Protocol Amendment 04.**

Endpoint	Statistical Analysis Methods
Primary	
Pathological Complete Response (pCR) in Arm A vs Arm C The pCR rate is defined as the proportion of randomized participants with absence of any cancer (T0, N0) in pathology specimens after RC, as assessed by blinded pathology review.	pCR rates and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each treatment group in the all randomized participants population. Participants who do not undertake surgery will be counted as non-pCR and will be included in the denominator. pCR rates will be compared using a 2-sided stratified Cochran Mantel Haenszel (CMH) test. Associated odds ratio and estimate of the difference with 99.9% and 95% CI will be calculated.
Event-Free Survival (EFS) in Arm A vs Arm C EFS is defined as time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause. Participants who die without a reported progression/disease recurrence will be considered to have experienced an event on the date of their death. Participants who did not report progression/recurrence of disease or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Further details on the censoring rules for consideration of subsequent therapies will be described in the Statistical Analysis Plan (SAP).	EFS will be analyzed in the all randomized participants population. EFS will be compared between 2 arms with a stratified 2-sided log rank test. The hazard ratio and the corresponding 95% and (100-adjusted alpha)% CI will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate. The EFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. In addition, EFS rates at specific time points will be estimated using KM estimates on the EFS curve for each randomized arm. Associated 2-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation). The EFS endpoint will be analyzed by BICR assessment (primary analysis) as well as by investigator (ie, all events assessed by the investigator)as sensitivity analysis. In the primary analysis by BICR assessment, type of events that can only be assessed by investigator (see Section 9.1, eg, worsening of disease precluding surgery, abandoned resection due to unresectable disease) will be considered as events. Additional sensitivity analysis on EFS will also be performed, and details will be included in the SAP .
Secondary	
pCR in Arm B vs Arm C Same definition as the corresponding primary endpoint.	Similar analyses of pCR in Arm B vs Arm C will be conducted. The hypothesis testing will only be performed if the higher hierarchical endpoints are met, as described in the SAP.
EFS in Arm B vs Arm C Same definition as the corresponding primary endpoint.	Similar analyses of EFS in arm B vs arm C will be conducted. The hypothesis testing will only be performed if the higher hierarchical endpoints are met, as described in the SAP.

Table 10.3-1: Efficacy Analyses

***Not Applicable per Protocol Amendment 04.**

Endpoint	Statistical Analysis Methods
OS in Arm A vs Arm C and in Arm B vs Arm C OS is defined as the time between the date of randomization and the date of death due to any cause. For participants still alive, OS is censored at the last date the participant is known to be alive.	OS will be analyzed in the all randomized participants population. The same analyses as described for EFS analyses will be performed for OS. The hypothesis testing will only be performed if the higher hierarchical endpoints are met, as described in the SAP.
pCR in Arm A vs Arm B Same definition as the corresponding primary endpoint.	pCR rates and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each treatment group in the all randomized participants population. Associated odds ratio and estimate of the difference with 95% CI will be calculated.
EFS in Arm A vs Arm B Same definition as the corresponding primary endpoint	The EFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. In addition, EFS rates at specific time points will be estimated using KM estimates on the EFS curve for each randomized arm. Associated 2-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation). The hazard ratio and the corresponding 95% will be estimated in a stratified Cox proportional hazards model using the randomized arm as a single covariate.
[redacted]	
[redacted]	

The stratification factors for analysis are the following:

- Clinical Stage (T2N0 vs T3-T4aN0 vs T1-T4aN1)
- PD-L1 status (≥ 1% vs < 1%/indeterminate)

Text related to alpha spending and hierarchical testing in the following paragraphs is not applicable in Protocol Amendment 04. The overall 2-sided alpha for this study is 0.05, which is split with 0.001 for pCR and 0.049 for EFS for both Arm A vs Arm C comparison.

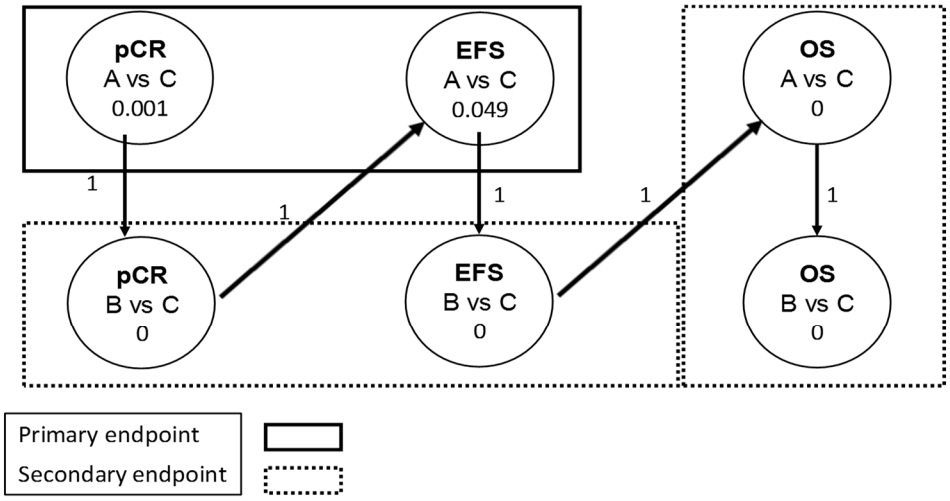
No formal powered comparison of Arm A versus Arm B is planned, therefore, it may not be possible to draw any conclusion from the trial results about the superiority of Arm A compared to Arm B.

To control the type I error rate, the following hierarchical testing approach will be implemented:

1) pCR: A vs C will be first tested at 0.001 alpha (two-sided)
2) pCR: B vs C will be tested at 0.001 alpha (two-sided) if i. was significant
3) EFS: A vs C will be tested at 0.049 (or 0.05 if ii. was significant) alpha (two-sided)
4) EFS: B vs C will be tested if iii. was significant and with the same alpha (two-sided)
5) OS: A vs C will be tested if iv. was significant and with the same alpha (two-sided)
6) OS: B vs C will be tested if v. was significant and with the same alpha (two-sided)

This approach has a graphical representation, which is illustrated in Figure 10.3-1.

Figure 10.3-1: *Not Applicable per Protocol Amendment 04. Graphical Representation of the Statistical Testing Approach



Number in the circle: initial alpha allocation
Arrows: if comparison is significant, alpha is passed to the next comparison with corresponding allocation rate

Given EFS and OS endpoints are tested hierarchically using a group sequential approach, the overall hierarchical testing approach will be used where each endpoint/comparison will have its own specific Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundaries.[73] Additional details around the interim analysis schedule is provided in Section 10.3.3.

10.3.1 Safety Analyses

All safety analyses will be performed on the all treated participants population.

Table 10.3.1-1: Safety Analyses

Endpoint	Statistical Analysis Methods
Secondary	Descriptive statistics of safety will be presented using NCI CTCAE version 5.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 5.0 criteria by system organ class and

Table 10.3.1-1: Safety Analyses

Endpoint	Statistical Analysis Methods
	preferred term. On-study laboratory parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 5.0 criteria. Additional safety analyses will be described in the statistical analysis plan finalized before first database lock.

[redacted]

10.3.3 Interim Analyses

Per Protocol Amendment 04 this section is not applicable.

Several interim analyses are planned for efficacy. Table 10.3.3-1 gives an overview of interim analyses purpose and timing.

Table 10.3.3-1: Interim Analyses Schedule

***Not Applicable per Protocol Amendment 04.**

Analysis	Purpose	Analysis Trigger	Projected Timing[a]	Number of Participants/Events
Final pCR Interim EFS 1	Demonstrate significant improvement in pCR and EFS	All randomized participants who underwent RC have pCR evaluation	~47 months	pCR: all randomized participants (~360 in Arms A and C) EFS: ~101 events (Arms A and C)
Interim EFS 2 Interim OS 1	Demonstrate significant improvement in EFS and OS	~133 EFS events in arms A and C	~56 months	EFS: ~133 events (Arms A and C) OS: ~109 events (Arms A and C)
Final EFS Interim OS 2	Demonstrate significant improvement in EFS and OS	~156 EFS events in arms A and C	~65 months	EFS: ~ 156 events (Arms A and C) OS: ~131 events (Arms A and C)
Final OS	Demonstrate significant improvement in OS	~156 OS events in arms A and C	~86 months	OS: ~156 events (Arms A and C)

[a] Approximate projected timing from the start of randomization

10.3.4 Interim Analyses for EFS

Per Protocol Amendment 04 this section is not applicable.

Two interim analyses for efficacy of EFS are planned. The first will take place at the time of final pCR analysis (approximately after 101 EFS events in Arms A and C). The second interim analysis will take place when approximately 85% of the total number of events have occurred (approximately 133 events in Arms A and C). Details are provided in Section 10.3.3. There is no futility analysis for EFS.

10.3.5 Interim Analyses for OS

Per Protocol Amendment 04 this section is not applicable.

Two interim efficacy analyses of OS are planned. The first will take place at the time of EFS interim analysis 2 (approximately after 133 EFS events in Arms A and C). The second OS interim analysis will take place at the time of final EFS analysis. In case EFS reaches significance at an interim analysis, the subsequent OS analyses timing will be based on the OS number of events (approximately 109 OS events in Arms A and C for interim 1 and 131 OS events in Arms A and C for interim 2). There is no futility analysis for OS.

These interim comparisons for EFS and OS will allow for early formal testing for superiority, and the boundaries for declaring superiority will be derived based on the actual number of events using

Lan-DeMets spending function with O'Brien and Fleming type of boundary in EAST version 6 based on the information fraction observed.

An independent statistician external to BMS will perform interim analyses (in conjunction with a review by the Data Monitoring Committee). The SAP 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]	
AE	adverse event
AEC	Absolute eosinophil count
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AEC	Absolute eosinophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
HCG	human chorionic gonadotrophin
Bcl-xL	B-cell lymphoma-extra large
BICR	Blinded independent central review
BMS	Bristol-Myers Squibb
BP	blood pressure
BTLA	B and T lymphocyte associated
BUN	blood urea nitrogen
Cavgss	steady state average concentration
CAD	coronary artery disease
CBC	complete blood count
[redacted]	
CD8+	CD8 positive
CD 122	interleukin-2 receptor subunit beta
CD-28	cluster of differentiation 28
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
CLcr	creatinine clearance
Cmaxss	steady-state peak concentrations

Term	Definition
CMH	Cochran-Mantel Haenszel
CMV	cytomeglovirus
COVID-19	coronavirus disease 2019
CR	complete response
CRC	Colorectal cancer
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
CVA	cerebrovascular accident
Cavgss	simulated steady state average concentration
[redacted]	
DFS	Disease free survival
dL	deciliter
DLT	dose-limiting toxicity
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulation
DWI	diffusion-weighted imaging
ECG	electrocardiogram
ECHO	echocardiogram
[redacted]	
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event Free Survival
eg	exempli gratia (for example)
[redacted]	
EOI	end of infusion
EU	European Union

Term	Definition
[redacted]	
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FSH	follicle stimulating hormone
g	gram
GC	gemcitabine and cisplatin
GFR	glomerular filtration rate
h	hour
H&E	hematoxylin and eosin
HBsAg	hepatitis B surface antigen
HCC	Hepato cellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
[redacted]	
HIV	Human Immunodeficiency Virus
HR	hazard ratio
[redacted]	
IB	Investigator's brochure
ICE	ischemic cerebrovascular event (ICE)
ICF	Informed consent form
ICOS	inducible T-cell costimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IHC	immunohistochemistry
IL-2	interleukin-2
IL-2Rβγ	IL-2-receptor beta gamma subunit
IMAE	Immune mediated adverse event
[redacted]	
INR	international normalised ratio

Term	Definition
IO	Immuno Oncology
IP	investigational products
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intention-to-treat
IV	intravenous
kg	kilogram
L	liter
[redacted]	
LDH	lactate dehydrogenase
LFT	liver function test
LMWH	low molecular weight heparin
LN	lymph node
LVEF	left ventricular ejection fraction
[redacted]	
mg	milligram
[redacted]	
MIBC	muscle-invasive bladder cancer
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
[redacted]	
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
µg	microgram
N	number of subjects or observations

Term	Definition
NAC	neoadjuvant chemotherapy
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
[redacted]	
NK	natural killer
NKTR	Nektar Therapeutics
NKTR-214	bempegaldesleukin
[redacted]	
NMIBC	non-muscle invasive bladder cancer
[redacted]	
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over the counter
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response
PD	Progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death ligand 1
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PGC	paclitaxel, gemcitabine, and cisplatin
PK	pharmacokinetics
PLND	pelvic lymph node dissection
PPK	population pharmacokinetics
PO	per os (by mouth route of administration)
[redacted]	

Term	Definition
PR	partial response
PSA	Prostate Specific Antigen
[redacted]	
Q2W	every two weeks
Q3W	every three weeks
[redacted]	
RC	Radical Cystectomy
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	relapse-free survival
RP2D	recommended Phase 2 dose
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SOC	standard of care
SOGUG	Spanish Oncology Genitourinary Group
t	temperature
T	time
T cell	regulatory T cell
TCR	T cell receptor
[redacted]	
TIA	Transient ischemic attack
[redacted]	

Term	Definition
[redacted]	
TME	tumor microenvironment
TNM	tumor, node, and metastasis
[redacted]	
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
TURBT	Transurethral Resection of Bladder Tumor
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States of America
[redacted]	
WOCBP	women of childbearing potential
[redacted]	

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 GuidelinesGood 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.

The rights, safety, and well-being of the study subjects 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 (eg, 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.

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.

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)

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.

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 9.2.9 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 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., 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: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

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 <u>User Dependent</u> *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) 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.

APPENDIX 6 MANAGEMENT ALGORITHMS

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

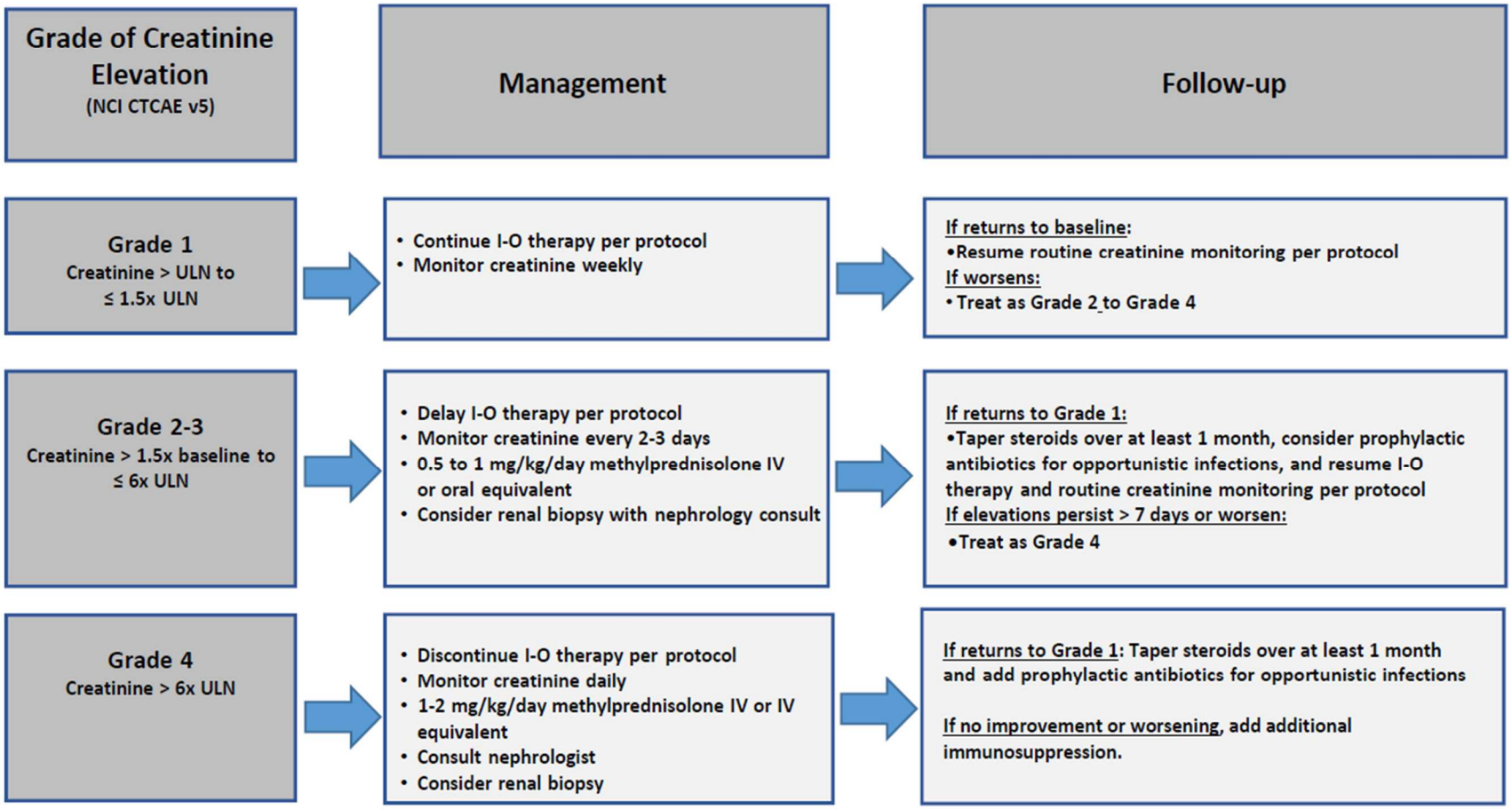
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

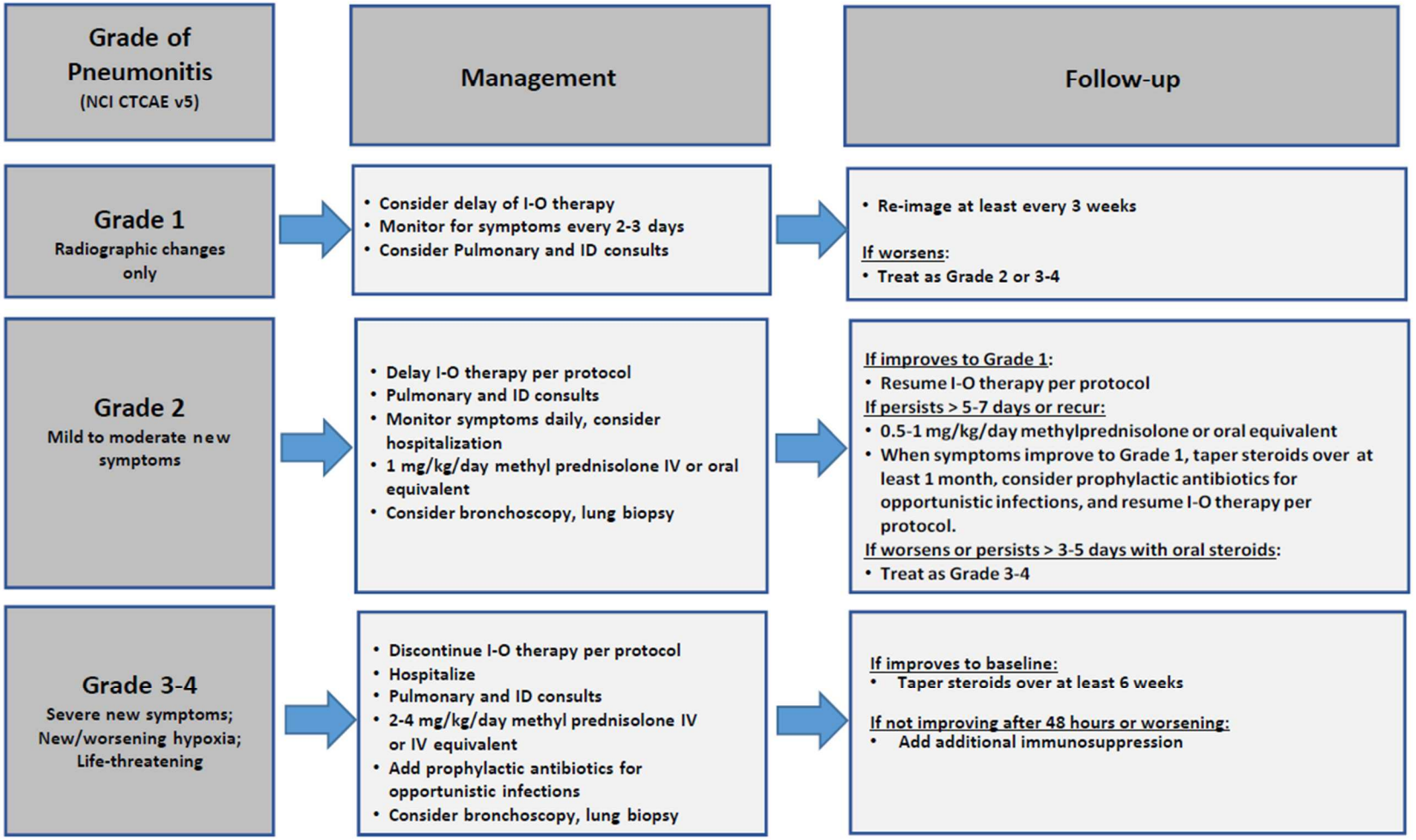


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

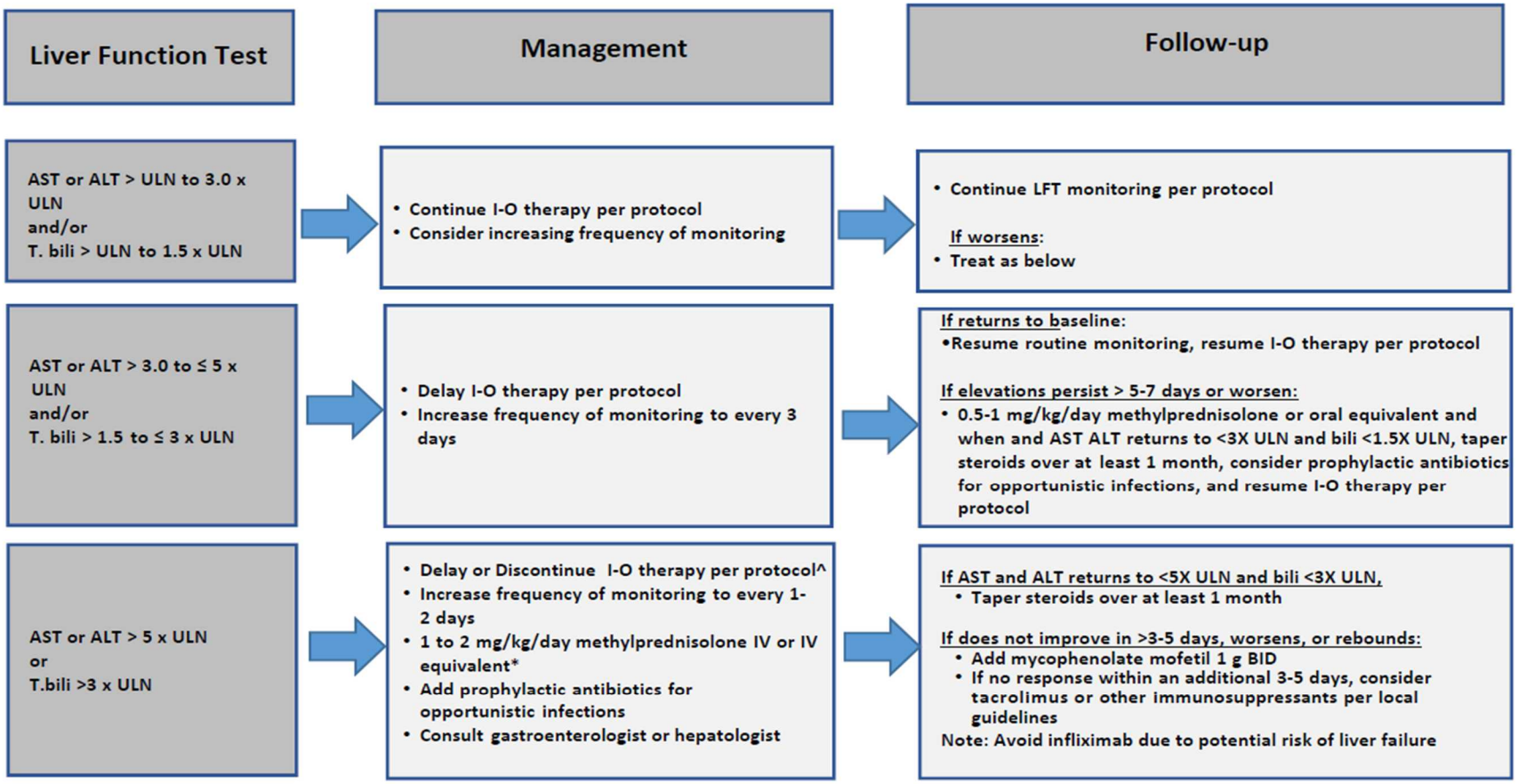


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

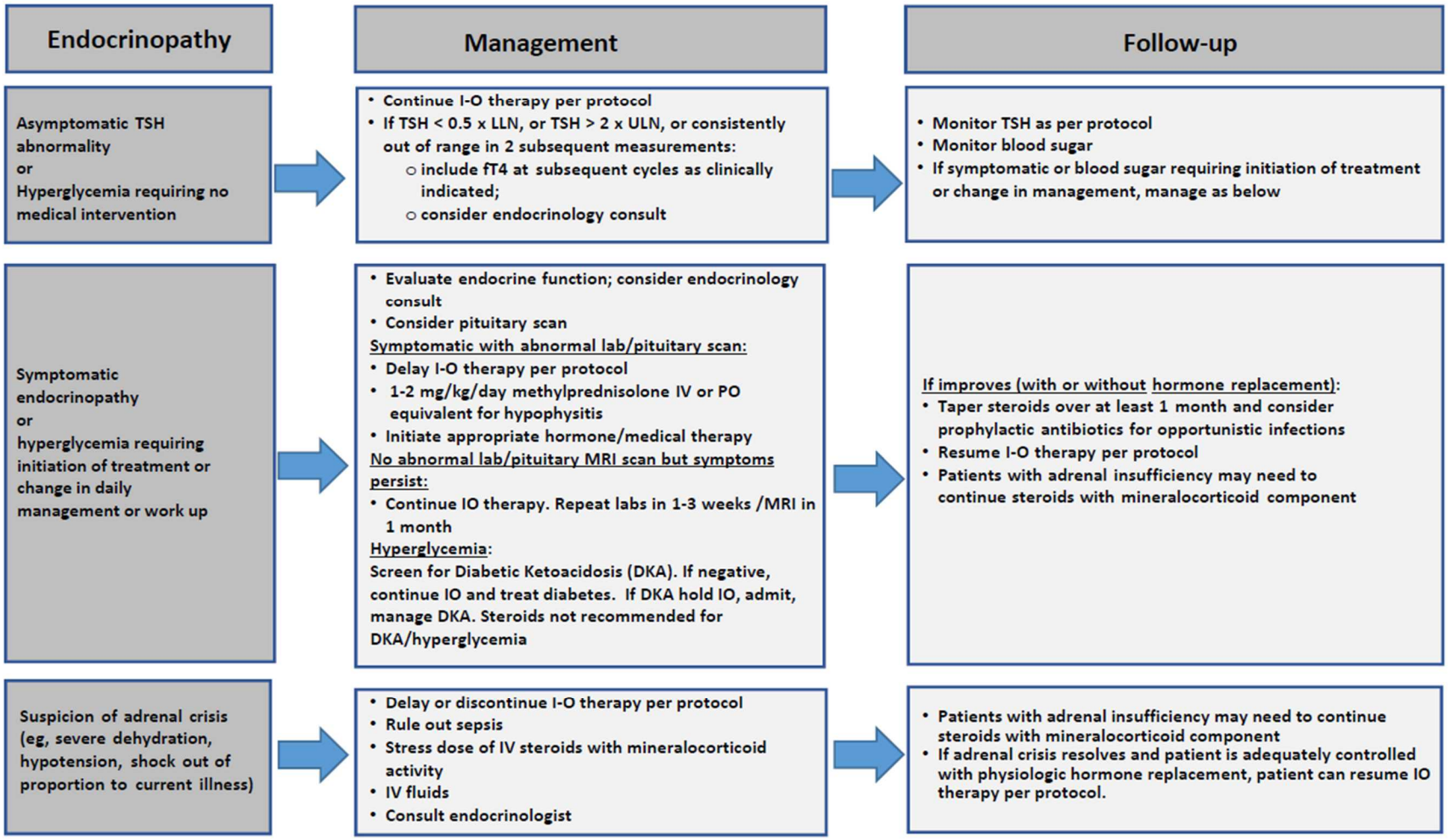


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

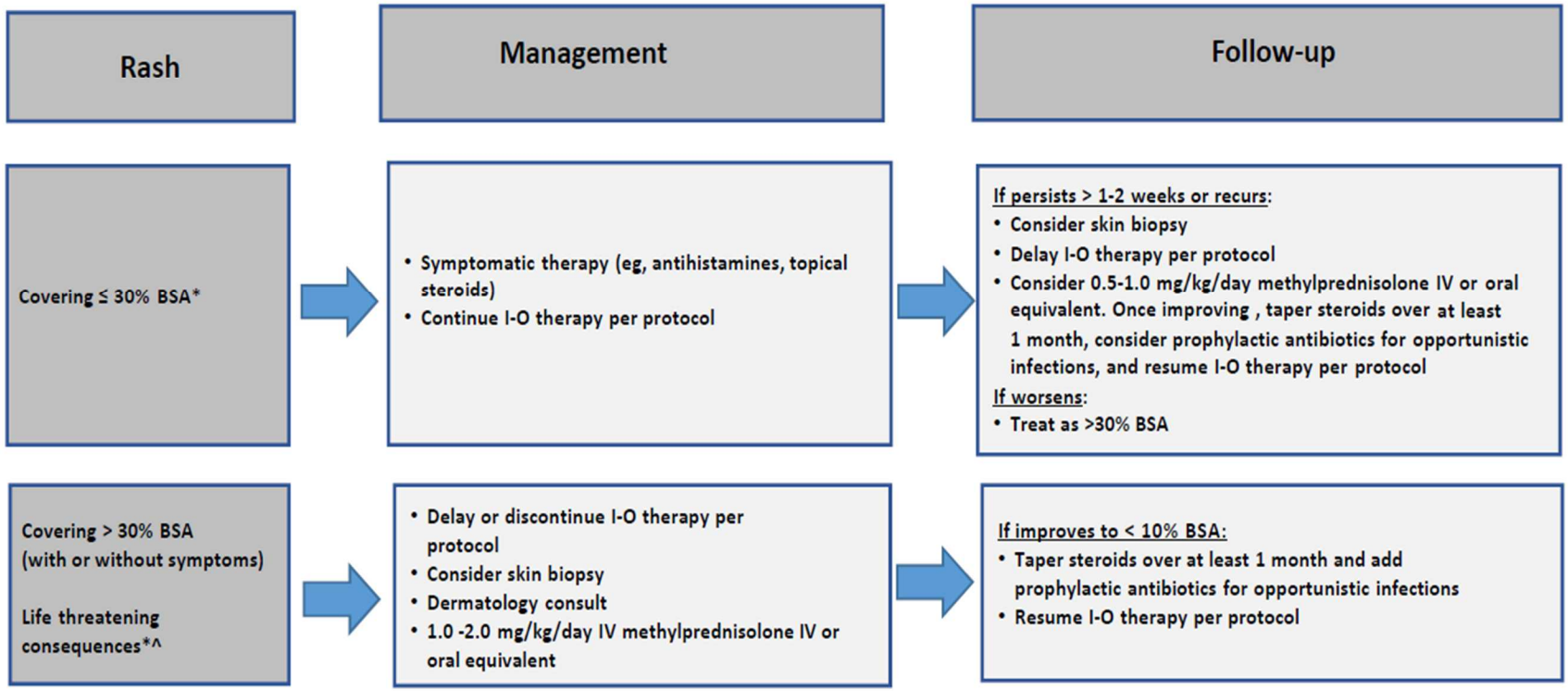


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

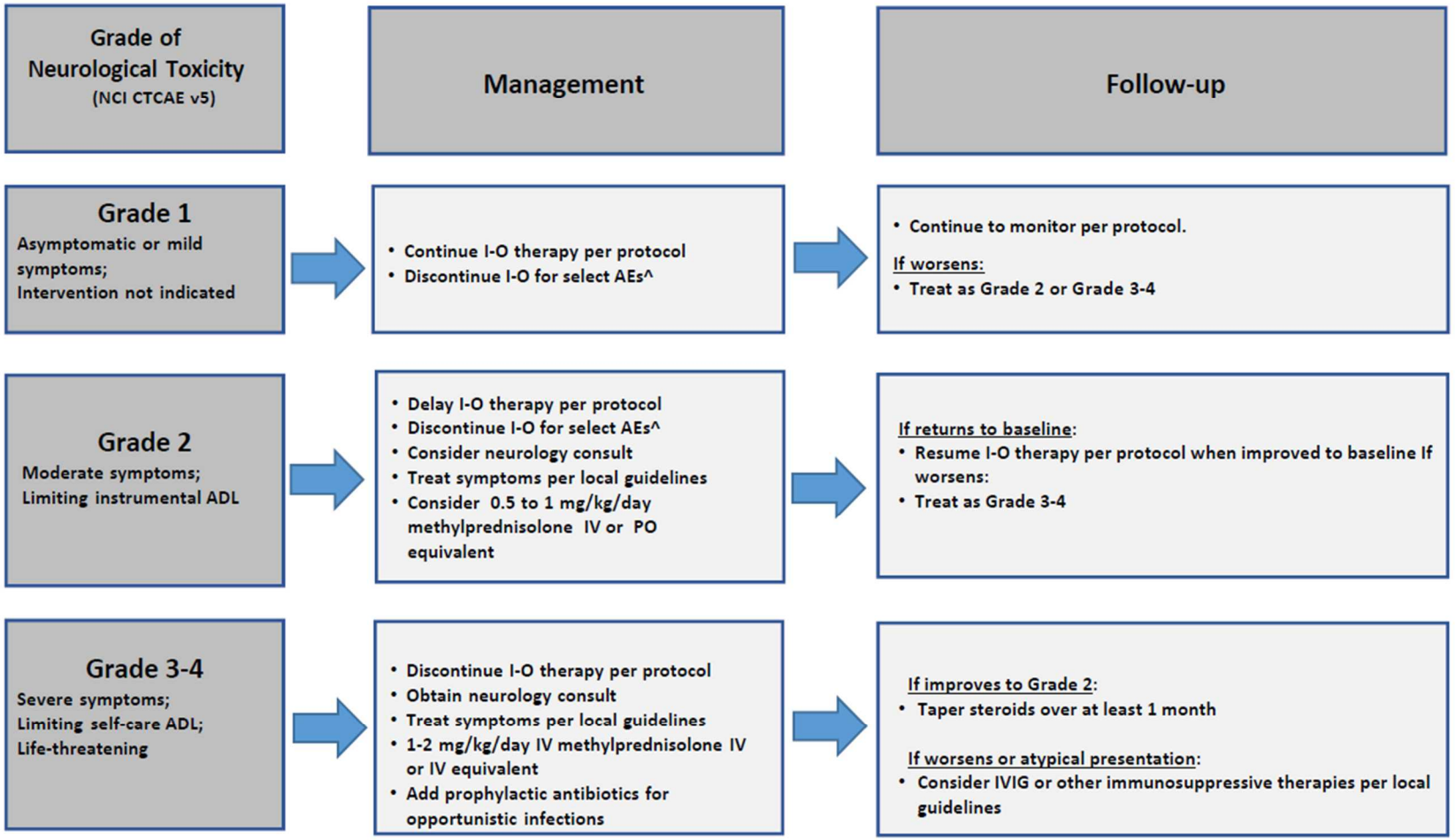
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^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.



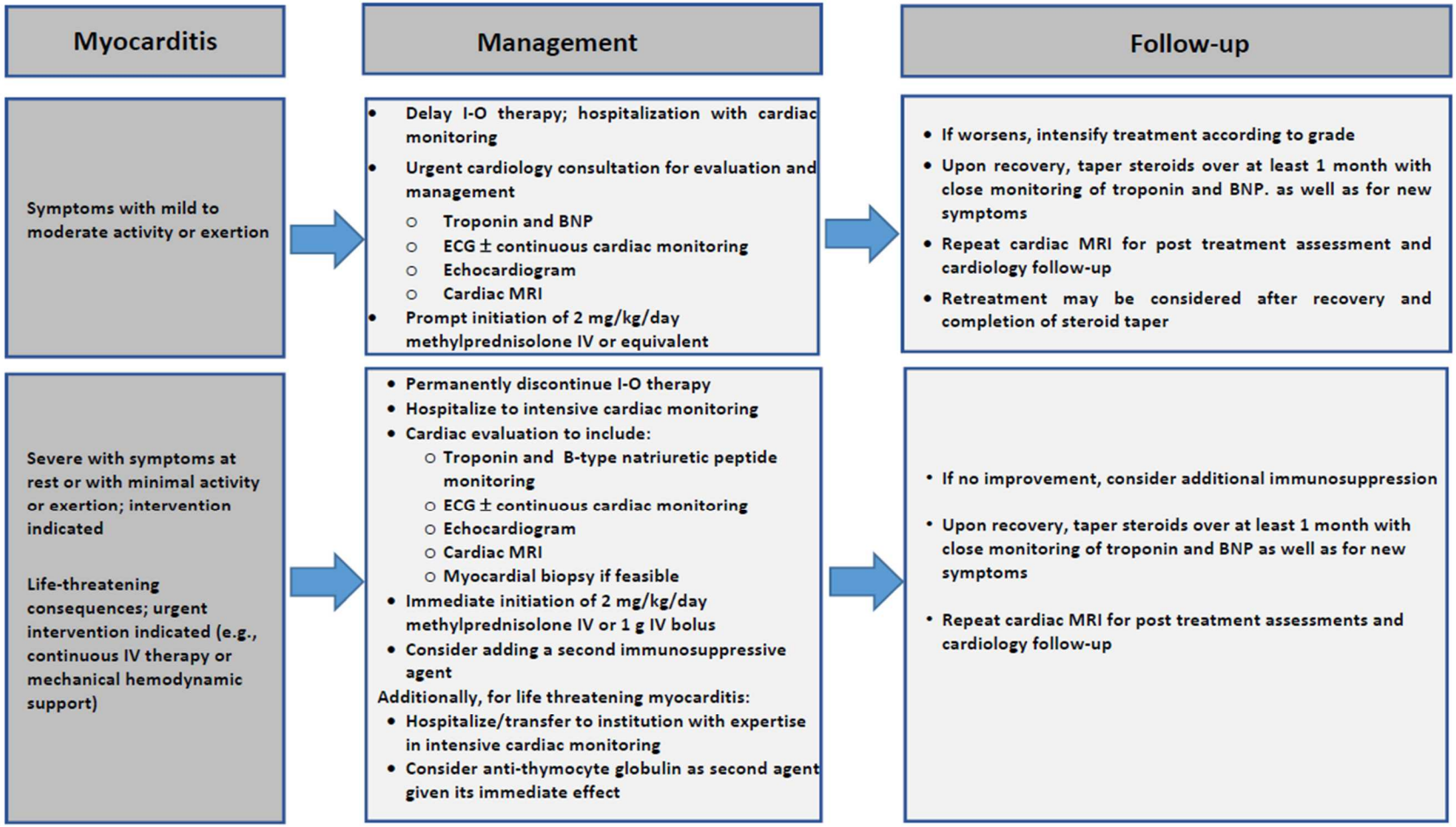
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



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 CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM *PER PROTOCOL AMENDMENT 04 NO LONGER APPLICABLE.

The table below provides a management algorithm for possible signs/symptoms of CVA for participants treated with the combination of bempegaldesleukin with a checkpoint inhibitor. This general guideline constitutes guidance to the Investigator and may be supplemented by clinical judgement 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 as 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: • Discontinue study treatment for participants receiving bempegaldesleukin in combination with a checkpoint inhibitor (ie, nivolumab).
2	Neurology consultation recommended.
3	Perform pertinent laboratory assessments including coagulation (D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine) [redacted], 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.

APPENDIX 8 CYTOKINE RELEASE SYNDROME (CRS) MANAGEMENT ALGORITHM *PER PROTOCOL AMENDMENT 04 NO LONGER APPLICABLE.

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% O2	• 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.

APPENDIX 9 DEFINITIONS OF AJCC TNM

The American Joint Committee for Cancer (AJCC) TNM Staging System is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

Adapted from Amin, M.B., Edge, S., Greene, F., Byrd, D.R., Brookland, R.K., Washington, M.K., et al. (Eds.) (2017). AJCC Cancer Staging Manual, 8th Edition. Switzerland:Springer International Publishing.

Table 1: Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma *in situ*: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

Table 2: Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac or sacral lymph node
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac or sacral lymph node metastasis
N3	Lymph node metastasis to the common iliac lymph nodes

Table 3: Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastasis

APPENDIX 10 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[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

Abbreviations: 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

Abbreviations: 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

Abbreviations: 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.

REFERENCE:

[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 11 COUNTRY SPECIFIC REQUIREMENTS

Any Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

Original Language/Section Number	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 2)j	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 12 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 03, 26-Aug-2021

Revisions made to include the addition of participants with high-risk urothelial carcinoma (UC) of the bladder with N1 disease and muscle-invasive bladder cancer (MIBC), addition of nivolumab + bempegaldesleukin vs nivolumab secondary endpoint comparisons, and the updated alpha allocation for the pathologic complete response (pCR) and event free survival (EFS) primary endpoints. Additional revisions made to align with Nivolumab and Bempegaldesleukin program standards. Other updates have also been made to align with changes to safety assessments including safety management algorithms. Guidance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) status as well as coronavirus disease 2019 (COVID-19) vaccine has also been included. This amendment incorporates the changes from the approved Administrative Letter 03.

Revisions are applicable to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Revised to include the National Clinical Trial (NCT) Number and Universal Trial Number (UTN) • Updated study contact information • Updated study title to include bempegaldesleukin • Bristol-Myers Squibb locations updated	To provide current information for the study
Synopsis	Updated synopsis to match relevant protocol revisions	Reflect changes in protocol body as summarized below
Table 2-1 Screening Procedural Outline	Notes section updated for: Informed Consent, UC of the bladder/MIBC Confirmation, Tumor Sample Submission, Oral Hydration Follow-up (Arm A only), Adverse Event (AE) and Serious Adverse Event (SAE) Assessments, Concomitant Medication Use, Clinical Laboratory Testing	To provide consistency
	• Updated Medical History notes to include T1 stage • Clarified staging to include N0, N1, or M0	Revised to incorporate updates to patient population
	Body Imaging notes updated to 35 days (from 28 days) prior to randomization	To provide clarification and increase the body imaging window at screening
	• Added UC of the bladder to MIBC Confirmation	Revised to incorporate updates to patient population

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Added Tumor Tissue Assessment procedure	
	Updated Prior and Concomitant Medication Review/Use	Include vaccine use
Table 2-1 Screening Procedural Outline Table 2-2 Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B) Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B) Table 2-5 Study Assessments - Arm C	Added "Measurements, Vital Signs, and Performance Status" to Physical Examination	To provide clarification
Table 2-2 Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B)	• Updated Cycle 2 and 3 to include "Day 3-5" • Updated Day 8 to include -1 day window • Updated Clinical Laboratory Testing procedure to include Day 8 collection; updated Notes to include instruction on when to repeat testing	Revised to align with language for BMS program updates
	• Concomitant Medication Use added note to record at each visit • Added note to complete [redacted] assessments within 14 days prior to radical cystectomy (RC)	To provide clarification
	Body Imaging updated from "within 4 weeks of completion of last dose of neoadjuvant therapy" to "after completion of last dose"	Revised to provide flexibility of scheduling procedures as well as provide clarification
	Deleted footnotes: • "All participants are required to have a visit at 60-90 days after RC to collect data related to RC and imaging is required at this visit. Participants who do not undergo RC for reasons other than disease progression, they may start their planned post-surgical treatment	Updated to provide clarification and align with Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	following the first post-baseline tumor assessment." • "If patients are dosed on a Thursday, Day 3 procedures may be done on Day 2" • "Arm A only"	
Table 2-2 Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)	Oral Hydration Follow-up notes: added instruction for sites to document the results of discussing hydration guidelines with participants	Added clarification on expectations for hypotension and syncope mitigation
Table 2-2 Pre-surgery (Neoadjuvant) Procedures and Assessments (Arm A + Arm B) Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B) Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B) Table 2-5 Study Assessments - Arm C Section 3.3.3 Bempegaldesleukin and Nivolumab Benefit and Risk Assessment Section 7.4.1 Nivolumab and Bempegaldesleukin Dose Delay, Resume, and Discontinuation Criteria	[redacted] • AE and SAE Assessments: added SARS-CoV-2 language • Updated to include benefit and risk considerations if participants had COVID-19 • Added criteria for delaying treatment in case of SARS-CoV-2 infection	Participant safety management due to COVID-19
Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B)	• Updated post-surgery adjuvant Cycle 1 "120 days" to "60 to 120 days" • Updated Notes header to delete "If a dose is delayed, then the procedures associated with that visit are delayed (with the exception of tumor assessments), which should continue per schedule;" added reference to footnote "d" to table column headers	To provide clarification

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Concomitant Medication Use added note to record at each visit • Cystoscopy notes updated to include information for participants who do not undergo RC • Added note for Clinical Laboratory Testing to include reference to Section 9.4.7 • Updated Body Imaging language to include RC; clarified tumor assessment frequency • Updated footnote "b" to clarify RC or cystoscopy • Footnote "e" added for participants who do not have RC	
	• Cystoscopy language updated to include window for monitoring disease recurrence (every 12 weeks ± 7 days and every 24 weeks ± 14 days) • Updated footnote "c" to include windows	Revised to provide flexibility of scheduling procedures as well as provide clarification
	Moved Submission of Tissue for pCR procedure [redacted] to Efficacy Assessments	For clarification of the two tissue collections occurring at the same time point
Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B) Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B) Table 2-5 Study Assessments - Arm C Section 5.1.2.2 Surgery (Radical Cystectomy)	• Clarified that maximal transurethral resection of bladder tumor (TURBT) to be performed at the time of the first cystoscopic examination (instead of first "on treatment" cystoscopy) • Added language on when monitoring should begin for participants who do not undergo RC	To provide clarification
Table 2-3 Post-surgery (Adjuvant) Procedures and Assessments (Arm A and Arm B) Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B) Table 2-5 Study Assessments - Arm C	Added window of ± 7 days for completion of [redacted] assessments	Revised to provide flexibility of scheduling procedures as well as provide clarification

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B)	• Updated Notes for AE Assessments • Concomitant Medication Use added note to record at each visit; removed collection at Survival Follow-up Every 3 months • Updated "CBC w/Differential, Chemistry Panel, Endocrine Testing" to "Clinical Laboratory Testing" • Pregnancy Test updated to specify serum or urine and requirements	To provide clarification
	Added Survival Status to Efficacy Assessments	Revised to align with most recent language for BMS program updates
	Updated Body Imaging notes from every 24 weeks ± 1 week to 2 weeks; specified maximum of 5 years "from the date of randomization"	To provide clarification and flexibility of scheduling
	Cystoscopy language updated to include window for monitoring disease recurrence (every 12 weeks ± 7 days and every 24 weeks ± 14 days)	Revised to provide flexibility of scheduling procedures as well as provide clarification
	Deleted footnote that stated "Including details on subsequent therapy such as start and stop dates, best response, date of progression"	Removed duplication of information included in the Notes section
Table 2-5 Study Assessments - Arm C	Updated Notes for Concomitant Medication use to record at each visit	To provide clarification
	Updated SAE Assessment to be performed continuously "until 100 days from RC"	To provide clarification for SAE collection for Arm C participants
	• Body Imaging language updated to include RC, clarified tumor assessments frequency [redacted]	To provide clarification
	Cystoscopy language updated: • To include window for monitoring disease recurrence (every 12 weeks ± 7 days and every 24 weeks ± 14 days) • To add "for reasons other than progression"	• Revised to provide flexibility of scheduling procedures as well as provide clarification • To provide clarification

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added note to complete [redacted] assessments within 14 days prior to RC	To provide clarification for completing [redacted] assessment
Table 2-4 Long-term Follow-up Assessments (Arm A and Arm B) Table 2-5 Study Assessments - Arm C	Notes updated for Subsequent Anti-cancer Therapy	Revised to align with most recent language for BMS program updates
Section 3 Introduction	Included updated tumor staging system groups	Provided further clarification
	Updated description of this study to include participants with UC of the bladder	Revised to align with updated patient population
Section 3.2.1 Epidemiology/Indication	• Updated background on patients with bladder cancer • Updated Management of UC, including MIBC section to include UC of the bladder information • Added results from CheckMate-274 study	More recent dataset
Section 3.2.3 Bempegaldesleukin	• Updated references • Updated clinical experience data with data from final database locks	Updated references to reflect final publications
Section 3.2.4.1 Study 15-214-01 (EXCEL; Bempegaldesleukin Monotherapy)	• Added text to clarify bempegaldesleukin dose of 0.006 mg/kg was tolerated well and that the MTD was determined to be 0.009 mg/kg • Deleted management guidelines to mitigate the risk of hypotension	Revised to align with most recent language for BMS program updates
	Provided additional information on best overall response for 28 patients evaluated in Study 15-214-01	More recent dataset
Section 3.2.4.2 Study 16-214-02 (PIVOT-02; Bempegaldesleukin and Nivolumab Combination Therapy)	• Replaced Oct-2018 data with Oct-2020 data for PIVOT-02 study • Updated tumor response to include data from Jan-2019	More recent dataset
	Updated to include text on serious events of cerebrovascular accident (CVA)	Revised to align with most recent language for BMS program updates
Section 3.2.4.3 Pooled Safety Analysis of Participants with Bempegaldesleukin and Nivolumab Exposure	Section added; as a result of the added section, the following section was re-numbered	Revised to align with language for BMS program updates

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.4.4 Observed Events of Cerebrovascular Accident	Updated to include section on initial and updated analysis of CVA accidents in PIVOT-02	Added and updated data and information to align with Bempegaldesleukin Investigator's Brochure (IB) v9
Section 3.3.3 Bempegaldesleukin and Nivolumab Benefit and Risk Assessment	Sentence added regarding benefit and risk considerations for COVID-19	Participant safety management due to COVID-19
	Added non-live COVID-19 vaccination text	Address [redacted] for the benefit-risk of COVID-19 vaccination during participation in the clinical trial
[redacted]		
Section 4 Objectives and Endpoints Section 9.1.1.3 Definition of pCR Table 10.3-1 Efficacy Analyses	Pathologic complete response definition updated from "T0, N0, M0" to "T0, N0"	Updated to remove M0 from definition
Section 4 Objectives and Endpoints	• Primary and secondary objectives updated to add "in all randomized participants," where applicable • Updated the secondary objective to compare the pCR rate of neoadjuvant nivolumab monotherapy to standard of care to delete "at the time of surgery" [redacted]	To provide clarification
	Added secondary objectives and endpoints to evaluate (descriptively) the pCR rate and EFS of neoadjuvant nivolumab + bempegaldesleukin versus neoadjuvant nivolumab followed by adjuvant nivolumab in all randomized participants	Better comprehend final study results
	[redacted]	
Section 5.1 Overall Design Figure 5.1-1 Study Design Schematic	Include updated stratification factors, added high-risk UC of the bladder to the patient population in the study design	T1-T4aN1 (high-risk UC of the bladder) participants were added to the study design

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Figure 5.1-1 Study Design Schematic	Study schematic updated from "Muscle invasive/resectable urothelial carcinoma" to "High-risk UC/muscle-invasive/resectable bladder cancer"	To provide clarification
Section 5.1.1 Screening Period	Updated text to specify tissue sample requirements prior to randomization	To provide clarification
Section 5.1.2.2 Surgery (Radical Cystectomy)	Updated text to specify timing of RC for participants in Arms A, B, and C	To provide clarification
	Updated text for pathology slides to include hematoxylin and eosin (H&E) and relevant immunohistochemistry (IHC)	
	Cystoscopy language updated to include window for monitoring disease recurrence (every 12 weeks ± 7 days and every 24 weeks ± 14 days)	Revised to provide flexibility of scheduling procedures as well as provide clarification
Section 5.1.2.3 Adjuvant (Post-surgical Treatment)	• Updated post-surgery adjuvant Cycle 1 "120 days" to "60 to 120 days"	To provide clarification
Section 5.1.4.1 Blinded Pathology and Radiology Review	• Added text to clarify that stained slides from the initial TURBT will be used to clinically diagnose UC of the bladder/MIBC • Updated radiology review text	To provide clarification
Section 5.3 End of Study Definition	• Updated final analysis for primary endpoint pCR to 47 months from 36 months • Updated final analysis for primary endpoint EFS to 65 months from 54 months	Revised study accrual projections
Section 5.4 Scientific Rationale for Study Design Section 5.4.2 Rationale for Study Comparator and Study Population	Added N1 stage to these sections	Added participants with high-risk UC of the bladder; addition of the N1 stage
Section 5.4 Scientific Rationale for Study Design	Updated recurrence rate for patients diagnosed with UC	More recent dataset
Section 5.4.2.2 Rationale for Including Participants with N1 in Bladder Cancer	Added section	Addition of the N1 stage
Section 5.4.5 Rationale for Stratification by Disease State and PD-L1 Section 7.2 Method of Treatment Assignment	Updated clinical stage stratification factors	Revised to align with updated patient population

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria	Revised inclusion criteria 2)a with 2)g and 2)c with 2)h	To provide clarification
	Revised inclusion criteria 3)g)iv with 3)g)ix, 3)g)v with 3)g)x, 3)g)vi with 3)g)xi, and 3)g)vii with 3)g)xii	Updated contraception requirements for bempegaldesleukin
Section 6.2 Exclusion Criteria	Updated exclusion criterion 1)a with 1)d	Align with updated participant population of high-risk UC
	Added exclusion criteria 2)m and 3)e	Clarify expectations for eligibility for participants with suspected or confirmed symptomatic COVID-19
	Updated exclusion criterion 4)e to not applicable	To provide clarification and remove inconsistency with inclusion criterion 2)f
Section 6.4.1 Retesting During Screening Period	Added COVID-19 language	Clarify expectations for retesting for participants with suspected or confirmed symptomatic COVID-19
Table 7-1 Study Treatments for CA045009/18-214-13	Updated to include available presentations of bempegaldesleukin	Include potency for commercial supply of bempegaldesleukin
	Deleted footnote “0.65 mg to be available only after local CMC regulatory requirements are fulfilled per region”	To provide clarification
Section 7.1.1 Bempegaldesleukin Dosing	Added sentence "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."	Revised to align with most recent language for BMS program updates
Section 7.1.1.1 Hydration Guidelines Section 7.6 Treatment Compliance	Added text to instruct participants on hydration and when to contact the treating oncologist	Added clarification on expectations for hypotension and syncope mitigation
	Updated to include instruction for sites to document the results of discussing hydration guidelines with participants	
Section 7.1.1.1 Hydration Guidelines	Deleted last sentence “Advise participants with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration.”	Removed duplicate text in section
Section 7.1.2 Nivolumab Dosing	Added sentence "In the event that bempegaldesleukin is permanently discontinued due to toxicities, see Section 8.1.1."	Revised to align with most recent language for BMS program updates

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Deleted "Nivolumab treatment can continue for participants randomized to NKTR-214 and nivolumab combination arm in the event that NKTR-214 is permanently discontinued due to toxicities, as noted above"	Removed duplicate text in section
Section 7.2 Method of Treatment Assignment	Added statement regarding new randomization schedule for participants with clinical stage T1-T4aN1M0	New randomization list needed for N1 participants
Section 7.4 Dosage Modification	Added second sentence in first paragraph	Revised to align with most recent language for BMS program updates
	Added last sentence to reference discontinuation criteria in Section 8.1.1	To provide clarification
Section 7.4.1 Nivolumab and Bempegaldesleukin Dose Delay, Resume, and Discontinuation Criteria	Updated section title	Revised to align with most recent language for BMS program updates
	Updated section to include statement regarding development and updating of management algorithms	Updated study treatment dose delay, resume, and discontinuation criteria to align with the current CTCAE v5 and to align with Bempegaldesleukin IB v9 and Nivolumab IB v19 Addendum 01
	Added: • Table 7.4.1-1 Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin • 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)	
	Added SARS-CoV-2 infection and COVID-19 vaccine language	Participant safety management due to COVID-19
	Updated to include corticosteroid taper text	Revised to align with most recent language for BMS program updates
Section 7.4.1.1 Dose Modification Criteria for Bempegaldesleukin and Nivolumab for Cycle 1 AST/ALT Elevations	Removed “Grade 2” and “Grade 3” sub headers	Revised to bridge bempegaldesleukin and nivolumab protocol updates to align with CTCAE v5 language
	Updated “Grade 0-1” to “Grade 1 or baseline”	
Section 7.4.3 Monitoring and Management of	Updated last sentence to specify that bempegaldesleukin may need to be withheld and participant should be treated as	Revised to align with most recent language for BMS program updates

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Bempegaldesleukin-induced Eosinophilia	clinically indicated, if participant is suspected to have hypereosinophilic syndrome	
Section 7.4.5 Criteria to Resume Bempegaldesleukin and/or Nivolumab	Section was deleted. As a result, the following sections were re-numbered.	Revised to align with Table 7.4.1-1
Section 7.4.6 Management Algorithms for Immuno-oncology Agents	Added reference to CVA and cytokine-release syndrome (CRS) management algorithms	Revised to align with most recent language for BMS program updates
Section 7.4.6.1 Management Algorithm for Cytokine-release Syndrome	Section added	To align with Bempegaldesleukin IB v9 on the management of this potential risk
Section 7.4.7 Treatment of Bempegaldesleukin-related or Nivolumab-related Infusion Reactions	Added text “Subsequent infusions may be administered at a reduced rate (eg, 50% of the original infusion rate)” for Grade 1 and Grade 2 symptoms	To align with Bempegaldesleukin IB v9
Section 7.7.1 Prohibited and/or Restricted Treatments	Added language for COVID-19 vaccines	Participant safety management due to COVID-19
Section 7.7.1.1 Effect of Bempegaldesleukin on PK of Concomitant Medications	Clarified effect of bempegaldesleukin on pharmacokinetics of concomitant medications	To align with Bempegaldesleukin IB v9
Section 7.7.2.3 Blood Pressure Precautions	Updated text for alpha-blockers	Revised to align with most recent language for BMS program updates
	Clarified that antihypertensive medications may be reinstituted "at any time" as clinically indicated for bempegaldesleukin	
Section 8.1 Discontinuation from Study Treatment	Replaced bullet point for “Disease progression” with “EFS event as defined in Section 9.1.1”	To provide clarification
Section 8.1.1 Nivolumab and Bempegaldesleukin Discontinuation Criteria	Updated to remove redundant criteria listed in Table 7.4.1-1	Revised to bridge bempegaldesleukin and nivolumab protocol updates to align with CTCAE v5 language
Section 9.1.1 Definition of Events in EFS	Removed references to BICR confirmation	Clarification that primary EFS analysis will be based on BICR assessment and analysis by investigator will be conducted as a sensitivity
	Updated definition for carcinoma in situ	To provide clarification
Section 9.1.1.1 Definition of Disease Recurrence	Updated window for first post-surgery assessment from "120 days" to "60 to 90 days" after RC	Revised to provide flexibility of scheduling procedures as well as provide clarification

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Definition of new lymph node updated to include "growth of ≥ 5 mm"	To provide clarification
Section 9.1.1.2 Definition of Disease Progression	Updated first sentence to clarify RECIST v1.1 should be used to evaluate disease progression	To provide clarification
Section 9.1.2.2 BICR Confirmation of Progression or Recurrence	Added statement regarding events that require BICR confirmation	To provide clarification
	Updated language on unequivocal disease progression/recurrence	
[redacted]		
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Added collection for AEs related to SARS-CoV-2	Participant safety management due to COVID-19
	Updated language to specify SAE collection for Arm C participants	To provide clarification
Section 9.2.2 Method of Detecting AEs and SAEs	Added language for collection of AEs following radical cystectomy	To provide clarification
Section 9.2.3 Follow-up of AEs and SAEs [redacted]	Added SARS-Cov-2 language	Participant safety management due to COVID-19
Section 9.2.5 Pregnancy	Updated first sentence of last paragraph to remove instructional text that was inadvertently included in Revised Protocol 01	Removal of model document instructional text
Table 9.4.7-1 Clinical Safety Laboratory Assessments	Updated "Fasting glucose" to "Glucose"	Revised to align with most recent language for BMS program updates
	Added table note for urinalysis	To provide clarification
[redacted]		

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1: Sample Size Determination	• Updated accrual projection for study • Updated final analysis of OS from 74 months to 86 months after study start	Revised study accrual projections
	• Updated 2-side alpha for pCR from 0.015 to 0.001 and EFS from 0.035 to 0.049 • Updated pCR rate for experimental arm from 30% to 36%; updated power for control arm from 81% to 90% • Updated 2-sided power for pCR from 81% to 90%; updated overall significance level from 0.015 to 0.001 • Updated EFS power from 85% to 88% and type I error from 0.035 to 0.049 • Updated boundary for statistical significance superiority from 0.006 to 0.01 for first interim analysis of EFS endpoint • Updated boundary for statistical significance superiority from 0.018 to 0.026 for second interim analysis of EFS endpoint • Updated boundary for statistical significance superiority from 0.029 to 0.04 for final analysis of EFS endpoint • Updated power from 85% to 88% and type I error from 0.035 to 0.049 for OS events	Updated statistical design to adjust alpha allocation between pCR and EFS endpoints [redacted]
	Added text about MRC/EORTC BA06 Phase 3 study	To provide clarification

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 10.1-1: Sample Size Calculations per Comparison for Primary Endpoints	• Updated Accrual Duration, pCR final/EFS Interim Analysis 1, EFS Interim Analysis 2, and EFS Final Analysis	Revised study accrual projections
	• Updated power from 81% to 90% for pCR and 85% to 88% for EFS • Updated Alpha from 1.5% to 0.001 for pCR and 3.5% to 0.049 for EFS • Updated Hypothesized Rates Control vs Experimental from 30% to 36% for pCR	Updated statistical design
Section 10.3: Statistical Analysis	• Removed "including subgroups of age, gender and race" from first sentence • Updated overall 2-sided alpha for pCR from 0.015 to 0.001 and EFS from 0.035 to 0.049 • Added hierarchical testing approach to control type I error rate for pCR, EFS, and OS • Removed sentence "Further details on the methodology and testing strategy for the control of the type I error rate (including OS endpoint) will be described in the statistical analysis plan."	Updated statistical design
	Updated clinical stage stratification factors	Revised to align with updated study design
	Added language regarding no planned formal powered comparison of Arm A vs Arm B	To provide clarification
Table 10.3-1: Efficacy Analyses	Updated CI to include 99.9% for Cochran Mantel Haenszel test	Updated statistical design
	• Removed reference to BICR assessment for EFS endpoint • Added text to clarify EFS Statistical Analysis Method to include BICR and investigator assessments	Clarification that primary EFS analysis will be based on BICR assessment and analysis by investigator will be conducted as a sensitivity
	Added secondary endpoints to include pCR in Arm A vs Arm B and EFS in Arm A vs Arm B	Secondary objectives added to better comprehend the final study results
Figure 10.3-1: Graphical Representation of the Statistical Testing Approach	Added graphical representation of the statistical testing approach	Updated statistical design

Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 10.3.3-1 Interim Analyses Schedule	Updated Projected Timing column for all analysis time points	Revised study accrual projections
Section 11 References	Updated references to remove duplicates in section and throughout protocol	Remove duplicate references
Appendix 2 Study Governance Considerations	Updated first paragraph in Monitoring section to include remote monitoring	To provide clarification
	Added new subsection on dissemination of study data	
Appendix 6 Management Algorithms	Updated the immuno-oncology (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	Updated CVA management algorithm	To clarify CVA and TIA algorithms and to align with Bempegaldesleukin IB v9
Appendix 8 Cytokine Release Syndrome (CRS) Management Algorithm	Added new appendix for CRS management algorithm. As a result, the following appendices were re-numbered.	Added new Appendix and align with Bempegaldesleukin IB v9
Appendix 11 Country Specific Requirements	• Updated sentence to “Any countries where exclusion of” • Corrected exclusion criterion referenced in table	To provide clarification
	Removed “Discontinuation of treatment due to pregnancy” row	Protocol has stricter language
All	Updated NKTR-214 to bempegaldesleukin	Revised to align with most recent language for BMS program updates
All	Minor typographical errors were corrected, and edits were made for consistency and clarity	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 02, 05-Mar-2020

Revisions made to include CVA mitigation. Additional revisions made to align with Nivolumab and NKTR-214 essential protocol elements updates. Revisions are applicable to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated synopsis	Reflect changes in protocol body as summarized below
Section 2: Schedule of activities	Specificity added to body imaging language Removed "60-90 days after RC" in Table 2-4 Long-term Follow-up Assessments Updated MIBC confirmation to include H&E and/or IHC stained slides Updated Table 2-2: Day 8 [redacted] Arm A	Clarification
Tables 2-2, 2-3: Oral hydration follow-up Section 7.1.1.1: Hydration guidelines Section 7.6: Treatment compliance	Updated to include hydration compliance contact	CVA mitigation
Tables 2-4, 2-5: Subsequent therapy	Added notes to subsequent therapy	Revised to align with most recent language for BMS program updates
Tables 2-2, 2-3: Clinical laboratory testing	Added language to include renal function assessment	Safety and clarifications
Section 3: Introduction	Replaced "NKTR-214" with "bempegaldesleukin" where applicable	Revised to align with most recent language for BMS program updates
Section 3.2: Background	Updated NKTR-214 mechanism of action Updated clinical experience with NKTR-214 Added observed events of cerebrovascular accident in PIVOT-02 study	More recent dataset
Section 3.3: Benefit-risk assessment	Updated NKTR-214 safety profile language Updated NKTR-214 and nivolumab benefit and risk assessment	More recent dataset
[redacted]		

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.1: Overall design	Updated Figure 5.1-1 Study design schematic	Visual clarity of study design schematic
Section 5.1.2: Treatment period	Updated details for diagnostic slides in surgery (RC) section	Clarification
Section 5.1.4.1: Blinded Pathology and Radiology Review	Language added in Pathology Review	Clarification
Section 5.2: Number of participants	Updated screen fail rate from 20 to 25%	More recent dataset
Section 5.3: End of study definition Section 5.4.3: Rationale for choice of endpoints	Removed reference to "co-primary" terminology	Reflect update [redacted]
Section 5.4.5: Rationale for stratification by disease state and PDL-1	Updated stratification from "pT2 vs pT3/T4a" to "clinical stage (T2 vs T3/T4a)"	Clarification
Section 6: Study population	Updated age and reproductive status	Revised to align with most recent language for BMS program updates
Section 6.2: Exclusion criteria	Updated to remove "or UC not confined to the bladder" in exclusion 1c Added CVA exclusion criteria Added adrenal insufficiency exclusion	Correction of typographical error CVA mitigation Safety and clarification
Section 7	Updated study treatments table Updated "pharmacy reference sheet" to "pharmacy manual" Updated NKTR-214 dosing	Clarification
Section 6.3: Lifestyle restrictions	Updated text to state "strenuous activities" and "long, hot showers"	CVA mitigation and IB update

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1: Treatments administered	Updated hydration guidelines	
Section 7.2: Method of treatment assignment	Updated to reference Appendix 8 Updated stratification language	Clarification
Section 7.4: Dose modification	Added language for nivolumab and NKTR-214 dose delay and reduction criteria Added dose modification criteria for Cycle 1 AST/ALT elevations Added monitoring and management of elevated hepatic transaminases Added monitoring and management of adrenal insufficiency hypophysitis Updated criteria to resume NKTR-214 and/or nivolumab Added myocarditis management algorithm	Safety and clarifications
Section 7.7: Concomitant therapy	Updated prohibited and/or restricted treatments Added effect of NKTR-214 on PK of concomitant medications section Added restricted treatments section Updated blood pressure precautions	CVA mitigation
Section 7.7.2.2: Imaging restriction and precautions	Updated restriction and precautions section	Revised to align with most recent language for BMS program updates
Section 8: Discontinuation criteria	Updated nivolumab and NKTR-214 discontinuation criteria Updated post-study treatment study follow-up	Safety and clarification
Section 9.1: Efficacy assessments	Updated methods of measurements	Clarification
Section 9.2: Adverse events	Updated time period and frequency for collecting AE and SAE information to include AEOSI bullet Added AEOSI section 9.2.7	CVA mitigation
Section 9.2.5: Pregnancy	Removed language about terminated pregnancy	Revised to align with most recent language for BMS program updates
Section 9.2.6: Immune-mediated adverse events	Moved section from 9.2.1 to 9.2.6	Revised to align with most recent language for BMS program updates

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.1: Vital signs and oxygen saturation	Removed "oral" from temperature assessment	Clarification
Table 9.4.7-1: Clinical safety laboratory assessments	Added "or serum urea" to BUN Removed "screening only" from albumin Updated to reference Appendix 10	Clarification
[redacted]		
Section 10.1: Sample size determination Section 10.3: Statistical analyses	Added "2-sided" to alpha Updated text for EFS interim analyses to remove "upper tract tumor recurrence"	Clarification
Table 10.2-1: Analysis populations	Added language to description of all treated participants	Clarification
Section 12: Appendix 1	Added definitions of AEOSI, ASCO, DOAC, DWI, EOI, H&E, IB, INR, LFT, LMWH, NKTR-214, TSH	Clarification
Section 12: Appendices	Updated study governance considerations (Appendix 2) Updated women of childbearing potential definitions and methods of contraception (Appendix 4)	Revised to align with most recent language for BMS program updates

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Updated country specific requirements (Appendix 10)	
Section 12: Appendices	Added myocarditis treatment algorithm to Appendix 6 Added Appendix 7: CVA algorithm	Safety; revised to align with most recent language for BMS program updates
Section 12: Appendix 5	Updated appendix title to remove "and Lansky (adolescents)"	Clarification
All	Updated header to replace "pegylated human recombinant Interleukini-2" with "bempegaldesleukin" Moved "NKTR-214" from left to right side of header	Revised to align with most recent language for BMS program updates
All	Re-numbering of sections or appendices due to insertion of additional sections Minor typographical errors were corrected and edits were made for consistency and clarity	Insertion or relocation of sections or appendices in protocol, as mentioned above Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 21-Jan-2019

Revisions made [redacted]. Additional revisions made to align with BMS policy and nivolumab/NKTR-214 program updates. Revisions are applicable 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**
Section 2	Specificity added to pregnancy language	Clarification
Table 2-1 and Section 6.1 Inclusion Criteria Section 5.1 Study Design Section 7.2 Method of Treatment Assignment	Updated language to emphasize receipt of MIBC confirmation prior to randomization added to screening table.	Confirmation of pathologic diagnosis added to ensure enrollment of intended patient population.
Table 2-1 Section 6.1 Inclusion Criteria	Tumor tissues submission criteria "non-evaluable" was removed from previously acceptable PD-L1 classification; "indeterminate/non-evaluable".	Tumor tissue samples must be evaluable Samples have "indeterminate" PD-L1 expression when a sample is otherwise evaluable.
Table 2.1 Screening Section 9.4.3 SoA / ECG	Medical Monitor approval removed for abnormal baseline ECG abnormalities.	Investigator to use existing Inclusion/Exclusion criteria and clinical judgment.
Table 2.2 Treatment SoA	Treatment changed for Cycle 1: (Day 5± 1day) replaced (Day 4-7)	Provide clarification
Table 2-3	Specified "once consent has been obtained" to heading Wording for timeframe to begin Cycle 1 changed from "within 60-120 days to "within 120 days"	Participants who have not completed radical cystectomy, must be reconsented before receiving adjuvant therapy Provide clarification
Clinical Experience Section 3.2.4.2	Updated PIVOT-02 data (07Ma018)	More recent dataset
Section 5.1.4 Data Monitoring Committees	The following sentence was added: "*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*"	Required text for studies involving external committees
Section 5.4.6 Scientific Rationale	Updated rationale for duration of treatment with NKTR-214	Aligned with hypothesized MoA
Section 6.1 Inclusion Criteria	Removed procedural time frames from Inclusion/Exclusion criteria (still	Not necessary to define the population

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	applicable in SoA, e.g. CT within 28 days)	
Section 6.1 Inclusion Criteria	Removed "Life expectancy ≥ 12 weeks	Inclusion criterion deemed irrelevant for this study population
Section 6.1 Inclusion Criteria	Window tissue submission increased from 8-12 weeks	Loosens time frame for archived tissue sample
Section 6.1 Inclusion Criteria	Added text to address fetal protection. Participants still must undergo monthly pregnancy testing Added contraception exception for abstinent WOCBP and removed exception for Azoospermic males	Updated BMS policy addressing WOCBP and Clinical Trials Risk of drug(s) passing into seminal fluid
Section 6.2 Exclusion Criteria	Adjusted arrhythmia criteria	Clinical judgment
Section 7.3 Blinding	Added standard blinding language	To allow limited [redacted] lab personnel to view treatment allocation
Section 7.4.1 Dose Delay	Updated NKTR-214 dose delay criteria	[redacted]
Section 7.4.3 Resumption	Added criteria to resume NKTR-214 and/or Nivolumab from Nivolumab program language. Added: ***Grade ≥3*** adrenal insufficiency requires discontinuation.	Clarification
Section 7.4.5 Infusion Reactions	Removed mandatory Medical Monitor contact for Grade 3+ infusion reaction	Clinical judgment and generally covered by 24 hour SAE reporting
Section 7.6 Compliance	Added compliance language	Standardization
Section 7.7.2.2 Blood Pressure Precautions	"5-10 days" to restart hypertensive medications was replaced with "as clinically indicated"	Clinical Judgement
Section 8.1.1 Discontinuation Criteria	Specified: ***Grade ≥ 3*** *adrenal insufficiency requires discontinuation regardless of control with hormone replacement* Removed mandatory Medical Monitor approval for partial discontinuations	[redacted] to specify dosing interruptions permission Clinical Judgement
Section 8.1.2 Post Treatment Follow-up	Added text to take into account roll-over studies	Allow continuation into roll-over study when applicable
Section 9.2.1 Immune-Mediated AEs	Added imAE language aligned with Nivolumab program and NKTR-214 select AE language	Specifies additional data may be collected

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.6 Pregnancy	Text added to address fetal protection Removed mandatory discontinuation (i.e. if pregnancy has ended)	Updated BMS policy
Section 9.2.8 DILI	Adjusted DILI definition	To account for patients with baseline transaminase elevations
Section 9.3 Overdose	Added overdose definition	To align with appendix update
Section 10 Number of Participants	Number of participants changed from 160 to 180	Typo corrected; 180 is correct number
Appendix 3 Adverse Events	Text added to AE definition of events not meeting the AE definition: *Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.* The following paragraph was removed from definition of SAE: *Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).*	Correction made; text inadvertently dropped from previous version Not applicable for oncology studies; only applies to protocols with endpoints that are excluded from regular reporting as SAE's.
Appendix 4 WOCBP	Replaced with nivolumab program specific appendix	Alignment
Appendix 9 Country Specific	Added appendix for HIV testing	Required appendix based on Nivolumab program; inadvertently left out of previous version