Official Title of Study:

Phase 1/2 Study of Bempegaldesleukin in Combination with Nivolumab in Children, Adolescents, and Young Adults with Recurrent or Refractory Malignancies (PIVOT IO 020)

PROTOCOL CA045-020

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CLINICAL PROTOCOL CA045020/19-214-27

Phase 1/2 Study of Bempegaldesleukin in Combination with Nivolumab in Children, Adolescents, and Young Adults with Recurrent or Refractory Malignancies (PIVOT IO 020)

Short Title:

Bempegaldesleukin + Nivo in Pediatric Malignancies

Protocol Amendment 01

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	28-Nov-2021	[redacted] • Updated flat dosing schema in Part A to include weight-based cohorts (A2F-W and A3F-W). • Modifications made to align with bempegaldesleukin and nivolumab Investigator's Brochure updates. • Added electrocardiogram assessments. • Added Safety Follow-up Visit 3. • Updated Phase 1 flat dosing de-escalation to age/weight. • Added stopping rules for Part B Expansion • Added suspension criteria for toxicity during Part B Expansion. • Updated study treatment dose delay, resumption and discontinuation, and adverse events management for National Cancer Institute Common Terminology Criteria for Adverse Events version 5. Added permanent discontinuation criteria for bempegaldesleukin treatment related to cerebrovascular accident (CVA) and transient eschemic attack (TIA). Updated CVA management algorithm (Appendix 6). • Updated guidance for severe acute respiratory syndrome coronavirus 2 status and coronavirus disease 2019 vaccine. • Added country specific requirements (Appendix 13) • Added cytokine-release syndrome information and management/algorithm (Appendix 14).
Original Protocol	08-Oct-2020	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

This is a protocol amendment to modify the flat dosing schema in Part A. In Part A, the flat dosing group will now include cohorts (A2F-W and A3F-W) of weight-based dosing of nivolumab 4.5 mg/kg in combination with both bempegaldesleukin 0.006 mg/kg and 0.003 mg/kg, in the event dose-limiting toxicities are observed in the A1F-W cohort of nivolumab 360 mg in combination with bempegaldesleukin 0.006 mg/kg. Stopping rules for Part B Expansion have also been added. Additional revisions have been made to align with nivolumab and bempegaldesleukin Investigator's Brochure (IB) and overall program standards including safety assessments and safety management algorithms. France and Germany country-specific requirements have also been added.

This protocol amendment also includes global changes to reduce redundancies, provide clarifications, and increase readability. The protocol synopsis has been updated accordingly.

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 01

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated title to "Clinical Trial Physician-Medical Monitor" and added Clinical Scientist title and contact information.	To align with updates to study contacts and roles.
Table 2-1: Screening Procedural Outline (CA045020) Section 5.1.1: Screening Period [redacted]	Revised tumor assessment [redacted]: • Moved Cerebrospinal Fluid (CSF) - Solid Tumors, Bone Marrow - Solid Tumors, CSF - Leukemia, Bone Marrow - Solid Tumors, CSF - Leukemia, and Bone Marrow - Leukemia [redacted] to Tumor Assessment row. [redacted]	To provide clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Table 2-2: On-treatment Procedural Outline (CA045020) Section: 9.4.3 Electrocardiograms	Safety Assessments: Added 12-Lead Electrocardiogram (ECG) assessment with the following visits: • Pre-dose Day 1 of all cycles. • Pre-PK blood draw on Cycle 1, Days 3, 5, and 8. • Pre-PK blood draw on Cycle 5, Days 3 and 5. Efficacy Assessments • Added PET-MRI for body imaging [redacted] Health Outcomes • Added clarification regarding time and format (electronic) of Patient-reported Outcomes (PRO) assessment form.	To ensure participant safety and to provide clarification.
Table 2-3: Long-term Follow-up Period (CA045020) Section 5.1.4: Long-term Follow-up Section 9.4.3: Electrocardiograms	Added Safety Follow-up Visit 3, which will occur approximately 150 days from the last dose of study treatment. Added row for 12-lead ECG for Safety Follow-up Visit 1. Added PET MRI to body imaging in Efficacy Assessment. [redacted] Deleted Health Outcomes Section. Added text to footnote "a" for Visit 3 follow-up visit 3 too occur approximately 150 days (± 7 days) from last dose of study drug.	To ensure participant safety and to increase participant convenience.
Section 2: Schedule of Activities	Added or modified text to address and clarify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vaccination during study participation.	Participant safety management due to COVID-19.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.3: Bempegaldesleukin and Nivolumab Benefit and Risk Assessment Section 5.1.2: Treatment Period Section 6.2: Exclusion Criteria (5d) Section 7.4.1: Nivolumab and Bempegaldesleukin Dose Delay, Resumption, and Discontinuation Criteria Section: 7.7.3.1: COVID-19 Vaccination	Guidance added for COVD-19 infection during study for benefit risk and non-live COVID-19 vaccines. Guidance added for investigational COVID-19 vaccines. Exclusion criterion 5) d) revised to previous SARS-CoV-2 infection, suspected or confirmed, within 4 weeks prior to first dose of study drug. Guidance for study drug administration during SARS-CoV-2 infection either suspected or confirmed. Guidance for COVID-19 vaccination during study participation.	
Section 3.2.2: Bempegaldesleukin Mechanism of Action	Updated references.	Updated references to reflect final publications.
Section 3.2.5.1: Study 15-214-01 (EXCEL; Bempegaldesleukin Monotherapy)	Updated text with recent participant clinical experience data and references.	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IB v9.
Section 3.2.5.2: Study 16-214-02 (PIVOT-02; Bempegaldesleukin and Nivolumab Combination Therapy)	Updated with recent participant clinical experience data.	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IB v9
Section 3.2.5.3: Pooled Safety Analysis of Participants with Bempegaldesleukin and Nivolumab Exposure	Newly added section of pooled safety analysis of participants who received bempegaldesleukin and nivolumab.	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IB v9.
Section 3.2.5.4: Observed Events of Cerebrovascular Accident Section 3.2.5.4.2: Updated Analysis of Cerebrovascular Accident Events Observed with Bempegaldesleukin	Modified into subsections and updated analysis of cardiovascular accident (CVA) events.	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IB v9.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.1: Bempegaldesleukin Safety Profile	Updated bempegaldesleukin safety profile.	Updated to align with Bempegaldesleukin IB v9.
Section 3.3.3: Bempegaldesleukin and Nivolumab Benefit and Risk Assessment	Modified text associated with immune-mediated AE's.	To align with most recent language for bempegaldesleukin program updates.
Table 4-1: Objectives and Endpoints	Secondary-Part B Expansion Expanded endpoint to include incidence of toxicity.	To support incorporation of stopping criteria rules.
Section 5: Study Design Section 5.1: Overall Design Figure 5.1-2 Section 5.1.2: Treatment Period Section 5.2: Number of Participants Section 7.1 Treatments Administered	Modified flat dosing schema in Part A, which will now include cohorts (A2F-W and A3F-W) of nivolumab weight-based dosing 4.5 mg/kg in combination with bempegaldesleukin (0.006 mg/kg and 0.003 mg/kg).	Modified to allow for the assessment of appropriate dosing combination in those ≥ 12 years and weighing ≥ 40 kg if safety findings are observed using flat nivolumab dosing.
[redacted]		
Section 5.1.3: Dose-limiting Toxicities Section 9.2: Adverse Events Section 5.1.3.3 Hematologic Dose-limiting Toxicity Section 5.1.3.4: Dermatologic Dose-limiting Toxicity Section 5.1.3.5: Other Dose-limiting Toxicities	Removed text pertaining to the management algorithms for nivolumab and bempegaldesleukin using CTCAE v4 definitions of AE grading. Added clarification that "study drug-related" events will be considered a dose-limiting toxicity (DLT).	To align with nivolumab IB v19 addendum 01. To provide clarity and alignment on the definition of DLT.
Section 5.1.3.6: Stopping Rules for Part B	Added stopping rules for Part B Expansion and Tables 5.1.3.6-1 (Suspension Criteria for Toxicity) and 5.1.3.6-2 (Suspension Probabilities for Toxicity).	To ensure participant safety.
Section 5.2: Number of Participants	Updated the total sample size number of participants from "between approximately 8	To align with updated study design.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	and 228" to "between approximately 10 and 234".	
Section 5.1.5: Data Monitoring Committee and Other External Committees Section 10.3.4: Interim Analyses	Removed reference to Study Steering Committee(SSC).	Removed for clarification.
Section 5.5.2: Justification for Dose of Nivolumab	Flat dosing cohort in Part A has been modified to allow for changing to weight-based dosing with nivolumab.	To support the assessment of appropriate dosing combination in those ≥ 12 years and weighing ≥ 40 kg if safety findings are observed using flat nivolumab dosing.
Section 6.1: Inclusion Criteria	Added text to clarify the following criteria: 2) f) "prior to first dose of study drug". 2) g) clarified for participants with CNS tumors dexamethasone doses should be stable for a minimum of a week. 2) i) "all Grade 2 or higher" for clinically relevant radiation-related toxicities. Information was rearranged within section. Modified: 3) a) i) and 3) b) i) "less than 30 years old". Updated male contraception requirements from 7 months to 3 months: No longer applicable: 3) b) iii), iv), v), and vi) Added 3) b) viii), ix), x), and xi)	To provide clarification and to update contraception requirements for bempegaldesleukin.
Section 6.2: Exclusion Criteria	Added: • 1) d) protocol-specific text for stable anti-hypertensive regimen and clarified antihypertensive medications with 2 drugs. • 1) e) clarified the cardiovascular exclusion • 1) i) excluding CNS tumors • 2) a) clarified on replication incompetent virus vaccines • 3) b) No longer applicable as per this amendment.	To provide clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• 3) i) "Neutrophils < 1000/uL (participants with leukemia or bone marrow infiltration are exempt)".	
Table 7-1 Treatments Administered	Modified table 7.1-1 to include bempegaldesleukin.	To align with most recent language for bempegaldesleukin program updates and. bempegaldesleukin IB v9.
Section 7.1.1: Bempegaldesleukin Dosing Section 7.6: Treatment Compliance	Added text regarding hydration guidelines. Added "at least once" to the frequency that site personnel must contact the participant to remind them of hydration guidelines.	To provide clarification.
Section 7.1.2: Nivolumab Dosing	Added text on weight-based dosing calculation.	To align with most recent language for nivolumab program updates and nivolumab IB v19.
Section 7.4: Dosage Modification and related subsections Section 7.4.1: Nivolumab and Bempegaldesleukin Dose Delay, Resumption, and Discontinuation Criteria Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed) Table 7.4.1-2: Bempegaldesleukin-specific Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one is delayed, both are delayed)	Updated study treatment dose delay, resume, and discontinuation criteria to align with the current CTCAE version (v5). Added Table 7.4.1-1 and Table 7.4.1-2 for nivolumab and bempegaldesleukin AE criteria and subsequent delay, resume, and discontinuation.	To align with nivolumab IB v19 addendum 01.
Section 7.4.3: Monitoring and Management of Eosinophilia	Modified the heading and added subsections: • 7.4.3.1 Bempegaldesleukin-induced Eosinophilia • 7.4.3.2 Eosinophilic Disorders	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IBv9.
Section 7.4.5: Management Algorithms for Immune-mediated Adverse Events and Cytokine-release Syndrome	Section and heading title changed previously was: Management Algorithms for Immuno-Oncology Agents (moved to section 7.4.1)	To align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IBv9.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Updated Subsection 7.4.5.1 Management Algorithms for Immune-Mediated Adverse Events Associated with Immuno-Oncology Agents • Added new subsection 7.4.5.2 Management Algorithm for Cytokine-Release Syndrome.	
Section 7.4.6: Treatment of Bempegaldesleukin-related or Nivolumab-related Infusion Reactions	• Added myalgia and hypersensitivity to list of possible symptoms of infusion reaction with bempegaldesleukin and nivolumab. • Added subsequent infusions may be administered at a reduced rate.	To provide guidance and to align with most recent language for bempegaldesleukin program updates and with Bempegaldesleukin IBv9.
Section 7.7.1: Prohibited and/or Restricted Treatments	Updated the number of days to "150" post last dose for any live/attenuated vaccine during treatment.	To ensure participant safety.
Section 7.7.3.2: Effect of Bempegaldesleukin on Pharmacokinetics of Concomitant Medications	Added text about decreased tolerability to concomitant medication and to reduce the dosage during each cycle of bempegaldesleukin.	To clarify effect of bempegaldesleukin on PK of concomitant medications and to ensure participant safety.
Section 7.7.4.1: Restricted Treatments	Added anticoagulation guidance.	To align with most recent language for bempegaldesleukin program updates.
Section 7.7.4.4: Volume of Blood [redacted]	Newly added section referring to pediatric guidelines manual to meet maximum daily and monthly blood draw limits.	To ensure participant safety.
Section 8.1.1: Nivolumab and Bempegaldesleukin Discontinuation Criteria Section 8.1.2: Treatment Beyond Progression Discontinuation From Study Treatment	• Removed redundant criteria now listed in Table 7.4.1-1. • Added discontinuation beyond progression should be balanced by clinical judgment.	Revised to align with Nivolumab IB 19 Addendum 01 and Bempegaldesleukin IB 9. Also to provide flexibility for discontinuing treatment.
Section 9.1.2.3: Non-Hodgkin Lymphoma	Added PET-MRI	To provide clarification and flexibility for imaging modality.
Section 9.1.2.5: Leukemia	Clarified instructions for samples of CSF and bone marrow aspirate with buccal swab where feasible will be provided in separate laboratory manual. Added: "Response assessment will be assessed using Modified NCCN Criteria for acute lymphoblastic leukemia or Modified Cheson et al International Working Group criteria for acute myeloid leukemia (see Appendix 12)"	For clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.4: Patient-reported Outcomes	• Added that a Caregiver for a child < 7 years, or older participants with a cognitive impairment will complete the Patient Reported Outcomes (PRO). • Added the age-related version of the PRO-CTCAE completed at the start of the trial should be used throughout the treatment period. • Added alternate administration methods may be required if there are exceptional circumstances.	To increase participant and site convenience.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Updated the minimum days from "100" to "150" days following discontinuation of drug for collection of all SAEs and non-serious AEs, including confirmed or suspected SARS-CoV-2 infection.	To ensure participant safety.
Section 9.2.6: Immune-mediated Adverse Events	Clarified additional information may also be collected on Immune-mediated adverse events (IMAEs).	To provide clarification.
Section 9.2.7: Additional Information Collected for Adverse Events Primarily Related to Bempegaldesleukin	New section created, which includes cytokine-release syndrome.	To align with most recent language for bempegaldesleukin program updates and Bempegaldesleukin IB 9.
Section 9.5.1: Pharmacokinetics and Immunogenicity Assessments Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling-Bempegaldesleukin Combined with Nivolumab (Parts A and B)	• Added draw blood samples from a site other than the infusion sites on days of infusion. • Updated immunogenicity sample and testing information. • Added Parts A and B to the table header. • Added "Part A and B" to the table title and updated table with times to collect samples throughout the study. • Added table footnote "c" predose samples should be collected within 24 hours before dose infusion. • Updated table footnote "f" to provide instruction for doses administered on Friday. • Clarified table footnote "h" that Day 8 samples can be collected on Day 7.	To provide clarification on PK and immunogenicity sampling.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 1: Abbreviations and Trademarks	Updated abbreviations	Abbreviations were updated for clarity and completeness.
Appendix 2: Study Governance Considerations	Updated first paragraph in Monitoring section to include remote monitoring; added new subsection on dissemination of study data.	To clarify expectations for monitoring and provide details on how clinical study information will be made available.
Appendix 5: Management Algorithms for Studies Under CTCAE Version 5.0	Updated management algorithms.	Revised to align with current safety management algorithms per CTCAE v5.0.
Appendix 6: Cerebrovascular Accident Adverse Event Management Algorithm for the Combination of Bempegaldesleukin with Checkpoint Inhibitors	Appendix was modified to include the latest updates.	To clarify CVA and TIA algorithms and to align with Bempegaldesleukin IB addendum v9.2.
Appendix 13: Country Specific Amendments	Updated countries with exclusion of HIV positive participants and amended text. Added country specific requirements/differences for France and Germany. France: • Treatment discontinuation for Grade 4 hyper and hypothyroidism. • Maximum blood volume specifications Germany: • "All SAEs will be recorded and reported to Sponsor or designee immediately, without undue delay."	Updated and added country specific requirements for France and Germany to facilitate use of CA045-020 Protocol Amendment 01 as the global protocol.
Appendix 14:Cytokine Release Syndrome - Pediatric Adapted Management Algorithm	Added new Appendix with cytokine-release syndrome management algorithm.	Added new Appendix to align with Bempegaldesleukin IB v9.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Phase 1/2 Study of Bempegaldesleukin in Combination with Nivolumab in Children, Adolescents, and Young Adults with Recurrent or Refractory Malignancies (PIVOT IO 020)

Short Title: Bempegaldesleukin + Nivo in Pediatric Malignancies

Study Phase:

Phase 1/Phase 2

Rationale:

Over the past several decades, survival of pediatric oncology patients has generally improved, largely due to the increased use of multimodality approaches and intensive multi-agent chemotherapy regimens. In contrast, despite the dramatic improvement in survival observed in the past 3 to 4 decades due to the multidisciplinary approach applied overall to pediatric malignancies, the outcomes in patients with relapsed or refractory tumors remain poor. Immuno-oncology (I-O) therapies aimed at enhancing the patient's immune response against the tumor represent an important new treatment option for improving outcomes in children with refractory or recurrent malignancies. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has been implicated in several pediatric solid tumor types. A number of pediatric clinical programs with PD-1 and PD-L1 inhibitors are currently underway in these and other pediatric tumors. To date, the use of single-agent I-O therapy in children has not provided sufficient evidence of activity to support a comprehensive development program in pediatrics. Bempegaldesleukin is an interleukin (IL)-2 pathway agonist that mobilizes, activates, and proliferates lymphocytes to the tumor microenvironment and is expected to increase PD-L1 expression on tumors due to secretion of interferon-gamma and other cytokines by increased numbers of tumor-infiltrating lymphocytes. Bempegaldesleukin in combination with the anti-PD-1 antibody nivolumab demonstrated clinical responses in the adult PIVOT-02 study. These observations, along with prior experience with the use of IL-2 (aldesleukin) in pediatric cancer patients, implies that bempegaldesleukin in combination with nivolumab may potentially benefit pediatric cancer patients.

Study Population:

- Females and males, ages less than 18 years old at the time of enrollment for Part A and Part B. For Part B, Cohorts B2, B3, and B4 participants less than 30 years old may be enrolled.
- Part A (safety lead in) will include pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking. Part B (cohort expansion) will include pediatric and young adult participants with neuroblastoma, Ewing sarcoma, rhabdomyosarcoma, miscellaneous solid tumors, non-Hodgkin lymphoma (NHL)/leukemia, high-grade glioma, medulloblastoma and central nervous system (CNS) embryonal tumors, ependymoma, and miscellaneous CNS tumors.

Key Inclusion Criteria

- Participants must have received standard-of-care-therapy, and there must be no potentially curative treatment available.
- A histologically confirmed malignant neoplasm that is refractory, relapsed, or patients for whom curative treatments are lacking, including poor prognosis newly diagnosed high-grade glioma.
- Participants must have measurable or evaluable disease based on Response Evaluation Criteria in Solid Tumors v1.1 for solid tumors, Response Assessment in Neuro-Oncology/Response Assessment in Pediatric Neuro-Oncology for CNS tumors, International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL, revised International Neuroblastoma Response Criteria for neuroblastoma, modified National Comprehensive Cancer Network Criteria for acute lymphoblastic leukemia, and modified Cheson et al International Working Group criteria for acute myeloid leukemia.
- Lansky play score for age ≤ 16 years or Karnofsky performance score for age > 16 years assessed within 2 weeks of enrollment must be ≥ 60. Participants who are unable to walk because of neurologic deficits but who are in a wheelchair will be considered ambulatory for the purpose of assessing the performance score.
- Substantial recovery (ie, no ongoing safety issues) from prior therapy.
- An interval of 4 weeks or 5 half-lives, whichever is longer, after the last administration of any anti-cancer therapy or any other treatment for malignancies (6 weeks for nitrosoureas), prior to first dose of study drug. The interval from most recent biological agent must be 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug.
- Participants with CNS tumors must not receive more than 0.05 mg/kg dexamethasone (or equivalent) per day and the dose should be stable for a minimum of a week.
- Participants who have received high-dose chemotherapy with autologous hematopoietic cell transplantation must be at least 6 months post-hematopoietic cell transplantation and they must have a CD4 count of at least 200.
- Prior palliative radiotherapy must be completed at least 2 weeks prior to first dose of study drug. Participants must have recovered from all Grade 2 or higher clinically relevant radiation-related toxicities. Participants with newly diagnosed malignant gliomas who may have received focal radiation or radiation and temozolomide are eligible. Note: Radiated lesions cannot be used as measurable lesions unless they have a new baseline scan after radiation or there is clear evidence of progression.
- Documented left ventricular ejection fraction >45% using standard echocardiogram or multigated acquisition scan test.

Key Exclusion Criteria

- Participants with osteosarcoma, T-cell/natural killer-cell leukemia/lymphoma, and Hodgkin's lymphoma.
- 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).

- Active infection requiring systemic therapy within 14 days prior to first dose.
- Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Participants with hypertension must be on a stable anti-hypertensive regimen for the 14 days prior to treatment assignment. Note: An antihypertensive medication that contains 2 drugs in 1 formulation is counted as 2 antihypertensive medications (eg, angiotensin-converting enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).
- Unstable or deteriorating cardiovascular disease, within the previous 12 months prior to screening, including, but not limited to, the following:
  - Unstable angina or myocardial infarction
  - Transient ischemic attack (TIA)/cerebrovascular accident (CVA)
  - Congestive heart failure (New York Heart Association Class III or IV)
  - Uncontrolled clinically significant arrhythmias
- History of pulmonary embolism, deep vein thrombosis, or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (eg, internal jugular vein thrombosis) within 3 months prior to treatment assignment.
  - Participants with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to treatment assignment and must be receiving a stable regimen of therapeutic anticoagulation (low-molecular-weight heparin or direct oral anticoagulation).
  - 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.
- Participants with inadequately treated adrenal insufficiency.
- 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.
- Participants with a condition (excluding CNS tumors) requiring systemic treatment with either corticosteroids (> 0.12 mg/kg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses > 0.12 mg/kg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
- Known human immunodeficiency virus (HIV) positive with an Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. (Participants with known HIV who are enrolled should receive ART therapy as clinically indicated and be monitored for CD4 counts and viral load per standard of care by a local health care provider.) NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally.

- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, agents that target IL-2 pathway or anti-cytotoxic T-lymphocyte-associated protein 4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
- Participants having had a prior allogeneic stem cell transplant.
- 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.
- Previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to first dose of study drug. 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.

Objectives and Endpoints:

Objectives	Endpoints
Primary - Part A Safety Lead-in	
• Safety Lead-in: To estimate the safety and tolerability of study treatment in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.	• Incidence of dose-limiting toxicities (DLTs), adverse events (AEs), serious AEs (SAEs), drug-related AEs, AEs leading to discontinuation, and death.
• To characterize the pharmacokinetics (PK) of bempegaldesleukin and nivolumab in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.	• PK parameters that are characterized by population PK models.
Primary - Part B Expansion	
• To estimate the preliminary efficacy (eg, ORR of study treatment separately in the following disease cohorts): – B1: Neuroblastoma – B2: Ewing sarcoma – B3: Rhabdomyosarcoma – B4: Miscellaneous solid tumors – B5: Non-Hodgkin lymphoma (NHL)/leukemia – B6: High-grade glioma – B7: Medulloblastoma and embryonal tumors	• Investigator-assessed objective response rate by: – B1: Revised International Neuroblastoma Response Criteria – B2 to B4: Response Evaluation Criteria in Solid Tumors v1.1 – B5: International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL – B5: Modified National Comprehensive Cancer Network Criteria for acute lymphoblastic leukemia

Objectives	Endpoints
– B8: Ependymoma – B9: Miscellaneous central nervous system (CNS) tumors	– B5: Modified Cheson et al International Working Group criteria for acute myeloid leukemia. – B6 to B9: Response Assessment in Neuro-Oncology/Response Assessment in Pediatric Neuro-Oncology
Secondary - Part B Expansion • To estimate the safety of study therapy in pediatric participants. • To estimate the progression-free survival (PFS) and overall survival (OS) of study therapy in pediatric participants.	• Incidence of AEs, SAEs, toxicities, drug-related AEs, AEs leading to discontinuation, and death. • Incidence of laboratory abnormalities. • PFS, OS

Abbreviations: AE = adverse event; CNS = central nervous system; DLT = dose-limiting toxicity; DOR = duration of response; NHL = non-Hodgkin lymphoma; NKTR-214 = bempegaldesleukin; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; SAE = serious adverse event.

Overall Design:

CA045-020 is an open-label, sequential-arm Phase 1b/2 clinical trial of bempegaldesleukin in combination with nivolumab in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.

Because pediatric participants vary in age and weight, the starting doses of nivolumab will be determined separately based on age or weight. Participants aged < 12 years or weighing < 40 kg will be given a weight-based dose of nivolumab (Figure 1-1), and participants aged ≥ 12 years and weighing ≥ 40 kg will be given a flat dose of nivolumab (Figure 1-2).

Number of Participants:

The total sample size of the study is estimated to be between approximately 10 and 234 participants depending on dose de-escalation contingencies in Part A and cohort expansions in Part B. The sample size of Part A is not based on statistical considerations, and it depends on the number of observed dose-limiting toxicities (DLTs). Accrual estimates for the expansion phase are based on the modified Simon 3-stage variant design, except for miscellaneous solid and CNS tumor cohorts (Cohorts B4 and B9). Participants in Part A treated at the dosing schema used in Part B can be counted in the accrual goals for Part B.

Treatment Arms and Duration:

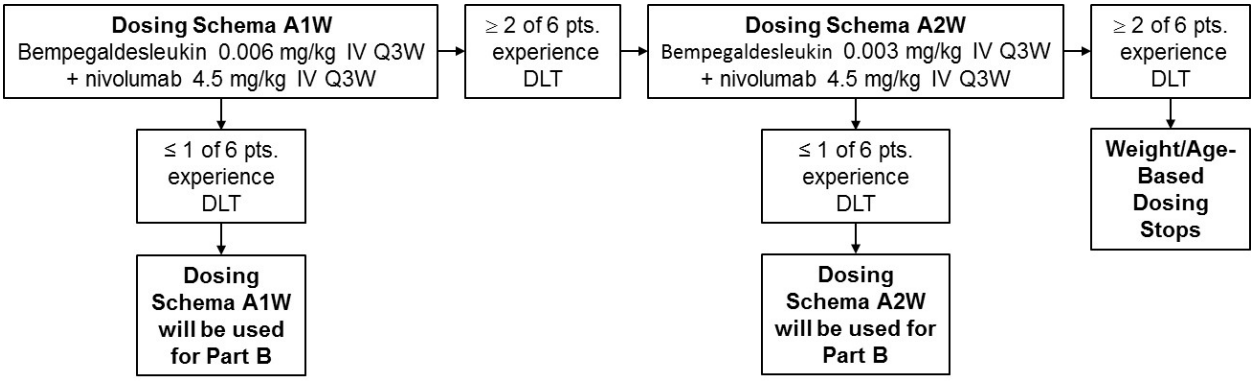
Study Treatment:

Study Treatments for CA045020		
Product Description/ Class and Dosage Form	**Content**	**IP/Non-IMP**
Investigational product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	1.0 mg of rhIL-2 per vial[a]	IP
Commercial product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.3 mg of rhIL-2 per vial[a]	IP
Commercial product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.5 mg of rhIL-2 per vial[a]	IP
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP

Abbreviations: IL-2=interleukin-2; IMP = Investigational Medicinal Product; IP = Investigational Product; mg=milligrams, mL= milliliters; rhIL-2 = recombinant human interleukin-2.

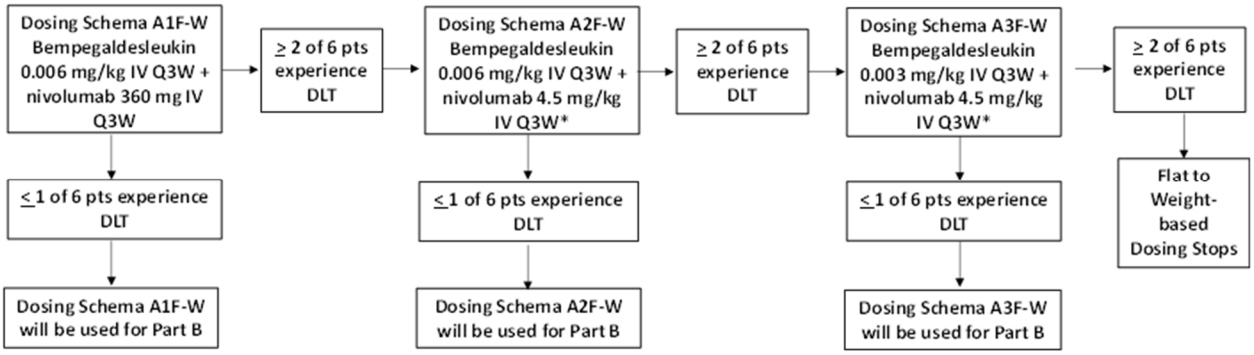
[a] For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.

Figure 1-1: Phase 1b (Part A) Dose-finding Study Design for Age- and Weight-based Dosing of Participants Aged < 12 Years or Weighing < 40 kg for Bempegaldesleukin in Combination with Nivolumab*



*For nivolumab 4.5 mg/kg in dosing schema A1W and A2W, up to 360 mg equivalent is the maximum dose.
Abbreviations: DLT = dose-limiting toxicity; IV = intravenous; pts = participants; Q3W = every 3 weeks; W = weight.

Figure 1-2: Phase 1b (Part A) Dose-finding Study Design for Flat to Weight-based Dosing of Participants Aged ≥ 12 Years and Weighing ≥ 40 kg for Bempegaldesleukin in Combination with Nivolumab*



*For nivolumab 4.5 mg/kg in dosing schema A2F-W and A3F-W, up to 360 mg equivalent is the maximum dose.
Abbreviations: DLT = dose-limiting toxicity; F = flat; F-W = flat to weight-based; IV = intravenous; pts = participant; Q3W = every 3 weeks.

Phase 1b consists of Part A. In Part A, a maximum of 30 participants (ie, up to 2 cohorts of 6 participants in the weight/age-based dosing schema and up to 3 cohorts of 6 participants in the flat to weight-based dosing schema) will be treated with both nivolumab and bempegaldesleukin intravenous every 3 weeks to determine the recommended dose of bempegaldesleukin to take into Part B and to determine if nivolumab flat or weight-based dosing will be used for those ≥ 12 years and weighing ≥ 40 kg. Assessments for the weight/age-based and for the flat to weight-based dosing schemas will run concurrently and are independent of each other.

Figure 1-3: Phase 2 (Part B) Study Design Schematic

Part B (Phase II Expansion Cohorts Modified Simon 3-Stage Variant Design)

9 patients per cohort	# Responses	Add to accrual	# Responses	Add to accrual	Max Total
B1 Neuroblastoma	If ≥ 1/9	7	If ≥ 2/16	8	24
B2 Ewing sarcoma	If ≥ 1/9	7	If ≥ 2/16	8	24
B3 RMS	If ≥ 1/9	7	If ≥ 2/16	8	24
B4 Miscellaneous solid tumors	Continue accrual to maximum 24 patients				
B5 NHL/leukemia	If ≥ 1/9	7	If ≥ 2/16	8	24
B6 High-grade glioma	If ≥ 1/9	7	If ≥ 2/16	8	24
B7 Medulloblastoma and ETs	If ≥ 1/9	7	If ≥ 2/16	8	24
B8 Ependymoma	If ≥ 1/9	7	If ≥ 2/16	8	24
B9 Miscellaneous CNS tumors	Continue accrual to maximum 24 patients				

Abbreviations: CNS = central nervous system; ET = embryonal tumor; NHL = non-Hodgkin lymphoma; RMS = rhabdomyosarcoma.

Phase 2 (Part B) will use a modified Simon 3-stage variant design to enroll at least 9 participants into 7 individual cohorts (B1 to B3 and B5 to B8) based on tumor type to be treated. For the miscellaneous solid tumor and miscellaneous CNS tumor cohorts, the Simon 3-stage variant design will not be applied and can accrue up to the maximum of 24 participants. All 9 cohorts will be treated with the selected dosing schema(s) from Part A of the study. The Phase 2 cohorts are disease and histology specific as presented in Figure 1-3.

The study consists of a screening, treatment, and long-term follow-up period. Participants will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant is lost to follow-up, BMS and Nektar Therapeutics conclude(s) the study, or for a maximum of 2 years of treatment. The total duration of the study is up to 5 years from first study treatment of the last participant or until the time of primary OS analysis, whichever occurs later.

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. Dose reductions are permitted for bempegaldesleukin but not nivolumab. Nivolumab treatment can continue in the event that bempegaldesleukin is permanently discontinued if the toxicities are considered related to bempegaldesleukin only and once the criteria to resume are met.

Data Monitoring Committee:

A data monitoring committee (DMC) will be utilized in this study. In Part A, any dosing level in which ≥ 2 participants' experience 1 or more DLTs are identified during the DLT period will be reviewed by the DMC before accrual into the dose reduced schema proceeds for weight/age-based or flat to weight-based dosing, respectively, as outlined in Figure 1-1 (A2W; weight/age-based dosing) and Figure 1-2 (A2F-W; A3F-W; flat to weight-based dosing). Since the weight/age-based dosing schemas (A1W/A2W) and the flat to weight-based dosing schemas (A1F-W/A2F-W/A3F-W) are independent from each other, they will be evaluated for DLTs separately.

The selection of the optimal dosing schema for Part B will be made at the completion of Part A and can occur separately for the 2 dosing schemas (weight/age-based and flat to weight-based dosing, respectively) in conjunction with the DMC.

2 SCHEDULE OF ACTIVITIES

An overview of the schedule of major assessments in this study are provided in Table 2-1 (Screening), Table 2-2 (On Treatment), and Table 2-3 (Long-term Follow-up).

Table 2-1: Screening Procedural Outline (CA045020)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain participant number. The participant or legally authorized representative should sign the informed consent prior to any study-related assessment is performed. Study allows for re-enrollment of a participant that is a pre-treatment failure and was not previously treated. 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 treatment. See Sections 6.1 and 6.2.
Medical History	X	All relevant medical history including smoking history, and prior anti-cancer therapies.
Safety Assessments		
Physical Examination	X	Include vital signs (blood pressure, heart rate, and temperature) plus height, weight, and pulse oximetry within 14 days prior to treatment.
Performance Status	X	Within 14 days prior to treatment, collect Lansky play score for ≤ 16 years or Karnofsky performance score for > 16 years of age (Appendix 7).
Prior and Concomitant Medication Use	X	Must be collected within 14 days prior to treatment. Vaccine use within 30 days prior to treatment must be collected.
Serious Adverse Events (SAE) Assessment	X	SAEs collected and reported from time of consent. All AEs (SAEs or non-serious AEs) related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection collected from time of consent.
Laboratory Tests		
Clinical Laboratory Testing	X	All laboratory assessments to be performed within 14 days prior to treatment, except for viral testing, which, if clinically indicated, is to be completed within 28 days prior to treatment (see Section 9.4.6 for a list of laboratory tests to conduct).
Electrocardiogram	X	Within 14 days prior to treatment (see Section 9.4.3).

Table 2-1: Screening Procedural Outline (CA045020)

Procedure	Screening Visit[a]	Notes
Echocardiogram or Multigated Acquisition Scan (MUGA)	X	Left ventricular ejection fraction > 45% within 60 days is required prior to treatment assignment. The investigator should further evaluate participants with other significant abnormalities on echocardiogram/MUGA. Decision regarding treatment should be based on investigator's best clinical judgment.
Pregnancy Test	X	Women of childbearing potential only. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) to be done at screening visit and within 24 hours of first dose of study therapy.
Tumor Assessment		
Body Imaging	X	• Imaging to be performed within 28 days prior to treatment. See Section 9.1.1 for further details. • Not applicable to participants with leukemia. • Skull base to mid-thigh [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) or PET-magnetic resonance imaging (PET-MRI); additional anatomy to include all sites of disease) for FDG-avid non-Hodgkin lymphoma. • Contrast-enhanced CT of the chest, contrast-enhanced CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease. • Participants with metaiodobenzylguanidine (MIBG)-avid neuroblastoma must also undergo MIBG scintigraphy in addition to CT/MRI as above.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants at baseline in participants with a history of brain metastasis or symptoms. Except for glioma, medulloblastoma, ependymoma, and other central nervous system tumors in which an MRI is required, CT of the brain (without and with contrast) can be performed if MRI is contraindicated. Brain imaging must be done within 28 days prior to treatment. See Section 9.1.1 for further details.
Cerebrospinal Fluid (CSF) - Solid Tumors	X	CSF cytopathology should be obtained in any participant with a suspicion or high likelihood of CSF dissemination up to 7 days prior to treatment. This sample can be used as the Cycle 1 Day 1 sample. If initially positive, CSF cytopathology should be followed as part of response assessment. See Section 9.1. [redacted]

Table 2-1: Screening Procedural Outline (CA045020)

Procedure	Screening Visit[a]	Notes
Bone Marrow and Buccal Swab - Solid Tumors	X	For participants with suspected bone marrow disease, bone marrow aspirate obtained where clinically indicated should be submitted along with buccal swab up to 28 days prior to treatment. If initially positive, bone marrow should be evaluated as part of response assessment. See Section 9.1. [redacted]
CSF - Leukemia	X	Screening sample collected up to 7 days prior to treatment initiation can be used as Cycle 1 Day 1 pretreatment sample. See Section 9.1.2.5. [redacted]
Bone Marrow and Buccal Swab - Leukemia	X	Bone marrow aspirate collected at screening and submitted along with buccal swab up to 28 days prior to treatment initiation can be used as Cycle 1 Day 1 pre-treatment sample. See Section 9.1.2.5. [redacted]
[redacted]		

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; FDG = [^{18}F]fluorodeoxyglucose; [redacted] IRT = Interactive Response Technology; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Some of the assessments referred to in this section may not be captured as data in the electronic case report form. 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: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
Safety Assessments							
Targeted Physical Examination, Vital Signs, and Performance Status	X			X*	X		Vital signs (blood pressure, heart rate, and temperature), weight, Lansky play score for ≤ 16 years or Karnofsky performance score for > 16 years of age (Appendix 7). Monitor and record vital signs at predose and within 30 minutes after administration of nivolumab. *At Day 8 visits collect vital signs only.
12-lead Electrocardiogram (ECG)	X	X	X	X	X	X (Cycle 5 only)	Pre-dose Day 1 of all cycles Pre-PK blood draw on Cycle 1, Days 3,5, and 8 Pre-PK blood draw on Cycle 5, Days 3 and 5 ECG should be performed within 30 minutes prior to PK blood draw. Participant should rest for 5 minutes prior to each ECG
Adverse Events Assessment (including Serious Adverse Events)		Continuously					Adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 5. Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously throughout the treatment period and for a minimum of 150 days after last dose of study treatment (Appendix 3).

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
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 drugs dosing must be available and assessed before dosing. Hematology and chemistry assessments can be drawn within 72 hours prior to treatment, though renal function (ie, serum creatinine) must be assessed within 24 hours prior to dosing with bempegaldesleukin or as soon as locally feasible. Refer to Section 9.4.6 for a list of laboratory tests to conduct.
Pregnancy Test	X				X		Serum or urine pregnancy test (minimum sensitivity units 25 IU/L or equivalent units of human chorionic gonadotropin) is required within 24 hours prior to treatment in women of childbearing potential.

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
Efficacy Assessments							
Body Imaging		• Imaging should occur every 9 weeks (± 7 days) from start of treatment for the first 54 weeks, then every 12 weeks (± 7 days) until disease progression or treatment discontinuation (including treatment beyond progression), whichever occurs later. Tumor assessment schedule should be maintained regardless of dose delays. Use same imaging method as was used at screening. • Not applicable to participants with leukemia. • Skull base to mid-thigh [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) or PET-magnetic resonance imaging (PET-MRI); additional anatomy to include all sites of disease) for FDG-avid non-Hodgkin lymphoma. • Contrast-enhanced CT of the chest, contrast-enhanced CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease. • Participants with metaiodobenzylguanidine (MIBG)-avid neuroblastoma must also undergo MIBG scintigraphy in addition to CT/MRI as above.					All study treatment decisions will be based on the investigator's assessment of tumor images. See Section 9.1.1 for additional details and to Section 8.1.2 for tumor assessment associated with treatment beyond progression.

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
Brain Imaging		• Participants in brain tumor-related cohorts and those with a history of brain metastasis or symptoms should undergo MRI of the brain without and with contrast every 9 weeks (± 7 days) from start of treatment up to 54 weeks, and then approximately every 12 weeks (± 7 days), or sooner if clinically indicated. Tumor assessment schedule should be maintained regardless of dose delays. Cerebrospinal fluid (CSF), if clinically indicated, should be followed as per Response Assessment in Pediatric Neuro-Oncology guidelines.					Except for glioma, medulloblastoma, ependymoma and other central nervous system tumors in which an MRI is required, CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
CSF - Solid tumors		Performed at time of imaging assessments for disease response as clinically indicated.					CSF cytopathology should be obtained in any participant with a previously positive CSF as part of response assessment (see Section 9.1). [redacted]
Bone Marrow-Solid tumors		Performed at time of imaging assessments for disease response as clinically indicated.					Bone marrow biopsy/aspirate should be obtained in any participant with a previously positive bone marrow aspirate as part of response assessment (see Section 9.1). [redacted]
CSF - Leukemia		Performed as clinically indicated.					CSF cytopathology should be obtained in any participant with a previously positive CSF as part of response assessment (see Section 9.1.2.5). [redacted]

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
Bone Marrow - Leukemia		Performed as clinically indicated.					Bone marrow biopsy/aspirate should be obtained in any participant with a previously positive bone marrow aspirate as part of response assessment. [redacted]
Pharmacokinetic (PK)/Immunogenicity Assessments[e]							
Bempegaldesleukin PK Plasma Samples		See Section 9.5.1 for further details.					
Nivolumab PK Serum Samples		See Section 9.5.1 for further details.					
Immunogenicity Samples		See Section 9.5.1 for further details.					
[redacted]							

[redacted]

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
[redacted]							
Health Outcomes							
Patient-reported Outcomes (PRO) Version of the CTCAE		See Notes					Questionnaire to be administered electronically in Part B only, on a weekly basis during the first 3 cycles of treatment, every cycle from Cycles 4 through 8, and then every other cycle (starting at Cycle 10) while on treatment until end of treatment. PRO-CTCAE™ for adults ≥18 years. Pediatric (Ped-PRO-CTCAE) for children ≥7 to <18 years. Ped-PRO-CTCAE [Caregiver] for children <7 years.
Study Drug							
Determine Dosing Schema	X						See Figure 5.1-1, Figure 5.1-2 and Figure 5.1-3.
Administer Intravenous Fluids	X				X		May be withheld if deemed by the investigator to be in the best interest of the participant. Refer to Section 7.1.1.1 for additional information.
Administer Bempegaldesleukin + Nivolumab (Parts A and B)	X				X		

Table 2-2: On-treatment Procedural Outline (CA045020)

Procedure	Cycle 1 Only[a,b] Cycle = 3 wks				Cycle 2 and Beyond[a,b,c] Each cycle = 3 wks		Notes
	Day 1	Day 3 (± 1 day)[d]	Day 5 (± 1 day)	Day 8 (- 1 day)	Day 1	Day 3-5	
Review Hydration Guidelines with Participants	X				X		See Section 7.1.1.1.
Oral Hydration Follow-up			X (Day 3-5)			X	For the first 2 doses of bempegaldesleukin, between Days 3 and 5 following infusion, site personnel must contact the participant (by telephone or clinic visit) to remind the participant of the oral hydration guidelines, to assess for any symptomatology and compliance with the guidelines, and document the results of the discussion. For subsequent administrations of bempegaldesleukin, the oral hydration follow-up should be conducted as clinically indicated for participants receiving bempegaldesleukin. See Section 7.1.1.1 for details.

Abbreviations: AE = adverse event; CSF = cerebrospinal fluid; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events version 5; ECG = electrocardiogram; FDG = [^{18}F]fluorodeoxyglucose; [redacted] MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; NCI = National Cancer Institute; Ped = pediatric; PET = positron emission tomography; PK = pharmacokinetic; PRO = patient-reported outcome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Some of the assessments referred to in this section may not be captured as data in the electronic case report form. 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.

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

[c] For Cycle 5 only, participants will return for additional sample collection at Days 3 and 5. Refer to Section 9.5.1 (Table 9.5.1-1) for all details, including allowed windows.

[d] Samples can be collected ± 3 hours. If participants are dosed on a Thursday, Day 3 samples may be collected on Day 2. If dosed on a Friday, Day 3 sample can be collected on Day 4.

[e] For participants who require blood draw volume modifications, blood collection volumes will be reduced per guidelines outlined in the laboratory manual. Omitted blood collection will likely be for [redacted] pharmacokinetic assessments, since all required safety assessments must be performed.

Table 2-3: Long-term Follow-up Period (CA045020)

Procedure	Safety Follow-up Visit 1[a]	Safety Follow-up Visit 2[a]	Safety Follow-up Visit 3[a]	Survival Follow-up Every 3 Months (± 14 Days)[b]	Notes[c]
Safety Assessments					
Vital Signs	X	X	X		Blood pressure, heart rate, temperature.
Performance Status	X		X		Lansky play score for ≤ 16 years or Karnofsky performance score for > 16 years of age (Appendix 7).
12-lead ECG	X				Participant should rest for 5 minutes prior to each ECG.
Adverse Events and Serious Adverse Events (SAE) Assessment	X	X	X	See Notes	All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 150 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.8) 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.
Subsequent Medications	X	X	X		
Review of Subsequent Anti-cancer Therapy	X	X	X	X	Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start and end date of each regimen, best response to the regimen, and date of progression to subsequent anti-cancer therapies will be collected.

Table 2-3: Long-term Follow-up Period (CA045020)

Procedure	Safety Follow-up Visit 1[a]	Safety Follow-up Visit 2[a]	Safety Follow-up Visit 3[a]	Survival Follow-up Every 3 Months (± 14 Days)[b]	Notes[c]
Laboratory Tests					
Laboratory Tests (includes blood and urine samples)	X	If toxicities are present.	If toxicities are present		See Section 9.4.6 for the list of laboratory tests.
Pregnancy Test	X	X	X		Women of childbearing potential only. Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of human chorionic gonadotropin) is required.
[redacted]					

Table 2-3: Long-term Follow-up Period (CA045020)

Procedure	Safety Follow-up Visit 1[a]	Safety Follow-up Visit 2[a]	Safety Follow-up Visit 3[a]	Survival Follow-up Every 3 Months (± 14 Days)[b]	Notes[c]
Efficacy Assessments					
Body Imaging	• Imaging should occur every 9 weeks (± 7 days) from start of treatment for the first 54 weeks, then every 12 weeks (± 7 days) until disease progression (including treatment beyond progression) or end of study, whichever occurs later. Use same imaging method as was used at screening. After completion of study therapy for participants without progression, results of additional imaging (including bone marrow and CSF, if applicable) are requested for the duration of the study. • Not applicable to participants with leukemia. • Skull base to mid-thigh [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) or PET-magnetic resonance imaging (PET-MRI); additional anatomy to include all sites of disease for FDG-avid non-Hodgkin lymphoma. • Contrast-enhanced CT of the chest, contrast-enhanced CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease. • Participants with metaiodobenzylguanidine (MIBG)-avid neuroblastoma must also undergo MIBG scintigraphy in addition to CT/MRI as above.				See Section 9.1.1 for further details.
Brain Imaging	• Participants in brain tumor-related cohorts and those with a history of brain metastasis or symptoms should undergo MRI of the brain without and with contrast every 9 weeks (± 7 days) from start of treatment up to 54 weeks, and then approximately every 12 weeks (± 7 days), or sooner if clinically indicated until disease progression (including treatment beyond progression) or end of study, whichever occurs later. Cerebrospinal fluid (CSF), if clinically indicated, should be followed as per Response Assessment in Pediatric Neuro-Oncology guidelines.				Except for glioma, medulloblastoma, ependymoma, and other central nervous system tumors in which an MRI is required, CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-3: Long-term Follow-up Period (CA045020)

Procedure	Safety Follow-up Visit 1[a]	Safety Follow-up Visit 2[a]	Safety Follow-up Visit 3[a]	Survival Follow-up Every 3 Months (± 14 Days)[b]	Notes[c]
CSF - solid tumors and leukemia	As clinically indicated.				CSF cytopathology should be obtained in any participant with a previously positive CSF as part of response assessment. See Section 9.1
Bone marrow aspirate - solid tumors and leukemia	As clinically indicated				Bone marrow aspirate should be obtained in any participant with a previously positive bone marrow aspirate as part of response assessment. See Section 9.1.
Survival Status	X	X	X	X	During safety follow-up and every 3 months (clinic visit or by telephone) thereafter and during survival phase. Include documentation of subsequent chemotherapy. See Section 5.1.4.
Pharmacokinetics (PK)/Immunogenicity Assessment					
PK Samples	See Section 9.5.1 for further details.				
Immunogenicity Samples	See Section 9.5.1 for further details.				

Abbreviations: CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; FDG = [18F]fluorodeoxyglucose; [redacted] MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PET = positron emission tomography; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Participants must be followed for at least 150 days after 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 last dose. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from last dose of study drug. Follow-up Visit 3 occurs approximately 150 days (± 7 days) from last dose of study drug. All 3 follow-up visits should be conducted in person.

[b] Survival follow-up visits to occur every 3 months subsequent to Follow-up Visit 3. 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 their survival status unless the participant has withdrawn consent for all contact.

[c] Some of the assessments referred to in this section may not be captured as data in the electronic case report form. 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.

3 INTRODUCTION

3.1 Study Rationale

Over the past several decades, survival of pediatric oncology patients has generally improved, largely due to the increased use of multimodality approaches and intensive multi-agent chemotherapy regimens. In contrast, despite the dramatic improvement in survival observed in the past 3 to 4 decades due to the multidisciplinary approach applied overall to pediatric malignancies, the outcomes in patients with relapsed or refractory tumors remain poor. Immuno-oncology (I-O) therapies aimed at enhancing the patient's immune response against the tumor represent an important new treatment option for improving outcomes in children with refractory or recurrent malignancies. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has been implicated in several pediatric solid tumor types. A number of pediatric clinical programs with PD-1 and PD-L1 inhibitors are currently underway in these and other pediatric tumors. To date, the use of single-agent I-O therapy in children has not provided sufficient evidence of activity to support a comprehensive development program in pediatrics.[1,2,3] Bempegaldesleukin is an interleukin (IL)-2 pathway agonist that mobilizes, activates, and proliferates lymphocytes to the tumor microenvironment and is expected to increase PD-L1 expression on tumors due to secretion of interferon-gamma (IFN-γ) and other cytokines by increased numbers of tumor-infiltrating lymphocytes (TILs). Bempegaldesleukin in combination with the anti-PD-1 antibody nivolumab demonstrated clinical responses in the adult PIVOT-02 study (Section 3.2.5.2). These observations, along with prior experience with the use of IL-2 (aldesleukin) in pediatric cancer patients, implies that bempegaldesleukin in combination with nivolumab may potentially benefit pediatric cancer patients.

3.1.1 Research Hypothesis

Treatment with bempegaldesleukin in combination with nivolumab will be safe and have clinical activity in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.

3.2 Background

3.2.1 Overview of Malignant Neoplasms in the Pediatric Population

Although pediatric cancer is rare, it is the leading cause of death by disease past infancy among children in the United States (US). In 2017, it is estimated that 15,270 children and adolescents between the ages of 0 to 19 years will be diagnosed with cancer and 1,790 will die of the disease in the US.[4] Significant advances have been made in the treatment of children and adolescent patients diagnosed with cancer over the past 5 decades. In spite of these advances, an unacceptable proportion of children are not cured up front with existing treatment modalities, and those with relapsed or metastatic disease still have a dismal outcome. Those who survive often have significant lifelong morbidity from toxicities associated with surgery, radiation, and chemotherapy. A significant increase in the incidence of childhood cancer has been observed over the past 3 decades. The overall incidence of cancer increased by 1.0% per year in children due to

an increased incidence of most tumor types, and by 1.5% in adolescents (15 to 19 years) mainly because of the increased incidence of leukemias/lymphomas, epithelial tumors, and melanoma.[5,6]

Improvement in the outcomes of pediatric patients with cancer has not been uniformly spread across all tumor types. Based on data from 54 population-based cancer registries over the period from 1988 to 1997,[7] the greatest reduction (greater than 50%) in 5-year mortality was observed for leukemia (all groups, and acute lymphocytic leukemia [ALL] in particular), lymphomas (all groups, and non-Hodgkin lymphoma [NHL] in particular), retinoblastoma, hepatic tumors, and germ cell tumors. The use of multidisciplinary approaches and intensive multi-agent chemotherapy regimens has substantially improved the outcomes of patients with leukemia, which is most commonly diagnosed in the first years of life. Five-year survival of children with neuroblastoma has also remarkably increased, ranging from 84% in infancy, which is also the age of highest incidence, to 47% for children aged 1 to 4 years, and 38% for those aged 10 to 14 years.[8] However, for medulloblastoma, osteosarcoma, and Ewing sarcoma, little change was noted in survival,[9] and broadly, the lowest reduction in mortality from 1988 to 1997 was observed in soft tissue sarcomas and central nervous system (CNS) tumors as compared with other pediatric solid tumors.[7] One of the major advances in pediatric oncology has been the acknowledgement that pediatric tumors are fundamentally different from those of adults, with the notable exceptions of Ewing sarcoma,[10] many osteosarcomas,[11] Hodgkin lymphoma (HL),[12] certain subtypes of medulloblastoma,[13] and melanoma.[14]

Pediatric Non-Melanoma Solid Tumors: The incidence of solid tumors in pediatric patients is rare. The incidence in people aged 14 and younger ranges from 3.9 per 100,000 to 10.2 per 100,000 (Krebsregister Saarland Cancer Registry [15]; North Rhine-Westphalia Cancer Registry [16]; Niedersachen Cancer Registry,[17] Cancer Registration Statistics England,[18] Cancer Registry France,[19] Cancer Registry Slovenia,[20] Majaslapa Onkologija,[21] Lithuanian Cancer Registry,[22] Netherlands Cancer Registry,[23] Surveillance, Epidemiology, and End Results Program [SEER] version 8.2.121[24]). The incidence of solid tumors is higher among those aged 0 to 4 years than those aged 5 to 14 years and increases with each subsequent 5-year age group, up to over 3,000 cases per 100,000 in people aged 80 or older (Cancer Registration Statistics England).[18] Based on the incidence rates of all solid tumors, there are approximately 6,600 children younger than 15 years diagnosed per year in the European Union's (EU's) 28 countries. Using the survival data from SEER from the US and incidence data from the EU, the prevalence estimate of children younger than 15 years at the end of 2017 with a solid tumor diagnosis and still alive is estimated to be approximately 73,000 across the US and EU. The age of diagnosis and prevalence of each solid tumor, however, varies depending on the underlying histology. For example, neuroblastoma is the most common pediatric solid tumor, particularly in children younger than 1 year. Osteosarcoma and Ewing sarcoma, however, are traditionally adolescent/young adult tumor types (for example, Ewing sarcoma has a median age at diagnosis of 15 years). Although all of the tumor types have low incidences in the US (below 1 per 100,000 among those aged 1 to 14 years [SEER version 8.2.1]), there is also variability within this, with the respective incidence rates per 100,000

for patients aged 0 to 14 years being 0.3, 0.8, 0.5, and 0.4 for Ewing sarcoma, neuroblastoma, rhabdomyosarcoma (RMS), and osteosarcoma, respectively. Using the US survival and incidence data from SEER, the prevalence of children younger than 15 years at the end of 2017 with a diagnosis of Ewing sarcoma, osteosarcoma, neuroblastoma, or RMS and still alive is estimated to be approximately 16,000.

Common types of solid tumors in children, including brain tumors, neuroblastoma, RMS, Wilms' tumor, osteosarcoma, and retinoblastoma, have seen significant improvement in survival rates with localized disease; however, improvement in survival with metastatic disease has been more limited.[25,26] Although the introduction of chemotherapeutic drugs into treatment regimens that were previously reliant on surgery and radiotherapy marked a major advancement in treatment, more still needs to be done because malignant neoplasms remain a leading cause of non-accidental death in children aged 5 to 14 years in the US.[27]

Neuroblastoma: Neuroblastoma is the most common extracranial solid tumor of infancy that arises from the sympathetic nervous system. Neuroblastomas are a clinically heterogeneous tumor with variable outcomes ranging from spontaneous regression, maturation to a benign ganglioneuroma, or aggressive disease with metastatic dissemination leading to death. The definition of neuroblastoma risk among various cooperative groups has been inconsistent due to the broad spectrum of clinical behavior exhibited by different tumors (eg, spontaneous regression or maturation despite multimodality treatment). Consequently, neuroblastomas are now staged using the International Neuroblastoma Risk Group Staging System, which was originally developed as part of an international collaboration to define risk based on image-defined risk factors.[28] However, treatment is based on the Children's Oncology Group (COG) neuroblastoma risk strata. Patients are classified into low-, intermediate-, and high-risk categories based on certain characteristics at the time of diagnosis, including age, disease stage, tumor histology, presence or absence of amplification of the *MYCN* oncogene, and quantitative deoxyribonucleic acid (DNA) content of the tumor (DNA index or ploidy). For patients with low-risk disease, multi-agent low- or moderate-intensity chemotherapy is reserved for unresectable tumors or for patients who have symptoms of spinal cord compression or respiratory or bowel compromise. Frequently used agents include combinations of cyclophosphamide, carboplatin or cisplatin, etoposide or teniposide, and doxorubicin. Moderately intensive multi-agent chemotherapy (eg, with doxorubicin cyclophosphamide, a platinum drug, and etoposide) is recommended for children with intermediate-risk neuroblastoma and is often applied before attempted resection.[29] Patients at the highest risk for disease progression and mortality are those who are older than 18 months and have disseminated disease or localized disease with unfavorable markers such as *MYCN* amplification. An aggressive multimodality approach including high-dose chemotherapy, surgical resection, hematopoietic stem cell rescue, and radiation therapy is used. The combination of IL-2, anti-GD2 monoclonal antibody (ch14.18, dinutuximab), and granulocyte-macrophage colony-stimulating factor (GM-CSF) with cis-retinoic acid was evaluated in a Phase 3 trial vs cis-retinoic acid alone (standard therapy) in participants with high-risk neuroblastoma in remission after stem cell transplant.[30,31] This study found improved rates of event-free survival (EFS) (66% vs 46% at 2 years, P = 0.01) and overall survival (OS) (86% vs 75% at 2 years, P = 0.02) compared with

standard therapy. However, the contribution of IL-2 in this combination is unclear. Subsequent trials performed by the Société Internationale d'Oncologie Pédiatrique (SIOP)-Europe have suggested that co-treatment with IL-2 is not beneficial. In this trial, high-risk neuroblastoma participants were randomized to receive either ch14.18 alone or in combination with subcutaneous IL-2.[32] All participants also received 6 cycles of cis-retinoic acid. The 3-year EFS and OS rates in participants who did not receive IL-2 were 60% and 66%, respectively, whereas the 3-year EFS and OS rates in those who received IL-2 was 57% and 65%, respectively. The differences in both EFS and OS between the arms were not significant. Direct comparisons between these 2 trials is difficult given the different routes and doses of IL-2 used and the addition of GM-CSF in the latter trial. Dinutuximab was approved, in combination with GM-CSF, IL-2, and cis-retinoic acid, for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response (PR) to prior first-line multi-agent, multimodality therapy by the US Food and Drug Administration (FDA) in Mar-2015. Despite intensive multimodality therapy, only approximately 40% of children remain disease free long-term, and the most common outcome of high-risk neuroblastoma is recurrence of disease followed by death. Improving survival in this group of children is a priority in international cooperative groups.

Rhabdomyosarcoma: RMS is a common pediatric malignant tumor of the muscle that accounts for 40% of all soft tissue sarcomas. These tumors can occur almost anywhere in the body, and symptoms are usually dependent on the location of the primary or metastatic lesions.[33] The current World Health Organization (WHO) classification recognizes 4 distinct histological RMS types: embryonal, alveolar, pleomorphic (which occurs most commonly in adults), and spindle cell/sclerosing.[34] Due to its diverse morphologies, integrated diagnostic methods, including immunohistochemical and molecular methods, are necessary to diagnose RMS type. Whereas embryonal RMS has no putative genomic markers, the majority of alveolar RMSs are characterized by a fusion between the *PAX3* or *PAX7* genes and *FOXO1* gene.[35] The prognosis varies significantly, from 70% survival for nonmetastatic disease to less than 20% survival for metastatic disease. Embryonal RMS and its variants, along with spindle cell RMS, are accepted as favorable pathologies, whereas alveolar RMS with its solid variant is accepted as an unfavorable pathology. This classification is significant for the evaluation of the clinical stage. The risk-stratification system currently used by the COG incorporates both pretreatment staging (based on anatomic site and tumor/node/metastasis status) and clinical group assignment (based on extent of disease following pretreatment surgical procedure).[33] Patients with recurrent disease have a very poor survival independent of treatment modality. The treatment of RMS requires multimodality therapy consisting of systemic chemotherapy, with either surgery, radiation therapy, or both surgery and radiation therapy to maximize local tumor control. When possible, surgery is performed prior to systemic chemotherapy.[36,37,38] The management and overall treatment philosophy for RMS differs between the Soft-tissue Sarcoma Committee of the COG (COG-STS), the Intergroup Rhabdomyosarcoma Study (IRS) Group, the US and Canadian precursor to COG, and the SIOP Malignant Mesenchymal Tumor (MMT) Group. The main COG-STS objective has been the use of local therapies soon after the initial operation or biopsy (except in patients with metastatic disease), using radiation therapy for patients with residual disease. The primary intent

of the COG-STS approach is avoiding relapse and subsequent salvage therapy. The main objective of the MMT Group has been to reduce the use of local therapies by using initial front-line chemotherapy followed by second-line therapy only in the presence of poor response. Surgery is preferred, and radiation therapy is used only after incomplete resection, regional lymph node involvement, or poor clinical response to chemotherapy. The intent of this approach is to avoid the risks associated with major surgical procedures and long-term morbidity from radiation therapy. Survival for most RMS patient subsets is improved with the use of early local therapy, including radiotherapy. OS rate with the MMT Group approach was 71%, compared with an OS rate of 84% in the IRS-IV study.[36] EFS rates at 5 years were 57% in the MMT89 study vs 78% in the IRS-IV study. Participants with extremity and head and neck nonparameningeal tumors experienced the greatest differences in outcome. Participants with bladder/prostate primary tumors who did not receive radiation therapy during initial therapy had lower failure-free survival, but there was no difference in OS between the MMT Group and IRS-IV approaches for these participants.[39] Although patients with recurrent or progressive RMS sometimes achieve complete remission with secondary therapy, the long-term prognosis is usually poor with treatment options of surgery and/or radiation therapy and chemotherapy.[40,41]

Ewing Sarcoma: Ewing sarcoma is the second most common primary malignant bone cancer in children and adolescents after osteosarcoma.[42] Ewing sarcoma occurs primarily in bones, with rare occurrences in soft tissues. The median age at diagnosis is 15 years, with a Caucasian male predilection, and occurs well into early adulthood. Ewing sarcoma has an average incidence of 2.93 cases/1,000,000 reported annually between 1973 and 2004 that has not increased appreciably over the past 30 years.[43] Prognostic factors for treatment stratification of Ewing sarcoma are metastases at diagnosis, primary site, and age.[44] However, there is no widely accepted formal staging system, with most studies in Ewing sarcoma being stratified by the presence or absence of metastatic disease. The current chemotherapy protocols used to treat Ewing sarcoma include various combinations of the following 6 drugs: doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide, and etoposide. Localized Ewing sarcoma is usually treated via surgical excision or radiotherapy, or a combination of both. In cases in which surgical excision is not possible due to the large size of the tumor, its anatomical location, or the fact that the acquired surgical margin is not sufficient to achieve local control, pre- or postoperative radiotherapy is usually selected. The current 5-year OS rate for patients with localized disease is 65% to 75%. Patients with metastases have a 5-year OS of 30%, except for those with isolated pulmonary metastasis (approximately 50%). Patients with recurrence have a dismal prognosis.[45]

Wilms' Tumor: Wilms' tumor is the most common pediatric kidney tumor of childhood and often arises secondary to molecular aberrations in normal renal development, which explains the rarity of this tumor in adults. It is often associated with a number of different genetic syndromes and has a strong hereditary component for which screening is available.[46] Since the late 1960s and early 1970s, 2 different approaches for the treatment of Wilms' tumor have been studied extensively by the COG and the SIOP. The COG established the standard treatment for Wilms' tumor in North America, consisting of primary surgery when possible except in certain circumstances such as

extensive, inoperable tumors at presentation or synchronous bilateral disease, followed by chemotherapy and, in high-risk patients, radiation therapy.[47,48,49,50] This approach allows for early and accurate histologic diagnosis and staging. In contrast, the SIOP established the standard treatment in Europe, consisting of initial front-line combination chemotherapy (vincristine and dactinomycin) in children with localized tumors, and additional doxorubicin in those presenting with metastases, followed by surgery, which results in fewer tumor ruptures during surgery and lower postoperative staging.[51,52] Due to excellent clinical outcomes seen with both the COG and the SIOP approaches, OS for patients with Wilms' tumor in high-income countries is greater than 90% for localized disease and 75% for metastatic disease.[53] Approximately 15% of patients with favorable-histology Wilms' tumor and 50% of patients with anaplastic Wilms' tumor experience recurrence.[54] The most common site of relapse is lung, followed by abdomen/flank and liver. As a result of modern treatment combinations, the outcome after recurrence has improved up to an approximately 60% 5-year survival rate.[55,56]

Retinoblastoma: Retinoblastoma is primarily a pediatric malignancy and is the most common primary intraocular malignancy of childhood, accounting for 10% to 15% of cancers that occur within the first year of life. Retinoblastoma occurs in approximately 1 in 15,000 to 1 in 16,600 live births in the US and Northern Europe. Between 2005 and 2009, the annual incidence of retinoblastoma in the US among children younger than 15 years was 4.1 per million.[57] Retinoblastoma presents unilaterally in approximately 60% to 70% of cases and bilaterally in the remaining 30% to 40%. Unilateral retinoblastoma is typically associated with sporadic mutations in *RB1* tumor suppressor gene, with heritable mutations of *RB1* occurring in approximately 10% of patients, and a subset of unilateral non-heritable retinoblastoma have high *MYCN* oncogene amplification without *RB1* mutation.[58] Bilateral retinoblastoma is frequently associated with germline mutations in *RB1*. First-line therapeutic options for retinoblastoma include local and systemic chemotherapy, cryotherapy, laser photoablation, radioactive plaques (I-125 brachytherapy), and enucleation. Retinoblastoma is a chemotherapy-sensitive malignancy. The agents used most commonly for ophthalmic artery chemosurgery include melphalan, carboplatin, and topotecan; various regimens are used for systemic therapy, most typically including carboplatin, vincristine, etoposide, and topotecan.[59] The overall 5-year survival rate for children with retinoblastoma in the US is over 95%. Patients who develop metastatic disease usually do so within 1 year of diagnosis; a child who remains recurrence free for 5 years after diagnosis is considered cured.[60]

3.2.1.1 Pediatric Tumors of the Central Nervous System

Brain and other tumors of the CNS are the second most frequent childhood cancer and the most common solid tumor in children, accounting for nearly 22% of all tumors diagnosed under the age of 15 years.[15,61] An estimated 4,620 new cases were diagnosed in 2015,[62] and more than 28,000 children are estimated to be living with this diagnosis in the US.[63] The most common primary CNS tumors are gliomas, medulloblastoma, and ependymoma, with high-grade gliomas (HGGs) accounting for about 20% of all childhood brain tumors. Whereas some types, such as

medulloblastoma, ependymoma, and germ-cell tumors, are associated with a reasonably good prognosis at diagnosis, others such as diffuse intrinsic pontine glioma (DIPG) and high-grade astrocytoma currently do not have any curative treatment options. The median life expectancy of children diagnosed with DIPG is less than 1 year, and pediatric patients with high-grade astrocytoma also suffer from an extremely poor prognosis.

High-grade Glioma: Pediatric HGGs are malignant, diffusely infiltrative, rapidly progressive tumors and are managed with surgical resection, adjuvant postoperative radiation, and chemotherapy; however, outcome remains dismal, a prognosis that has been unchanged for decades, and most patients eventually relapse and die of disease. Although pediatric HGGs resemble their adult counterparts histologically, the molecular abnormalities driving these tumors are dramatically different. The majority of malignant pediatric HGGs have somatic mutations in histone genes and genomic hypomethylation, whereas adult HGGs more frequently have abnormalities in signal transduction pathways.[64] The classification of HGGs has undergone significant changes in the past few years, which were highlighted by the recent amendments to the WHO classification of these tumors. Although this category comprises multiple subtypes of tumors, the standard treatment approaches are relatively uniform and are comprised of maximal safe surgical resection followed by focal radiation therapy. Although transient responses with this approach are observed, the majority of patients will succumb to their disease. The addition of chemotherapy, typically temozolomide, may provide a small benefit. For example, the COG trial ACNS0126 of surgery, radiation, and temozolomide achieved a 3-year EFS rate for anaplastic astrocytoma and glioblastoma multiforme of 13% and 7%, respectively. The 2-year EFS rate was 17% among participants without O6-methylguanylmethyltransferase (MGMT) overexpression and 5% among those with MGMT overexpression (P = 0.045).[65] For patients with DIPG, surgery is limited to small biopsies; focal radiation therapy is standard; and chemotherapy, including temozolomide, has not shown an advantage. The mean OS remains at 9 to 12 months, and most patients had died by 2 years from diagnosis.

Medulloblastoma, Atypical Teratoid/Rhabdoid Tumors, Pineoblastoma, and Other Rare Embryonal CNS Tumors: Medulloblastoma are small, round, blue-cell tumors of the posterior fossa now divided into multiple molecular subtypes based on the molecular pathway affected in the tumor.[13] Although the majority of subtypes are predominantly identified in children, the sonic hedgehog (SHH) subtype is identified in both children and adults and is thought to have similar biology.[66] Although outcome depends significantly on the tumor subtype, treatment approaches are relatively uniform, and almost all patients continue to receive maximal safe surgical resection, risk-adapted craniospinal radiotherapy, and multi-agent chemotherapy, typically consisting of vincristine, cisplatin, 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea (lomustine/CCNU), and/or cyclophosphamide. Cure rates are excellent for certain molecular subtypes (eg, windgless > 90%) and poor for others (eg, Group 3 *MYC* amplified < 50%).[66, 67] Although the outcome for medulloblastoma has improved with traditional therapies, for those with Group 3 tumors, as well as those with relapsed disease, the prognosis remains poor. Additionally, therapy can cause delayed complications, including neurocognitive impairment, hearing loss, endocrine

abnormalities, cerebrovascular disease, and second malignancies, with profound effect on quality of life in survivors.

Atypical teratoid rhabdoid tumors (AT/RTs), pineoblastoma, and other rare embryonal CNS tumors are predominantly pediatric malignancies of the CNS and are biologically distinct molecular subtypes of pediatric brain tumors, although morphologically they resemble medulloblastoma and are treated with similar approaches. AT/RTs arise mostly in children younger than 3 years and are associated primarily with loss of *SMARCB1* or *SMARCA4* gene expression. Treatment with conventional postoperative chemotherapy alone results in less than 20% survival, whereas treatment with multimodal regimens designed specifically for AT/RTs containing radiation therapy, intrathecal chemotherapy, and/or high-dose chemotherapy with stem cell rescue have achieved 2- or 3-year survival rates ranging between 20% to 50% depending on the treatment protocol.[68]

Pineoblastomas are highly malignant WHO Grade IV[69] tumors located in the pineal region that usually present with obstructive hydrocephalus. Treatment with the combination of surgery, radiation, and chemotherapy is similar to that used for high-risk medulloblastoma and results in 5-year survival rates of about 60%. Embryonal tumors outside the posterior fossa or pineal region are treated similar to pineoblastoma and medulloblastoma, although the long-term survival of this group of patients is less than 50%. A complicating factor for many of these patients, including those with medulloblastoma, is young age at the time of diagnosis. Due to severe effects of radiation therapy on the developing brain, radiation sparing approaches are used. Although slightly less effective than the combined surgery, radiation, and chemotherapy approaches mentioned above for older children, patients who receive maximal surgery, multi-agent chemotherapy, and high-dose chemotherapy with stem cell rescue have a better cognitive outcome. Despite improvement in the cure rates of pediatric brain tumors during the past 2 decades of the 20th century, which was largely a result of technologic advances in imaging, neurosurgery, radiation oncology, and the introduction of combination chemotherapy, outcomes have remained static for all of these tumors except medulloblastoma and low-grade gliomas. Developing effective, as well as less toxic, treatments for pediatric CNS tumors arguably represents one of the major remaining unmet medical needs in pediatric oncology.

Ependymomas: Ependymomas are the third most common brain tumors in the pediatric population, comprising 5% to 10% of all brain tumors. Pediatric ependymomas typically arise intracranially, in the supratentorial compartment, and within the posterior fossa, and are biologically different from spinal cord ependymomas, which typically occur in adults.[70] Four pediatric subtypes have been further identified through genome methylation profiling.[71] The initial treatment for ependymoma in the brain consists of maximal safe resection and adjuvant radiation therapy. About half the cases of malignant pediatric ependymoma relapse, mostly local recurrences that can sometimes be completely surgically resected. However, long-term prognosis for patients with recurrent disease is poor, and most will eventually die from relapse. Like many of the other primary CNS tumors, ependymomas have seen a significant evolution in their molecular categorization and classification. Unfortunately, the molecular pathways identified in these tumors

have not lent themselves to treatment with targeted drugs. As such, the standard treatment for ependymoma has not changed significantly over the past 2 decades and is comprised of maximal safe surgical resection and focal radiation therapy. Although the 5-year EFS and OS of those with complete resection is approximately 80%, there are increasing data that this may continue to drop to 50% or less over time. For those with incompletely resected ependymoma, the 5-year EFS is much lower and less than 20% of patients will survive long term. Although the addition of chemotherapy can induce transient responses, it is typically used for patients with bulk residual disease and is still being evaluated for its role in improving outcome. At the time of recurrence, especially in patients who have already received focal radiation therapy, the long-term prognosis of these patients is very poor.

3.2.1.2 Pediatric Hematologic Malignancies

Non-Hodgkin Lymphoma: Lymphomas rank third in the list of most common childhood malignancies, constituting 10% to 12% of cancers in children. Nearly two-thirds of the lymphomas diagnosed in children are NHL.[72] Although the outcome for NHL at diagnosis is excellent using treatment strategies that are tailored to the specific patient and disease subtype, those with recurrent or refractory disease do poorly and are in need of novel approaches. In children, NHL is distinct from the common lymphomas observed in adults and is almost always high grade at presentation. Approximately 70% of children with NHL present with advanced disease and/or have metastatic involvement, including bone marrow, CNS, and/or bone,[73] as opposed to NHL in adults, which tends to present as low or intermediate grade. NHL of childhood and adolescence falls into 3 main histological categories: mature B-cell (Burkitt and Burkitt-like lymphomas [30%] and diffuse large B-cell lymphoma [DLBCL; 10 to 20%]), lymphoblastic lymphoma (20%), and anaplastic large cell lymphoma (10%). Other types of lymphoma, including T-cell lymphoma, cutaneous lymphomas, and indolent B-cell lymphomas such as follicular lymphoma (FL), are more commonly seen in adults and only rarely diagnosed in children.[74] NHL accounts for approximately 7% of cancers in children younger than 20 years. Childhood NHL occurs most commonly in the second decade of life and occurs infrequently in children younger than 3 years. In children, NHL consists predominantly of mature, aggressive B-cell lymphomas, with Burkitt lymphoma being most common in 5- to 14-year-olds and DLBCL predominating in 15- to 19-year-olds. Both have superior outcomes relative to adults, with OS rates greater than 90%.[74,75,76,77] Using gene expression profiling (GEP), DLBCL has been further differentiated into the germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, both of which are biologically and clinically diverse entities.[78] Adult patients with the GCB subtype have a significantly better OS compared with those with the ABC subtype.[78,79,80,81] Compared with adults, children and adolescents with DLBCL have a better OS. One explanation may be the difference in biology, because pediatric DLBCL shares more features with Burkitt lymphoma, including high proliferation, increased *MYC* expression, decreased BCL2 expression, higher incidence of *MYC* translocation, and germinal center phenotype (75%).[82,83] In addition, using GEP to distinguish the GCB and ABC subtypes of DLBCL, Deffenbacher et al[81] more recently reported a 3:1 predominance of the GCB subtype vs ABC subtype in pediatric DLBCL. Although there was a

homogeneity between the pediatric and adult GCB sinusoidal large B-cell lymphoma subtype, some subtle differences in gene expression and genetic alterations suggested underlying differences in tumor biology between childhood and adult cases. Of the other histological subtypes most commonly diagnosed in children and adolescents, lymphoblastic lymphomas (20% of childhood NHL) are usually positive for terminal deoxynucleotidyl transferase, with more than 75% having a T-cell immunophenotype and the remainder having a precursor B-cell phenotype.[84] Chromosomal abnormalities are not well characterized in patients with lymphoblastic lymphoma. Anaplastic large cell lymphoma accounts for approximately 10% of childhood NHL.[85] Although the predominant immunophenotype of anaplastic large cell lymphoma is mature T-cell, null-cell disease (ie, no T-cell, B-cell, or natural killer [NK]-cell surface antigen expression) does occur. All anaplastic large cell lymphoma cases are CD30-positive, and more than 90% of pediatric anaplastic large cell lymphoma cases have a chromosomal rearrangement involving the *ALK* gene. About 85% of these chromosomal rearrangements will be t(2;5)(p23;q35), leading to the expression of the *NPM-ALK* fusion protein; the other 15% of cases are comprised of variant *ALK* translocations. Although FL is the second most common lymphoma worldwide, it mainly affects adults and rarely occurs in the pediatric population and young adult patients.[86] In addition, the other types of lymphoma, such as peripheral T-cell lymphoma, T-cell/NK-cell lymphomas, and cutaneous lymphomas, more commonly seen in adults, also occur rarely in children. According to the National Cancer Institute (NCI) SEER database, from 2007 to 2011, the incidence of NHL (except Burkitt lymphoma) increased steadily with age, from 4.5 cases per million individuals in the 1- to 4-year-old age group to 14.1 cases per million individuals in the 15- to 19-year-old age group. The incidence of NHL was nearly twice as high in males as compared with females, with an age-adjusted incidence of 1.5 cases per 100,000 males vs 0.8 cases per 100,000 females.[87] Risk factors for development of pediatric NHL include congenital and acquired immunodeficiencies such as human immunodeficiency virus (HIV) or immunodeficiency after solid organ transplantation. Most cases of NHL in the immunocompromised population are associated with Epstein-Barr virus (EBV). In endemic Africa, 85% of Burkitt lymphoma is associated with EBV, whereas EBV is only associated with 15% of cases of Burkitt lymphoma in Europe and the US.[74] The primary therapy for childhood NHL is multi-agent chemotherapy, and the intensity and length of therapy are usually determined by the subtype and stage of disease. The prognosis for children with NHL, both limited- and advanced-stage disease, has improved significantly over the past 2 decades. The OS for NHL in children across all age groups has continued to steadily improve, with a 5-year survival from 2004 to 2010 of 86.5%. Children with limited-stage NHL have an excellent prognosis with an estimated 5-year EFS of 90 to 95%.[88,89] The prognosis for advanced-stage disease has also improved and varies based on subtype (60% to 90% 5-year EFS).[89,90,91,92,93] The following are known prognostic factors in pediatric NHL: age, site of disease, chromosomal abnormalities, tumor burden, and early response to therapy (Burkitt lymphoma).[85] In children with relapsed or refractory NHL, the prognosis is not as promising, and the best treatment approach for this poor-risk group continues to be a challenge.[94,95] There is little consistency in therapeutic approaches, and there is no formal recommendation on the best approach for this poor prognostic subgroup; new treatment options are needed.

Pediatric Leukemias: Leukemias are the most common cancer observed in children and have seen a dramatic improvement in outcome over the past 50 years. Although significant differences in the upfront treatment exist between the different subtypes of ALL and acute myeloid leukemia (AML), those with recurrent disease, especially AML, do poorly and are difficult to salvage or, in the case of ALL, require intensive treatment (eg, stem cell transplant) associated with significant long-term morbidity, although 30% to 50% overall with relapsed ALL can be cured. ALL accounts for 25% of new cancer diagnoses, or approximately 3,100 new cases in the US per year under the age of 20, the majority of which occur in early childhood (younger than 8 years).[96] The incidence is significantly higher in Hispanic and White children compared with Black children (Section 29 of the SEER Cancer Statistics Review).[97] ALL is divided into T- and B-cell subsets. There are a number of genetic syndromes that predispose patients to ALL, the most common of which is Down syndrome. Based on new molecular analyses, the B-cell subtypes are categorized based on their dominant molecular translocation[98] and are major components of prognostic determination and treatment intensity. With current approaches, overall cure rates for children with ALL hover around 85% to 90% using risk-adapted multi-agent chemotherapy. Risk-based stratification has become a central component of treatment for pediatric ALL because it impacts prognosis.[99] The features that differentiate low-, intermediate-, and high-risk patients vary by group; however, age and white blood cell (WBC) count at presentation are thought to be especially important, and age younger than 1 year or older than 10 years and WBC > 50,000 at presentation are regarded as high-risk features.[100] Patients on steroids are also considered high-risk because this agent, which has potent anti-leukemia cell effects, can artificially reduce the diagnostic WBC count. Another important variable for high-risk disease is the presence of disease in sanctuary sites (sites where chemotherapy penetration is thought to be more difficult) and includes the CNS and testes. Immunophenotyping has become an important component of ALL categorization. Although in general those with pre-B-cell phenotype are most likely to be cured, more aggressive therapy for the T-cell phenotypes (except early T-precursor ALL) has improved the outcome for both groups.[101] Approximately 5% of leukemias have mixed or undifferentiated lineages, and these patients tend to have a very poor outcome.[102] More recently, cytogenetic profiles of pediatric leukemias have further refined the prognostic classification of this disease. For example, hyperdiploidy (51-65 chromosomes per cell) and the *ETV6/RUNX1* translocation both have favorable outcomes and are seen in approximately 25% of cases of pre-B-cell ALL.[100] In contrast to hyperdiploidy, hypodiploidy (< 44 chromosomes) is a poor prognostic indicator. Finally, response to initial induction therapy is also an important predictor of outcome in pediatric ALL.[103] Although initial responses based on residual blasts in the bone marrow at end of induction are commonly used, the sensitivity of polymerase chain reaction can detect the molecular signature of residual blasts to less than 1 cell per 100,000.[104] Treatment for ALL typically consists of intensive induction with multi-agent chemotherapy (vincristine, corticosteroids, and asparaginase and an anthracycline) lasting 4 to 6 weeks and results in remission in 95% of patients. This is followed by consolidation, and the duration and drugs used vary between studies. In general, this phase lasts 6 to 9 months and often adds mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide, and/or cytarabine. During these first 2 phases, CNS treatment or prophylaxis are added

and can include intrathecal chemotherapy, systemic chemotherapy that can penetrate the blood-brain barrier, or cranial radiation. Treatment is completed with maintenance chemotherapy, which typically lasts a few years and tends to be antimetabolite based (methotrexate and mercaptopurine).[100] For patients with high-risk disease (infants, elevated WBC at diagnosis, T-cell disease, and those with *MLL* gene rearrangements), the therapy (especially induction and consolidation) is intensified but follows the same general principles as discussed previously. After induction failure or relapse, high-dose chemotherapy with stem cell rescue has proved to be an important salvage strategy that can result in cure in up to 40% of children.[105] The reinduction regimens are similar to those used at the time of initial diagnosis and can result in initial remission in the majority of patients.[106] The subsequent choice of therapy is dependent on a number of factors but usually includes high-dose chemotherapy and stem cell rescue. A number of new and exciting treatment options are now being developed for relapsed ALL, many of which focus on harnessing the power of the immune system to identify and kill tumor cells. Chimeric antigen-receptor T-cells use the patient's own T-cells genetically modified to express a receptor for a leukemia cell target (such as CD19)[107] and have been approved for patients with relapsed disease. Bispecific (dual specificity) antibodies against CD19 and CD3[108] or antibodies fused with toxins[109] have also demonstrated exciting results in subsets of patients.

Although advances for AML have paralleled those for ALL, current cure rates hover around 65%.[110] These leukemias account for approximately one-fifth of all leukemias and are thought to arise from bone marrow-derived stem or progenitor cells. These are differentiated from chronic leukemia by blast counts greater than 20% in the marrow at the time of diagnosis. Like ALL, there are a number of associated genetic and environmental factors that can predispose to AML, including Down syndrome. The treatment of AML, like that for ALL, is risk adapted and chemotherapy based. Pediatric patients with AML are typically treated using 2 main elements:

1) Induction is made up of daunorubicin (daunomycin), cytarabine (ara-C) etoposide, and/or 6-thioguanine and is usually more compressed and thus with greater toxicity. This therapy continues until morphologic remission in the blood and bone marrow is achieved (typically 2 to 3 cycles and successful in 85% to 90%). Concurrent intrathecal chemotherapy similar to that used in ALL is typically added to prevent CNS relapse.
2) Consolidation, sometimes referred to as intensification, is designed to kill the residual tumor cells that survived induction.

For many patients with a human leukocyte antigen-matched sibling, an allogeneic transplant is often the next step, especially in AML patients with poor prognostic markers. Therapy is generally much more intense than that used for ALL and does not typically include a maintenance phase. At the time of recurrence or for those patients who do not achieve induction remission, attempts at salvage with repeat intensive chemotherapy, especially if the interval between initial diagnosis and relapse is many years, can be considered. Unfortunately, the overall outcome for relapsed AML remains poor, and the majority of patients will succumb to their tumor.

3.2.1.3 Overview of Melanoma in the Pediatric Population

Advanced melanoma is generally regarded as a similar disease in adolescents and adults and is treated similarly. Metastatic melanoma does not commonly occur in the pediatric population from age 0 to less than 12 years.[14] The incidence reported in the US population for the age groups of 1 to 5 years, 5 to 9 years, and 10 to 14 years is 0.10, 0.16, and 0.37 per 100,000, respectively. The incidence in the US is higher in adolescents: 1.72/100,000 (15 to 19 years) (The SEER Carcinoma Statistics Review).[24] In the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) study of melanoma incidence in Italy, Poland, Germany, and France, incidence of cutaneous melanoma was reported as 0.7 to 0.8 per million per year for ages 0 to 10 years and 10 per million per year for ages 15 to 19 years.[111] Overall, the pediatric incidence rates (5.4 per 1 million children and adolescents in the US)[112] are dramatically lower than the adult incidence and add to the difficulty of evaluating adolescent melanoma in clinical trials. The diagnosis of pediatric melanoma is complicated by histologic uncertainty and disease characteristics. Melanoma can be confused with Spitz nevi, dysplastic nevi, traumatized nevi, halo nevi, and some congenital melanocytic nevi.[113] The key primary tumor characteristics, such as the site of the primary tumor, stage at diagnosis, tumor thickness, and level of invasion, are comparable between adolescent and adult melanoma patients. In contrast, prepubescent patients appear to have different characteristics (eg, with thicker tumor lesions) compared with adult melanoma patients. In an analysis of 1,255 children (age younger than 20 years), the 10 to 19-year-old age group had similar baseline characteristics compared with the 20- to 24-year-old age group.[114] There were significant differences in baseline characteristics of young children (younger than 10 years) compared with adolescents and young adults. Young children were more likely to be non-White and to have metastases; nodular or other histology; head, face, or neck primaries; thicker lesions; and history of cancer. There are limited clinical studies evaluating treatment outcomes in pediatric and adolescent participants with melanoma. Despite the small number of participants, results of these studies showed that safety profiles and treatment effects (such as tumor shrinkage or pharmacodynamic effects of immunotherapy) in pediatric participants are comparable with adult participants. The surgical treatment of the primary tumor in children is not different from that in adult participants.[115,116,117,118,119] Similar to adult patients, surgical resection, if feasible, for limited metastatic disease is recommended for pediatric patients. The National Comprehensive Cancer Network (NCCN) outlined the surgical management of melanoma based on stages.[120] As in adults, there is no chemotherapy with proven efficacy for the small subset of pediatric patients with metastatic melanoma. Radiotherapy is rarely indicated in the management of primary pediatric melanoma. However, it can be considered in patients with head and neck melanomas at high risk for parotid or cervical metastases, and in those who develop brain metastases. Brain metastases have been reported to occur during the course of the disease in up to 18% of children with melanoma.[121] Clinical studies with radiotherapy and chemotherapy in pediatric participants with melanoma showed a comparable safety profile to adult participants. Tumor shrinkages in individual participants and small studies were reported. However, the study design and the small

number of adolescent melanoma participants enrolled (n = 4 to 10) do not allow for a conclusive comparison of efficacy to adult studies.[122,123,124]

Immunotherapy in Melanoma: The FDA approved the expanded indication of ipilimumab (YERVOY®) for the treatment of unresectable or metastatic melanoma in pediatric patients aged 12 years and older.[125] In the EU, Yervoy as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents aged 12 years and older.[126] Nivolumab monotherapy is approved in multiple regions, including the US and EU, for unresectable or metastatic melanoma and adjuvant treatment of melanoma. Nivolumab monotherapy has demonstrated durable response exceeding 6 months and statistically significant improvement in OS vs the standard of care (SOC) for adult melanoma participants.[127]

Anticancer Therapy in Pediatric Oncology: Almost all children with cancer undergo treatment in the framework of clinical studies.[128] There are no guidelines providing specific recommendations for off-label use of anticancer medications in children.

Summary: The majority of pediatric malignancies are different molecularly and histologically from common adult malignancies, with the exception of melanoma, Ewing sarcoma, some osteosarcomas, SHH medulloblastoma, and HL. Although the large array of pediatric malignancies are different from each other, at the time of recurrence or progression they all share an equally poor prognosis. Because there are no known mechanisms common to these tumor types, immune-based therapies may provide an approach to control disease progression by enhancing the immune system and preventing immune evasion. Based on the potential benefit and expected safety profile of treatment of malignant tumors with bempegaldesleukin in combination with nivolumab described hereafter, a Phase 1b/2 study to evaluate safety, PK, and anti-tumor activity of bempegaldesleukin and nivolumab will be undertaken. This study will enroll participants younger than 18 years with refractory/relapsed malignant tumors, including advanced and metastatic melanoma, or those who have malignancies of poor prognosis, including newly diagnosed HGG/DIPG after initial radiation. Signals for anti-tumor activity from the proposed Phase 1b/2 study will help inform the choice of target tumor types for a subsequent therapeutic confirmatory study in subjects with non-melanoma tumor types.

3.2.2 Bempegaldesleukin Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T cells. As a PEGylated human recombinant IL-2 molecule of aldesleukin with an average of 6 releasable polyethylene glycol (PEG) chains, bempegaldesleukin can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. The polymer conjugation renders the cytokine initially inactive. Upon intravenous (IV) administration, the PEG chains slowly release to generate the active cytokine species (mainly 2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration of 24 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1-PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high-dose IL-2.

The polymer conjugation of bempegaldesleukin promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). Specifically, the location of the bempegaldesleukin PEG chains interferes with the binding to the IL-2 alpha receptor subunit responsible for the undesirable effect of activating regulatory T cells (Tregs) in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor. Upon infusion, bempegaldesleukin preferentially increases the proliferation, activation, and effector function of tumor antigen-specific CD8+ T cells and NK cells within the tumor microenvironment (TME) over expansion of unwanted intratumoral Tregs that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ).[129,130,131,132,133] Consistent with this mechanism of action, recent nonclinical studies demonstrate strong synergy of bempegaldesleukin with adoptive T-cell therapy, with PD-1 checkpoint blockade, and with tumor antigen-specific vaccination, in a variety of mouse models.[131,132] 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 PD-L1 on tumor cells.[134, 135]

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 complementary combination partner with checkpoint inhibitors.

3.2.3 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[136,137,138] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[139] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), inducible T-cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[140] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, IFN-γ, and Bcl-xL. PD-1 expression has also been

noted to inhibit T-cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop a variety of autoimmune phenotypes.[141] 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 (half maximal effective concentration, 0.39 to 2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (half maximal inhibitory concentration ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a cytomegalovirus (CMV) restimulation assay with human PBMC, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, PAN02).[142]

3.2.4 Clinical Experience with Nivolumab

3.2.4.1 Study ADVL1412 (Nivolumab Monotherapy)

Study ADVL1412 (NCT02304458) is the first study to demonstrate safety and assess anti-tumor activity of nivolumab monotherapy in children and young adults with relapsed or refractory solid tumors or lymphoma. Part A was a dose confirmation phase where children aged 1 to 18 years with recurrent or refractory solid tumors received nivolumab 3 mg/kg IV monotherapy on Days 1 and 15 of a 28-day cycle. Twelve out of 13 participants were evaluable in Part A (embryonal RMS [n=1], epithelioid sarcoma [n=2], Ewing sarcoma [n=1], neuroblastoma [n=4], osteosarcoma [n=3], undifferentiated sarcoma [n=1], and unspecified sarcoma [n=1]). Nivolumab 3 mg/kg was well tolerated and was confirmed as the pediatric recommended Phase 2 dose (RP2D); no dose de-escalation was required, and no dose-limiting toxicities (DLTs) were observed.[1]

Part B was a dose-expansion phase in children and young adults aged 1 to 30 years to test the safety and anti-tumor activity of the RP2D from Part A in participants with RMS, Ewing sarcoma, osteosarcoma, neuroblastoma, HL, and NHL. Participants with nonmeasurable neuroblastoma detected only by metaiodobenzylguanidine (MIBG) scintigraphy and participants younger than 18 years with recurrent, measurable melanoma were also enrolled. In Part B, 72 participants were enrolled and 63 were evaluable for toxicity; 5 participants experienced DLTs (Grade 3 elevated lipase for more than 7 days [n=1], Grade 4 neutropenia [n=1], Grade 3 pain at tumor site [n=1], Grade 3 upper gastrointestinal hemorrhage [n=1], and Grade 2 enterocolitis infection [n=1]), 2 participants required dose modifications (Grade 2 wheezing and Grade 2 transaminitis), and 7 discontinued due to adverse events (AEs; prolonged elevation of liver enzymes [n=2], prolonged elevated lipase [n=1], prolonged fever [n=1], gastrointestinal bleeding [n=1], infection [n=1], and autoimmune disorder, including thyroiditis, elevated creatine kinase, elevated creatinine [n=1]).

Anti-tumor activity was observed in 10 HL participants (1 complete response [CR], 2 PR, 5 stable disease [SD], and 2 mixed response [MR]) and in 1 participant with NHL (PR), but single-agent activity was not observed for the common, non-lymphoma, non-CNS pediatric solid tumors studied.[1]

The most common toxicities attributable to therapy among all participants evaluable for toxicity (n = 75) were hematological: anemia (47%), decreased WBCs (32%), decreased lymphocytes (29%), and decreased platelets (19%). The most common nonhematological toxicity was fatigue (37%). The most common immune-related AE was hepatic toxicity (aspartate aminotransferase [AST] increase in 29% and alanine aminotransferase [ALT] increase in 24% of participants). Thirty-seven participants died on study or during follow-up, but none were attributable to study therapy.[1]

The data show that nivolumab is well tolerated in the pediatric age group. Additional details on the clinical experience with nivolumab in adults are provided in the nivolumab Investigator Brochure (IB).[127]

3.2.5 Clinical Experience with Bempegaldesleukin

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

The bempegaldesleukin clinical development program started with the monotherapy study EXCEL (Study 15-214-01 [NCT02869295]: A Phase 1/2, Open-label, Multicenter, Dose-Escalation and Dose Expansion Study of NKTR-214 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 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 predefined DLT criteria. The RP2D was determined to be 0.006 mg/kg Q3W. Enrollment was closed after 28 participants 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 participants 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 participant dosed at 0.012 mg/kg experienced cytokine-release syndrome (CRS) and the DLTs of hypotension and syncope; this participant 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 final database lock date of 29-March-2018, 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 treatment-related AEs as flu-like symptoms, rash, and pruritus were generally mild or moderate in severity, predictable, manageable, and short-lived. These IL-2-mediated 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 nonsteroidal anti-inflammatory drugs, and the cases of rash/pruritus were either self-limiting or treated with antihistamines (steroids were administered for occasional participants who had severe rash/pruritus).

Six of 28 participants reported Grade 3 treatment-related AEs, which included hypotension, abdominal pain, infusion-related reaction, headache, and syncope. The cases of Grade 3 hypotension were rapidly reversed with IV fluids, and a hydration-management guideline was implemented during the study which mitigated the hypotension severity. One participant, 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 1 event of hypothyroidism, no other immune-mediated AEs (IMAEs) consistent with checkpoint inhibitors were reported. No participant experienced capillary leak syndrome, and no Grade 4 treatment-related AEs or treatment-related deaths were reported on the study.

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

In the 28 participants evaluable for efficacy in Study 15-214-01, best overall response (BOR) included SD in 14 participants (50%), progressive disease in 12 participants (42.9%), and not evaluable for 2 participants (7.1%). Although no objective responses were observed in Study 15-214-01, 9 participants experienced tumor shrinkage between 1% and 30%, and 2 participants, after progressing on multiple prior therapies, had durable SD over 1 year. One participant with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of bempegaldesleukin and had durable SD for 18 months. A second participant 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 SD for 14 months. Given the biological properties of bempegaldesleukin and nivolumab, these observations further supported the rationale for combining these two agents.

3.2.5.2 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 anticancer therapies in participants 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), urothelial carcinoma, breast cancer, gastric cancer, colorectal carcinoma (CRC), and small cell lung cancer. 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 participants with metastatic RCC, urothelial carcinoma, melanoma, or NSCLC who are treatment naïve.

The bempegaldesleukin plus 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 Q3W indicating no DLTs and no Grade ≥ 3 treatment-related AEs at the time of completion. Bempegaldesleukin 0.006 mg/kg in combination with nivolumab 360 mg Q3W was the recommended dose regimen to be taken forward into expansion cohorts in Part 2.

As of 28-Oct-2020, a total of 557 participants had been treated with bempegaldesleukin in combination with nivolumab (503 participants with doublet [bempegaldesleukin and nivolumab], 43 participants with triplet [bempegaldesleukin, nivolumab, and ipilimumab], and 11 participants with doublet [bempegaldesleukin and nivolumab] plus other anticancer study drug). Of the 557 participants, most have NSCLC (184 patients [33%]), RCC (139 [25%]), or melanoma (102 [18%]), followed by urothelial carcinoma (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 anticancer drug, 113.0) (range, 1 to 817 days).

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

- 94.6% (476 of 503) of participants reported treatment-related AEs; 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 participants reported treatment-related Grade ≥ 3 AEs; the most frequent were syncope (2.8%), hypotension (2.6%), and lipase increased (2.2%).
- 16.3% (82 of 503) of participants reported treatment-related SAEs; the most frequent were pyrexia (3.0%), hypotension (2.0%), and pneumonitis (1.0%).

Tumor response data are available for 37 of the dose-escalation participants, including 11 with metastatic melanoma, 21 with RCC, and 5 with NSCLC. Of these 37 response-evaluable participants, 25 were treated at 0.006 mg/kg bempegaldesleukin combined with nivolumab 360 mg flat dose Q3W. As of 18-January-2019, 22 of 37 evaluable participants (59.5%) achieved an investigator-assessed response (complete or partial response) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). [135]

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 1 dose of study treatment and having undergone at least 1 scan) were as follows:

- In first-line RCC participants, a 46% (12 of 26 participants) ORR was observed (N = 48 enrolled; N = 26 in the N1 + N2 population; 29-May-2018 cutoff).[143]
- In first-line melanoma participants, a 53% (20 of 38 participants) 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). [144]
- In first-line metastatic urothelial carcinoma participants, a 48% (13 of 27 participants) ORR was observed (N = 41 enrolled; N = 27 in the efficacy evaluable population; 03-Dec-2018 data cutoff).[145]
- In metastatic triple-negative breast cancer (TNBC) participants, a 13% (5 of 38 participants) ORR was observed (N = 43 enrolled; N = 38 in the efficacy evaluable population; 01-Jul-2019 data cutoff).[146]

To date, there have been no clinical studies in pediatric participants with bempegaldesleukin.

Additional details on the clinical experience with bempegaldesleukin are provided in the bempegaldesleukin IB.[147]

3.2.5.3 Pooled Safety Analysis of Participants with Bempegaldesleukin and Nivolumab Exposure

A pooled safety analysis (28-Oct-2020 data cutoff) is available of patients who received the bempegaldesleukin and nivolumab doublet from the ongoing combination Phase 1/2 studies (16-214-02 and 16-214-05), the ongoing combination Phase 2 study (18-214-10), and the completed Phase 1 study (CA045-010). Of the 696 patients who received the bempegaldesleukin and nivolumab doublet:

- 93.0% (647 of 696) of patients reported treatment-related AEs; the most frequent were pyrexia (42.1%), fatigue (39.9%), pruritis (37.6%), nausea (27.9%), rash (24.6%), decreased appetite (23.7%), influenza-like illness (22.4%), and chills (22.1%).
- 24.6% (171 of 696) of patients 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 patients reported treatment-related SAEs; the most frequent were pyrexia (2.6%), hypotension (1.7%), dehydration (0.9%), pneumonitis (0.7%), acute kidney injury, and atrial fibrillation, and myocarditis (0.6% each).

3.2.5.4 Observed Events of Cerebrovascular Accident

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

Serious events of cerebrovascular accident (CVA), including 1 fatal event, have been observed in participants who have received bempegaldesleukin in the triplet combination with nivolumab and ipilimumab, in the doublet combination with nivolumab, 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) had CVA events, including 1 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 1 of the study treatments in 4 participants (3 related to the doublet therapy and 1 related to nivolumab only); and 1 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.

3.2.5.4.2 Updated Analysis of Cerebrovascular Accident Events Observed with Bempegaldesleukin

A cumulative search of the bempegaldesleukin global safety database was conducted on 28-October-2020, which included 1345 patients 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, CA045-001 (17-214-08), CA045-009 (18-214-03), CA043-010 (18-214-14), SP-IND, and 17-262-01.

Overall, 1.9% (26 of 1345) of patients exposed to bempegaldesleukin reported CVA events. Of the 26 patients, 13 patients experienced Grade 3 or 4 events and 4 patients 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 patients with CVA events received a doublet combination with a checkpoint inhibitor, which included 1.7% (19 of 1116) of patients 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 AE of special interest (AESI) and mitigations were put in place to reduce the risk of CVA. These mitigations include implementation of a CVA AE management algorithm (Appendix 6) 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 IB.[147]

3.3 Benefit/Risk Assessment

3.3.1 Bempegaldesleukin Safety Profile

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

Additional details on the clinical experience with bempegaldesleukin are provided in the bempegaldesleukin IB.[147]

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.[127]

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 drug-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 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Nivolumab monotherapy has been studied in a Phase 1/2 trial in children and young adults with relapsed or refractory solid tumors or lymphoma. Nivolumab was considered to be safe and well tolerated. The study established a favorable safety profile for nivolumab in children and young adults (see Section 3.2.4).[1]

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[127]

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

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

While significant improvement in the outcome of children diagnosed with cancer has been achieved over the last 5 decades, in patients with recurrent or refractory disease as well as those with newly diagnosed malignant glioma, the over prognosis remains dismal and the majority will succumb to their disease. Based on the mechanism of action of bempegaldesleukin and nivolumab, this combination offers an opportunity to activate an immune response that has the potential to provide benefit to these children. While all treatments have associated risk, nivolumab[1] and other PD-1/PD-L1 inhibitors[2,3] have been well tolerated in pediatric patients at the same doses and schedules proposed in this study. Soluble IL-2 is a cytokine that has been extensively evaluated in both adult and pediatric patients and is currently approved for use in children with neuroblastoma. Based on the adult toxicity profile of bempegaldesleukin, which due to its unique properties, has a significantly improved adverse event profile compared to the approved soluble formulation of IL-2, it is anticipated that the risk associated with the administration in pediatric participants will be less than the currently approved formulation.

In conclusion, the currently available safety data demonstrate that bempegaldesleukin and nivolumab is a well-tolerated I-O combination therapy. Given the encouraging clinical activity and manageable and generally nonoverlapping toxicity profile, the potential for direct benefit in participants 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 has 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.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary - Part A Safety Lead-in	
• Safety Lead-in: To estimate the safety and tolerability of study treatment in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.	• Incidence of dose-limiting toxicities (DLTs), adverse events (AEs), serious AEs (SAEs), drug-related AEs, AEs leading to discontinuation, and death.
• To characterize the pharmacokinetics (PK) of bempegaldesleukin and nivolumab in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.	• PK parameters that are characterized by population PK models.
Primary - Part B Expansion	
• To estimate the preliminary efficacy (eg, ORR of study treatment separately in the following disease cohorts): – B1: Neuroblastoma – B2: Ewing sarcoma – B3: Rhabdomyosarcoma – B4: Miscellaneous solid tumors – B5: Non-Hodgkin lymphoma (NHL)/leukemia – B6: High-grade glioma – B7: Medulloblastoma and embryonal tumors – B8: Ependymoma – B9: Miscellaneous central nervous system (CNS) tumors	• Investigator-assessed objective response rate by: • B1: Revised International Neuroblastoma Response Criteria • B2 to B4: Response Evaluation Criteria in Solid Tumors v1.1 • B5: International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL • B5: Modified National Comprehensive Cancer Network Criteria for acute lymphoblastic leukemia • B5: Modified Cheson et al International Working Group criteria for acute myeloid leukemia. • B6 to B9: Response Assessment in Neuro-Oncology/Response Assessment in Pediatric Neuro-Oncology
Secondary - Part B Expansion	
• To estimate the safety of study therapy in pediatric participants.	• Incidence of AEs, SAEs, toxicities, drug-related AEs, AEs leading to discontinuation, and death. • Incidence of laboratory abnormalities.
• To estimate the progression-free survival (PFS) and overall survival (OS) of study therapy in pediatric participants.	• PFS, OS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Tertiary/Exploratory - Part A and Part B	
• To investigate the objective response rate (ORR; Part A), PFS (Part A), and duration of response (DOR) in participants with measurable disease at baseline.	• ORR, PFS, DOR
[redacted]	
• To characterize the PK in Part B of bempegaldesleukin and nivolumab in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.	• PK parameters that are characterized by population PK models.
• To characterize the immunogenicity of bempegaldesleukin and nivolumab.	• Anti-NKTR-214, anti-interleukin-2, and anti-polyethylene glycol antibodies and anti-nivolumab antibody and their relationship with select PK measures, safety, and efficacy, if appropriate.
• To evaluate changes in patient-reported tolerability (Part B only).	• Proportion of patients with score >3 during treatment and proportion of patients reporting improvement/worsening during treatment in selected items from the Patient-Reported Outcome – Common Terminology Criteria for Adverse Events (PRO-CTCAE).
[redacted]	

Abbreviations: AE = adverse event; CNS = central nervous system; DLT = dose-limiting toxicity; DOR = duration of response; Ig = immunoglobulin; NHL = non-Hodgkin lymphoma; NKTR-214 = bempegaldesleukin; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO-CTCAE = Patient Reported Outcome-Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

5 STUDY DESIGN

5.1 Overall Design

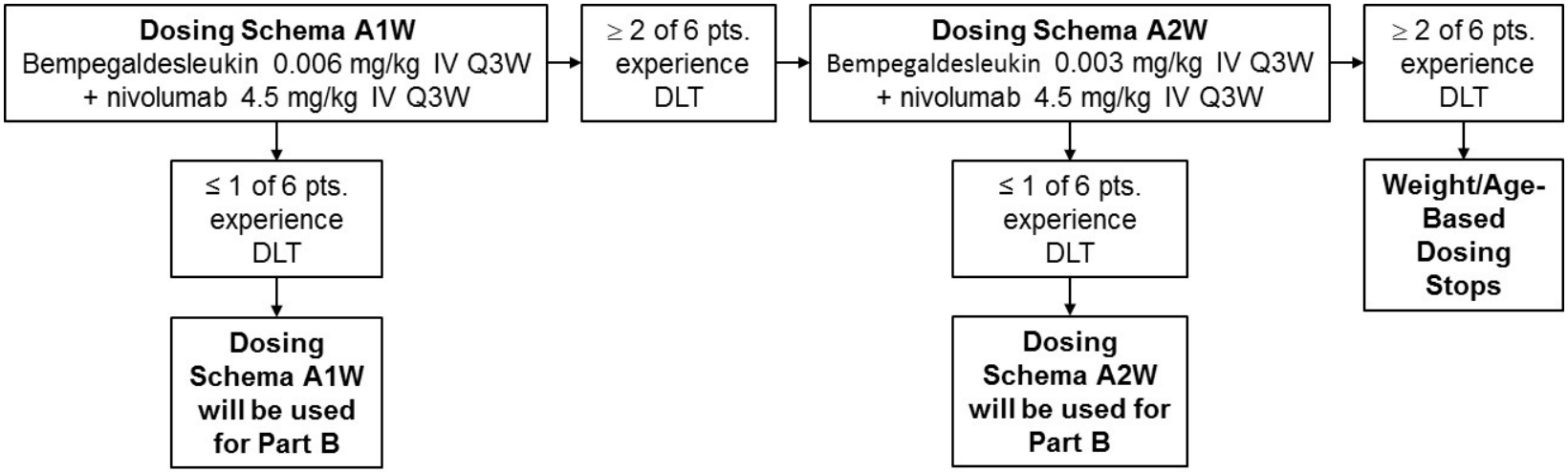
CA045-020 is an open-label, sequential-arm Phase 1b/2 clinical trial of bempegaldesleukin in combination with nivolumab in pediatric participants with malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking.

Because pediatric participants vary in age and weight, the starting doses of nivolumab will be determined separately based on age or weight. Participants aged < 12 years or weighing < 40 kg will be given a weight-based dose of nivolumab (see Figure 5.1-1), and participants aged ≥ 12 years and weighing ≥ 40 kg will be given a flat dose of nivolumab (see Figure 5.1-2).

Phase 1b consists of Part A. In Part A, a maximum of 30 participants (ie, up to 2 cohorts of 6 participants in the weight/age-based dosing schema and up to 3 cohorts of 6 participants in the flat to weight-based dosing schema) will be treated with both nivolumab and bempegaldesleukin IV Q3W to determine the recommended dose of bempegaldesleukin to take into Part B and to determine if nivolumab flat or weight-based dosing will be used for those ≥ 12 years and weighing ≥ 40 kg.

The study design schematic is presented for Part A in Figure 5.1-1 and Figure 5.1-2 and for Part B in Figure 5.1-3.

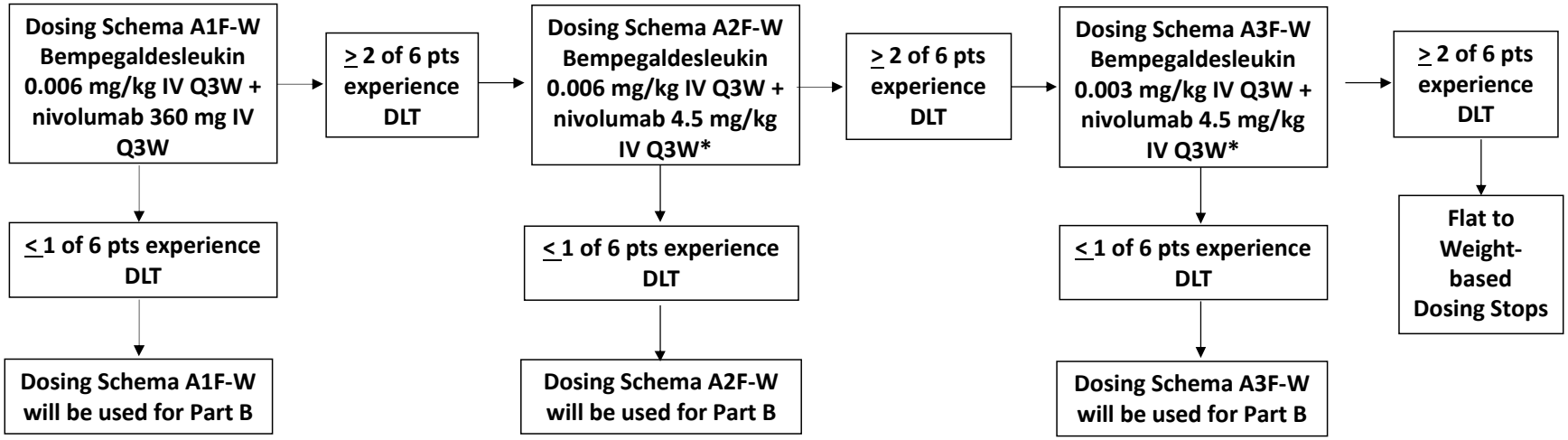
Figure 5.1-1: Phase 1b (Part A) Dose-finding Study Design for Age- and Weight-based Dosing of Participants Aged < 12 Years or Weighing < 40 kg for Bempegaldesleukin in Combination with Nivolumab*



*for nivolumab 4.5 mg/kg in dosing schema A1W and A2W, up to 360 mg equivalent is the maximum dose

Abbreviations: DLT = dose-limiting toxicity; IV = intravenous; pts = participant; Q3W = every 3 weeks; W=weight/age-based dose.

Figure 5.1-2: Phase 1b (Part A) Dose-finding Study Design for Flat to Weight-based Dosing of Participants Aged ≥ 12 Years and Weighing ≥ 40 kg for Bempegaldesleukin in Combination with Nivolumab*



*for nivolumab 4.5 mg/kg in dosing schema A2F-W and A3F-W, up to 360 mg equivalent is the maximum dose

Abbreviations: DLT = dose-limiting toxicity; F=flat dose; IV = intravenous; pts = participant; Q3W = every 3 weeks.

Phase 2 (Part B) will use a modified Simon 3-stage variant design[148] (Section 10.1) to enroll at least 9 participants into 7 individual cohorts (B1 to B3 and B5 to B8) based on tumor type to be treated. For the miscellaneous solid tumor and miscellaneous CNS tumor cohorts, the Simon 3-stage variant design will not be applied and can accrue up to the maximum of 24 participants. All 9 cohorts will be treated with the selected dosing schema(s) from Part A of the study. The Part B cohorts are disease and histology specific, as presented in Figure 5.1-3. Further details on the progression of enrollment can be found in Section 5.1.2.

Figure 5.1-3: Phase 2 (Part B) Study Design Schematic

Part B (Phase II Expansion Cohorts Modified Simon 3-Stage Variant Design)

9 patients per cohort	# Responses	Add to accrual	# Responses	Add to accrual	Max Total
B1 Neuroblastoma	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B2 Ewing sarcoma	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B3 RMS	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B4 Miscellaneous solid tumors	Continue accrual to maximum 24 patients				
B5 NHL/leukemia	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B6 High-grade glioma	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B7 Medulloblastoma and ETs	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B8 Ependymoma	If ≥ 1/9 →	7 →	If ≥ 2/16 →	8	24
B9 Miscellaneous CNS tumors	Continue accrual to maximum 24 patients				

Abbreviations: CNS = central nervous system; ET = embryonal tumor; NHL = non-Hodgkin lymphoma; RMS = rhabdomyosarcoma.

The total duration of the study is up to 5 years from start of study treatment of the last participant, or until the time of primary OS analysis, whichever occurs later.

5.1.1 Screening Period

Written informed consent (and assent where appropriate) must be obtained before starting any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. Once informed consent/assent is received, participants will be evaluated for entry criteria during the Screening period prior to the administration of the study drug.

[redacted]

Palliative radiation to non-target lesions is permitted. Participants receiving palliative radiation to target lesions require reimaging post radiation and prior to initiation of drug therapy.

5.1.2 Treatment Period

Phase 1b - Part A

For Part A, up to 6 participants will be enrolled in each dosing schema (total maximum of 30 participants) starting with dosing schemas A1W (weight/age-based dosing) and A1F-W (flat to weight-based dosing) for 1 cycle (each cycle is 21 days). Assessments for the weight/age-based and for the flat to weight-based dosing schemas will run concurrently and are independent of each other. Any dosing level in which ≥ 2 participants experience 1 or more DLTs identified during the DLT period will be reviewed by the data monitoring committee (DMC; Section 5.1.5) before accrual into the dose-reduced schema proceeds for weight/age-based or flat to weight-based dosing, respectively, as outlined in Figure 5.1-1 (A2W; weight/age-based dosing) and Figure 5.1-2 (A2F-W; flat to weight-based dosing).

Since the weight/age-based dosing schemas (A1W/A2W) and the flat to weight-based dosing schemas (A1F-W/A2F-W/A3F-W) are independent from each other, they will be evaluated for DLTs separately. If dosing in one schema must be reduced or stopped due to DLTs, the other schema will continue as outlined. For participants in any tolerated dosing schemas, participants will continue treatment until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant is lost to follow-up, Bristol-Myers Squibb (BMS) and Nektar Therapeutics conclude(s) the study, or for a maximum of 2 years of study treatment.

Participants in Part A treated at the dosing schema used in Part B can be counted in the accrual goals for Part B. The selection of the optimal dosing schema for Part B will be made at the completion of Part A and can occur separately for the 2 dosing schemas (weight/age-based and flat to weight-based dosing, respectively) in conjunction with the DMC.

Phase 2 - Part B

For Part B, 9 participants will be enrolled into each of the following tumor-specific cohorts using the optimal dosing schemas identified in Part A:

- B1: Neuroblastoma
- B2: Ewing sarcoma
- B3: RMS
- B5: NHL/leukemia
- B6: High-grade glioma
- B7: Medulloblastoma and CNS embryonal tumors
- B8: Ependymoma

For each of the cohorts above, if ≥ 1 of 9 participants shows a response, an additional 7 participants will be enrolled. If ≥ 2 of 16 participants shows a response, an additional 8 participants will be enrolled for a maximum of 24 participants per cohort.

For the following tumor types, the study will enroll up to a maximum of 24 participants per cohort regardless of response:

- B4: Miscellaneous solid tumors
- B9: Miscellaneous CNS tumors

Participants from Part A treated at the same dose as in Part B (for both dosing cohorts) can be included in the accrual numbers for Part B. Participants in Part B will be treated at the appropriate dose defined in Part A for each stratum and will therefore be a mixture of participants from the weight/age-based and flat to weight-based dosing groups. Participants who initiate therapy in 1 group (weight/age-based or flat to weight-based dosing) will not switch over during the study, even if there is a change in age or weight while on therapy.

For this study, response will be assessed by institutional review using RECIST v1.1 for solid tumors, Response Assessment in Neuro-Oncology (RANO)/Response Assessment in Pediatric Neuro-Oncology (RAPNO) for CNS tumors, International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL, revised International Neuroblastoma Response Criteria (INRC) for neuroblastoma, modified NCCN Criteria for acute lymphoblastic leukemia, and modified Cheson et al International Working Group criteria for acute myeloid leukemia.

Participants will be treated until disease progression, death, unacceptable toxicity, symptomatic deterioration, the Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant is lost to follow-up, BMS and Nektar Therapeutics conclude(s) the study, or for a maximum of 2 years of treatment.

In certain circumstances, participants with progressive disease using disease-specific criteria, but with otherwise stable or improved performance and clinical status, may continue to be treated for a total of 2 years from Cycle 1 Day 1, in the event of a perceived benefit per Investigator; see Section 8.1.2 for treatment beyond progression criteria.

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

5.1.3 Dose-limiting Toxicities

For the purpose of guiding decisions regarding dose de-escalation in Parts A and B, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will start on Cycle 1 Day 1 and end at Day 42 (therefore, 6 weeks). The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5 (CTCAE v5). In addition to DLTs, the Sponsor

will evaluate the overall tolerability of the dose determination in Part A before deciding if Part B will be evaluated in this participant population.

For the purpose of participant management, DLTs that occur at any time will result in study drug being delayed pending evaluation of the event in relation to study drug, in accordance with Section 7.4. A participant is considered DLT evaluable after receiving 1 dose of any study drug.

Participants who withdraw from the study during the 6-week DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the 6-week DLT evaluation period will be used to help guide de-escalation decisions and to define the MTD/RP2D. AEs occurring after the 6-week DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor and Investigators. Participants experiencing a DLT will be evaluated to determine if they are eligible to continue study drug at modified dosing (Section 7.4.1) or if they should discontinue from the study.

5.1.3.1 Gastrointestinal Dose-limiting Toxicities

Any one of the following study drug-related events will be considered a gastrointestinal DLT:

- Grade 2 colitis that lasts longer than 7 days, despite best supportive treatment.
- Grade 3 colitis that lasts more than 5 days.
- Grade 4 colitis or diarrhea.
- Grade 3 diarrhea that lasts longer than 72 hours with adequate supportive treatment.

5.1.3.2 Hepatic Dose-limiting Toxicity

Any 1 of the following study drug-related events will be considered a hepatic DLT:

- Grade 2 elevations in AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, and pruritus).
- Grade 3 or above elevation of AST and/or ALT, as below
  - ≥ 8 times ULN
  - >5.0 - < 8 times ULN persisting for > 7 days
- Grade 4 elevations in AST, ALT, ALP, or total bilirubin.
- Grade 4 elevations in AST, ALT, ALP, or total bilirubin in the absence of cholestasis.
- AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis (elevated ALP; eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [pDILI]). Note that this specific category of DLT uses ULN rather than CTCAE grade for definition.
- For participants with hepatic metastases, AST or ALT > 8 × ULN or AST or ALT > 5 × ULN for ≥ 14 days.

5.1.3.3 Hematologic Dose-limiting Toxicity

Any of the following study drug-related events will be considered a DLT:

- Febrile neutropenia.
- Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids).
- Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion.
- Grade 4 neutropenia > 7 days in duration.
- Grade 4 thrombocytopenia.
- Grade 4 anemia not explained by underlying disease.

5.1.3.4 Dermatologic Dose-limiting Toxicity

Any of the following study drug-related events will be considered a DLT:

- Grade 3 rash if no improvement (ie, resolution to < Grade 1) after a 1- to 2-week infusion delay. Topical steroid treatment is allowed for symptom control.
- Grade 4 rash.

5.1.3.5 Other Dose-limiting Toxicities

Any of the following study drug-related events will be considered a DLT:

- Any AE that requires discontinuation of nivolumab per the local labeling information
- Any grade immune-related encephalitis.
- Any incidence of Grade 3 prolongation of QT interval corrected using Fridericia's correction formula (QTcF) on electrocardiograms (ECGs).
- Any death not clearly due to the underlying disease or extraneous causes.
- Grade 2 drug-related uveitis, episcleritis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks/until the following dose OR requires systemic treatment.
- Grade 2 pneumonitis that does not respond to dose delay and systemic steroids within 14 days.
- Grade 3 fatigue lasting ≥ 1 week.
- Grade 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm, or neurologic toxicity.
- Grade ≥ 3 myocarditis.
- Grade ≥ 3 electrolyte abnormality associated with clinical symptoms.
- Grade ≥ 3 electrolyte abnormality that lasts > 72 hours.
- Grade 4 hypersensitivity/infusion reaction, or Grade 3 that does not resolve to Grade 1 in < 6 hours.

Other ≥ Grade 3 study drug-related toxicities will be considered DLTs, except those clearly and incontrovertibly due to disease progression and extraneous causes. However, the following Grade 3 or 4 events will NOT be considered DLTs:

- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities not associated with clinical symptoms and either resolve spontaneously or are corrected with supplementation/appropriate management within 72 hours of their onset. Confirmatory laboratory test is required within 72 hours.
- Grade 3 nausea or vomiting that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention.
- Grade 3 or Grade 4 elevation of amylase or lipase not associated with symptoms or clinical or radiographic evidence of pancreatitis.
- Grade 3 fever not associated with hemodynamic compromise or neutropenia (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion).
- Grade 3 endocrinopathy that is well controlled by hormone replacement.
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue.
- Grade 3 infusion reaction that returns to Grade 1 in < 6 hours.
- Grade > 3 AE resulting from non-compliance with oral hydration guidelines.

5.1.3.6 Stopping Rules for Part B

During Part B, monitoring of toxicity events (as specified in Section 5.1.3) will be performed in each cohort. The monitoring function for toxicity is defined as the posterior probability of the toxicity rate > 30% given cumulative data >0.90. This criterion implies that the given cohort may be stopped for enrollment if there is a greater than 90% probability that the toxicity rate will be > 30%. The monitoring process will be applied first when at least 5 toxicity-evaluable participants are treated in a cohort and for every 5 additional toxicity-evaluable participants thereafter.

This monitoring process is based on a Bayesian sequential monitoring design[149] where one assumes a beta (0.6, 1.4) prior distribution for the toxicity rate, which has a mean of 0.3 corresponding to a 30% approximate target toxicity rate in Part A. The posterior distribution at any time point is beta (0.6 + n, 1.4 + [m-n]), where n is the number of participants observed with toxicity and m is the total number of toxicity-evaluable participants in the cohort.

The resulting boundaries are presented in Table 5.1.3.6-1 and Table 5.1.3.6-2. Table 5.1.3.6-2 also summarizes the probability to cross those boundaries as well as average sample size reached at suspension in a cohort for different toxicity rates.

If the boundary in a cohort is met at any time during Part B, the accrual will be suspended for that cohort and the DMC will meet to review the safety data, taking into account all available safety information across all cohorts before making a final recommendation to the Sponsor.

Table 5.1.3.6-1: Suspension Criteria for Toxicity During Part B Expansion

Number of Toxicity-Evaluable Participants in the Cohort (Cumulative)[a]	Suspend Accrual if ≥ Number of Participants with Toxicity
4	Not applicable
5	4
10	6
15	8
20	9

[a] Assuming cohort can enroll up to 24 participants.

Table 5.1.3.6-2: Suspension Probabilities for Toxicity During Part B Expansion

Toxicity Rate	Average Number of Accrual Reached at Suspension[a]	Probability of Suspending Accrual
10%	24	0.00
20%	24	0.02
30%	23	0.14
40%	19	0.44
50%	15	0.77
60%	11	0.95
70%	8	1
80%	6	1

[a] Assuming cohort can enroll up to 24 participants.

5.1.4 Long-term Follow-up

Long-term follow-up should continue until withdrawal of consent, death, or study termination by the Sponsor. The total duration of the study is up to 5 years from first study treatment of the last participant. Timing for long-term follow-up will be as follows:

- Assessments should continue as described in Table 2-3.
- Participants must be followed for at least 150 days after the last dose of study treatment. The first 3 follow-up visits should be conducted in person.
  - 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.
  - Follow-up Visit 3 occurs approximately 150 days (± 7 days) from the last dose of study treatment.

- Additional assessments may occur when the decision is made to discontinue treatment.
- Subsequent to Follow-up Visit 3, 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. Additional assessments described in Section 2 will also be collected. After completion of study therapy for participants without progression results of additional imaging, including bone marrow and CSF, if applicable, are requested for the duration of the study.
- Per clinical judgment, the participant may come in earlier to all follow-up visits.
- In case of a clinically significant AE, the participant will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drugs (bempegaldesleukin and/or nivolumab). If the participant discontinues study drug for a clinically significant AE, the participant will be followed until resolution of the AE or the event is considered to be stable and/or chronic. Tumor scans will also continue as described in Section 2.

5.1.5 Data Monitoring Committee and Other External Committees

A DMC will be established to provide oversight of safety and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants. 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. The DMC will meet at least every 6 months or more frequently as needed on an ad-hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad-hoc meeting on its own initiative. 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. The DMC will review all available data (safety and efficacy) at each meeting. At the conclusion of each DMC meeting, the committee will provide the Sponsor with a recommendation to continue, modify, or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the Sponsor in conjunction with feedback from Investigators and the DMC.

5.2 Number of Participants

The total sample size of the study is estimated to be between approximately 10 and 234 participants depending on dose de-escalation contingencies in Part A and cohort expansions in Part B. A complete description of the sample size is provided in Section 10.1. Accrual estimates for the expansion phase are based on the modified Simon 3-stage variant design and are provided in Figure 5.1-3.

In Part A, if ≥ 2 participants in the weight/aged-based cohort experience DLTs (A1W/A2W; n = 2), then the weight/aged-based group would drop to the lower dose of bempegaldesleukin. If ≥ 2 participants in the flat to weight-based dosing schema experience DLTs (A1F-W; n=2), then the flat to weight-based dosing group would maintain the bempegaldesleukin dose and change to

weight-based dosing of nivolumab (A2F-W; n=2). If ≥ 2 participants in the flat to weight-based dosing schema had DLTs in the A2F-W cohort, then the flat to weight-based dosing group would drop to the lower dose of bempegaldesleukin and maintain the weight-based dosing of nivolumab (A3F-W; n=2). If ≥ 2 participants in each of the weight/aged-based or flat to weight-based dosing schemas at the lowest doses again had DLTs (A1W/A2W; n = 4/A1F-W/A2F-W/A3F-W; n = 6), the trial would close. Therefore, the actual minimal accrual is 10 participants.

In Part A, if 6 participants are treated in each of the weight/aged-based or flat to weight-based dosing schemas (A1W/A1F-W; n =12) and there is a need to dose reduce in both cases due to DLTs, another 6 participants would be enrolled in the lower dose levels (A2W/A2F-W/A3F-W; n = 18). If this lower dose was tolerated, then Part B will start using the lower dose level (see Figure 5.1-1 and Figure 5.1-2).

Part B allows up to a maximum of 24 participants in each of the 9 cohorts (n = 216). Since the participants in Part A treated at the RP2D could be counted in the accrual Part B, 12 of the 30 participants in Part A would be accounted for, leaving only 18 more to be added to the total. As such, the maximum number of participants would be 234.

5.3 End of Study Definition

This study will consist of 3 periods: screening, treatment, and follow-up. The start of the trial is defined as the first visit for the first screened participant. End of trial is defined as the last scheduled procedure shown in the Schedule of Activities in Section 2 for the last participant. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if it is not the same. Follow-up for a minimum of 3 years (from study entry) is planned, if applicable, but no more than 5 years.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for the Combination of Bempegaldesleukin and Immune Checkpoint Inhibitors

This study is designed to evaluate the safety and efficacy of study therapy in pediatric malignant tumors, including leukemias, NHL, neuroblastoma, RMS, Ewing sarcoma, high-grade glioma, medulloblastoma, ependymoma, and miscellaneous solid and CNS tumors. These tumor subtypes have quite different molecular genetics, natural disease histories, survival outcomes, and responses to current therapies that preclude use of 1 endpoint for all groups and require analysis in distinct cohorts, recognizing that there is important heterogeneity even within these cohorts.

Single agent PD-1 and PD-L1 inhibition has had very limited activity to date in pediatric solid and central nervous system tumors.[1,2,3] It is likely that some of this is related to the low mutational burden characteristic of most pediatric malignancies that limit the stimulatory response needed to activate T cells. Bempegaldesleukin, an IL-2 derivative that induces T cell activation and proliferation may overcome this problem and in conjunction with a checkpoint inhibitor, allow for both the activation of the T cell response while providing the needed dis-inhibition to allow it function.

5.4.2 Rationale for Study Comparator and Study Population

Pediatric patients with cancer are in need of new therapies and this combination has the potential to activate an anti-tumor response while inhibiting the checkpoint molecules that could suppress a response. As per the new FDA guidelines, assessment of new agents in pediatrics is based on the MOA of the agent(s) being tested.

5.4.3 Rationale for Permitting Treatment Beyond Suspected Progression

Accumulating clinical evidence indicates some participants treated with immune system-stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or SD. This phenomenon was observed in approximately 10% of participants in the Phase 1 study of nivolumab. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace antitumor immune activity. With sufficient time, the antitumor activity will dominate and become clinically apparent. Therefore, participants initially meeting radiologic criteria for disease progression (see Section 9.1) will be allowed to continue study therapy until a second radiologic confirmation of progression as long as the following criteria are met: (1) the participant experiences investigator-assessed clinical benefit and (2) the participant is tolerating the study treatment.

5.4.4 Rationale for Choice of Endpoints

Part B of this trial is designed as a signal-seeking study and includes a large number of different tumor types with heterogeneous biology and outcomes. Although radiographic or other disease-appropriate defined measures of response may not always directly correlate with improved participant outcome, ORR remains the best and most reliable measure of treatment effect.

ORR will be used to evaluate for potential signals of activity of the study treatment. Trials of nivolumab are either recently completed in pediatric participants with solid tumors, including lymphoma (CA209-070; NCT02304458),[1] or nearing completion for CNS tumors (CA209-908; NCT03130959) and will provide important comparators to this study with the addition of bempegaldesleukin (see Section 3.2.4).

5.4.5 Rationale for Open-label Design

This trial seeks to identify the toxicity and appropriate dose of the combination under study in addition to an assessment of an early efficacy signal. A placebo-controlled, double-blinded trial would not be appropriate at this stage of pediatric development. Additionally, due to the hydration program and the special restrictions for withholding antihypertensive in the bempegaldesleukin arm, a placebo-controlled, double-blinded study is not appropriate for this study.

5.4.6 Rationale for Stratification

Part B of this trial is designed as a signal-seeking study and includes a large number of different tumor types with heterogeneous biology and outcomes. In order to maximize the chances of

observing an efficacy signal, participants in Part B will be assessed in 9 different disease cohorts (see Figure 5.1-3).

5.4.7 Duration of Treatment with Nivolumab/Bempegaldesleukin

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab 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. A recent analysis in a melanoma study suggests that the majority of participants who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[150]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in adult participants with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[151] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29% and 3-year OS rates of 16 to 18% for squamous and non-squamous NSCLC, respectively).[152]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized, Phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg Q3W) vs docetaxel in participants with previously treated, PD-L1-positive, advanced NSCLC that specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (hazard ratio [HR]: 0.72; P = 0.00017) and pembrolizumab 10 mg/kg (HR: 0.60; P < 0.00001) compared with docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 participants who received pembrolizumab, 47 participants completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2participants (4%) having confirmed progression after stopping at 2 years.[153]

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

In contrast, a shorter duration of nivolumab treatment of only 1 year was associated with increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab

had significant improvement in progression-free survival (PFS) compared with those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively (HR: 0.42 [95% confidence interval (CI): 0.25 to 0.71]). With a median follow-up of 14.9 months post-randomization, there also was a trend for participants on continued treatment to live longer (OS HR: 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[154]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond 2 years in advanced tumors. However, although immunotherapy is well tolerated, participants will be at risk for additional toxicity with longer-term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

Given the hypothesis that co-administration of bempegaldesleukin with nivolumab will potentiate the pharmacological effects of nivolumab, the duration of bempegaldesleukin therapy will also be restricted to 2 years to match the duration of nivolumab therapy.

5.5 Justification for Starting Dose

5.5.1 Justification for Dose of Bempegaldesleukin

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. Please refer to Section 3.2.5.2 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, classical HL, squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma, using body weight-normalized dosing (mg/kg) and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, classical HL, SCCHN, and urothelial carcinoma, using a regimen of either nivolumab 240 mg Q2W, nivolumab 3 mg/kg Q2W, or nivolumab 480 mg every 4 weeks.

Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kg Q2W. Population pharmacokinetics (PPK) analyses have shown that the pharmacokinetics (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 is 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 maximum concentration at steady state (Cmaxss) following nivolumab 360 mg Q3W is predicted to be less than that 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.[127]

Finally, nivolumab 360 mg Q3W is currently being investigated in combination with a number of other agents, including bempegaldesleukin in Study 16-214-02 (PIVOT-02), and platinum-doublet chemotherapy dosing, with no new or increased safety events observed to date. This study will therefore initiate treatment at the same dose level of bempegaldesleukin and nivolumab that will include flat dosing with nivolumab 360 mg Q3W for participants aged 12 years and older and weighing at least 40 kg or the weight-based equivalent (nivolumab 4.5 mg/kg Q3W) for participants younger than age 12 years or weighing less than 40 kg.

In Protocol Amendment 01, the flat dosing cohort in Part A has been modified to allow for changing to weight-based dosing with nivolumab. This update is based on a recent population pharmacokinetic modeling analysis of nivolumab concentration data that included data from pediatric subjects (NCI# NCT02304458) in Nivolumab IBv20. It is predicted that adolescents aged ≥ 12 years and weighing ≥ 40 kg and < 80 kg receiving a flat dose of nivolumab (ie, 360 mg Q3W) may be exposed to higher levels of nivolumab in the blood than adults receiving the same flat dosing regimen. This is based on the estimate of lower clearance of nivolumab in pediatric patients, including adolescents in the modeling analysis. It is not known whether the predicted increased exposure to nivolumab may be associated with an increased risk of side effects. This prediction is based on modeling, as there are no available data for pediatric or adolescent patients treated with the flat dosing. Although the reason for the estimated lower clearance of nivolumab is not definitely known, it may be due to differences in physiological disease states between pediatric and adult tumors. It should be noted that nivolumab exposure in adolescent subjects receiving the flat dose was predicted to be below the exposure observed in adults receiving the well-tolerated nivolumab monotherapy regimen of 10 mg/kg Q2W. In Part A, should any DLTs be observed with the flat dosing of nivolumab, the addition of weight-based dosing will allow for the evaluation of weight-based nivolumab with bempegaldesleukin in those ≥ 12 years and weighing ≥ 40 kg.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Prior to study participation, written informed consent from participants, or in the case of minors, written permission (informed consent) from parents (both, if required by local law), guardians, or legally acceptable representatives must be obtained according to local laws and regulations.

b) Assent from minor participants, where appropriate, should be obtained per local laws and regulations and should be documented in accordance with local requirements.

c) Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (applies to covered entities in the US only) must be obtained from

the participant/legal representative prior to performing any protocol-related procedures, including screening evaluations (that are not part of normal participant care).

d) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study, including disease assessment. Participants with glioma, medulloblastoma, ependymoma, and other CNS tumors must be able to undergo magnetic resonance imaging (MRI) with and without contrast because computed tomography (CT) scan is not permitted for these tumor types.

2) Type of Participant and Target Disease Characteristics

a) Participants must have received SOC therapy, and there must be no potentially curative treatment available.

b) Histologically confirmed malignant neoplasms that are refractory, relapsed, or participants for whom curative treatments are lacking, including newly diagnosed high-grade glioma.

c) Participants must have measurable or evaluable disease based on RECIST v1.1 for solid tumors, RANO/RAPNO for CNS tumors, International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL, revised INRC for neuroblastoma, modified NCCN Criteria for acute lymphoblastic leukemia, and modified Cheson et al International Working Group criteria for acute myeloid leukemia.

d) Lansky play score for age ≤ 16 years or Karnofsky performance score for age > 16 years assessed within 2 weeks of enrollment must be ≥ 60. Participants who are unable to walk because of neurologic deficits but who are in a wheelchair will be considered ambulatory for the purpose of assessing the performance score (Appendix 7).

e) Substantial recovery (ie, no ongoing safety issues) from prior therapy.

f) An interval of 4 weeks or 5 half-lives, whichever is longer, after the last administration of any anti-cancer therapy or any other treatment for malignancies (6 weeks for nitrosoureas), prior to first dose of study drug. The interval from most recent biological agent must be 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug.

g) Participants with CNS tumors must not receive more than 0.05 mg/kg dexamethasone (or equivalent) per day and the dose should be stable for a minimum of a week.

h) Participants who have received high-dose chemotherapy with autologous hematopoietic cell transplantation must be at least 6 months post-hematopoietic cell transplantation and they must have a CD4 count of at least 200.

i) Prior palliative radiotherapy must be completed at least 2 weeks prior to first dose of study drug. Participants must have recovered from all Grade 2 or higher clinically relevant radiation-related toxicities. Participants with newly diagnosed malignant gliomas who may have received focal radiation or radiation and temozolomide are eligible. Note: Radiated lesions cannot be used as measurable lesions unless they have a new baseline scan after radiation or there is clear evidence of progression.

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

k) Participant re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented (Section 6.4.1).

3) **Age and Reproductive Status**

a) Female Participants

i) Females, ages less than 18 years old at the time of enrollment for Part A and Part B. For Part B, Cohorts B2, B3, and B4, participants less than 30 years old may be enrolled.

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 serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) 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.

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

vi) 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.

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

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

ix) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 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-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants

i) Males, ages less than 18 years old at the time of enrollment for Part A and Part B. For Part B, Cohorts B2, B3, and B4, participants less than 30 years old may be enrolled.

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) **Not applicable as of Amendment 01; see 3) b) viii) for updated criterion:** 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 post-treatment completion.

iv) **Not applicable as of Amendment 01; see 3) b) ix) for updated criterion:** 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 post-treatment completion in the male participant.

v) **Not applicable as of Amendment 01; see 3) b) x) for updated criterion**: 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 post-treatment completion.

vi) **Not applicable as of Amendment 01; see 3b(xi) for updated criterion:** Male participants must refrain from donating sperm during the intervention period and for at least 7 months post-treatment completion.

vii) 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.

viii) 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 post-treatment completion.

ix) 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 post-treatment completion in the male participant.

x) 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 post-treatment completion.

xi) Male participants must refrain from donating sperm during the intervention period and for at least 3 months post-treatment completion.

Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, 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.

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with osteosarcoma, T-cell/NK-cell leukemia/lymphoma, and HL.

b) 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).

c) Active infection requiring systemic therapy within 14 days prior to first dose.

d) Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Participants with hypertension must be on a stable antihypertensive regimen for the 14 days prior to treatment assignment. Note: An antihypertensive medication that contains 2 drugs in 1 formulation is counted as 2 antihypertensive medications (e.g., angiotensin-converting-enzyme [ACE] inhibitor plus diuretic, calcium channel blocker plus ACE inhibitor).

e) Unstable or deteriorating cardiovascular disease within the previous 12 months prior to screening, including, but not limited to, the following:

(1) Unstable angina or myocardial infarction

(2) Transient ischemic attack (TIA)/CVA

(3) Congestive heart failure (New York Heart Association Class III or IV)

(4) Uncontrolled clinically significant arrhythmias

f) History of pulmonary embolism, deep vein thrombosis, or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (eg, internal jugular vein thrombosis) within 3 months prior to treatment assignment.

(1) Participants with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to treatment assignment and must be receiving a stable regimen of therapeutic anticoagulation (low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]). Note: See Section 7.7.4.1 (Restricted Treatments) for further guidance.

(2) 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.

g) Participants with inadequately treated adrenal insufficiency.

h) 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.

i) Participants with a condition (excluding CNS tumors) requiring systemic treatment with either corticosteroids (> 0.12 mg/kg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses > 0.12 mg/kg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

j) Known human immunodeficiency virus (HIV) positive with an Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. (Participants with known HIV who are enrolled should receive ART therapy as clinically indicated and be monitored for CD4 counts and viral load per standard of care by a local health care provider.) NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 13).

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

l) Participants with serious or uncontrolled medical disorders.

2) Prior/Concomitant Therapy

a) Participants who have received a live/attenuated vaccine within 30 days before first treatment (see Section 7.7.3.1). Replication-incompetent virus vaccines are not considered live vaccines (live vaccines are defined as those that are capable of transmitting infectious viruses).

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

c) 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 treatment. Refer to Section 7.7.1 for prohibited therapies.

d) Participants having had a prior allogeneic stem cell transplant.

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.

3) Physical and Laboratory Test Findings

a) WBC < 2000/µL (participants with leukemia or bone marrow infiltration are exempt)

b) **Not applicable as of Amendment 01; see 3) i) for updated criterion:** Neutrophils < 1500/µL (participants with leukemia or bone marrow infiltration are exempt)

c) Platelets < 100 x 10^3/µL (participants with leukemia or bone marrow infiltration are exempt)

d) Hemoglobin < 9.0 g/dL (can be transfused; there is no limit on the number of transfusions)

e) Serum creatinine > 1.5 × ULN for age, unless creatinine clearance (CrCl) ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula or as per institutional practice)

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

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

f) AST/ALT: > 3.0 × ULN

g) Total bilirubin > 1.5 × ULN (except participants with Gilbert's syndrome, who must have a total bilirubin level of < 3.0 × 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).

i) Neutrophils < 1000/μL (participants with leukemia or bone marrow infiltration are exempt)

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

5) Other Exclusion Criteria

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

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

c) Inability to comply with restrictions as listed in Section 6.3 (Lifestyle Restrictions).

d) Previous SARS-CoV-2 infection either suspected or confirmed within 4 weeks prior to first dose of study drug. 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.

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

Please see Section 7.1.1.1 for hydration guidelines and limitations on strenuous activities, long hot showers, and sauna use.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered 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 or Lead-in Period

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

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

The most current result prior to first study treatment 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 SARS-CoV-2 infection, for example by RT-PCR or viral antigen is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive reverse transcription polymerase chain reaction (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 Noninvestigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Nivolumab Solution for Injection
- Bempegaldesleukin (NKTR-214) Powder for Solution for Injection

An IP, also known as IMP 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-IPs.

Table 7-1: Study Treatments for CA045020

Product Description/Class and Dosage Form	Content	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Investigational product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	1.0 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
Commercial product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.3 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
Commercial product: Bempegaldesleukin (NKTR-214) Powder for Solution for Injection	0.5 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	100 mg (10 mg/mL)	IP	Open-label	Vial (multiple vials per carton)	Refer to the label on container and/or pharmacy manual

Abbreviations: IL-2 = interleukin-2; IMP = Investigational Medicinal Product; IP = Investigational Product; mg = milligrams; mL = milliliters; rhIL-2 = recombinant human IL-2.

[a] For bempegaldesleukin (NKTR-214), IL-2 and rhIL-2 refer to the same molecule.

7.1 Treatments Administered

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Bempegaldesleukin (NKTR-214)[a]	0.003 mg/kg and 0.006 mg/kg	Q3W	IV
Nivolumab	360 mg or 4.5 mg/kg	Q3W	IV

Abbreviations: IV = intravenous; mg = milligrams; Q3W = every 3 weeks.

[a] Bempegaldesleukin dose is based on IL-2 content.

Study agent(s) should be administered in an area with access to resuscitation equipment. Dosing calculations should be based on the actual body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the participant's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram or per institutional standard.

After participants are assigned to an initial nivolumab regimen (either weight/age-based or flat to weight-based dosing), participants should remain on that regimen for the duration of the study.

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

Doses of study treatment may be interrupted during infusion (see Section 7.4.6), delayed (see Section 7.4.1), or discontinued (see Section 8.1) depending on how the participant tolerates treatment. Dosing visits (cycles) are not skipped or omitted, but they may be delayed. Within a specified dosing schema, there will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of study therapy. Study therapy may be administered within 3 days before or after the scheduled dose.

7.1.1 Bempegaldesleukin Dosing

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 IV via infusion or syringe pump. Bempegaldesleukin will be administered first before nivolumab. Bempegaldesleukin will be administered as an IV infusion over approximately 30 minutes (exclusive of the flush time) at a starting dose of 0.006 mg/kg Q3W (± 3 days). After the bempegaldesleukin IV infusion is administered, flush the intravenous line with an appropriate amount of diluent (e.g, 0.9% Sodium Chloride or 5% Dextrose in Water) to ensure that the complete dose is administered. However, if a syringe pump is used, no flush is

permitted unless otherwise permitted by institutional procedures. Nivolumab administration should start at least 30 minutes from the end of the 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 7.4.1. In the event that nivolumab is permanently discontinued due to toxicities, see Section 8.1.1.

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

Please refer to the Pharmacy Manual/current IB for details regarding preparation, storage, and administration.[147]

7.1.1.1 Hydration Guidelines

Important safety information and hydration instructions are to be provided to participants. Hydration and renal function should be assessed within 24 hours prior to study drug administration or as soon as locally feasible (Table 2-2). Underlying reasons for decreased oral intake (such as nausea) should be addressed and treatment (such as IV hydration) should be provided. Participants may receive additional hydration precautions in a participant card/handout.

Adult Hydration Guidelines:

For adult participants assigned to bempegaldesleukin, administer at least 1 liter of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days (Days 2-4) after administration of bempegaldesleukin, participants are to be instructed to drink at least 2 liters per day of self-administered oral hydration (see Table 2-2).

Pediatric Hydration Guidelines:

Hydration guidance for pediatric participants is weight and age based. Participants who weigh ≥ 40 kg and are aged ≥ 12 years will follow the Adult Hydration Guidelines.

For pediatric participants who weigh < 40 kg but are ≥ 10 kg, administer 500 mL of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle).

For the next 3 days after administration of bempegaldesleukin (Days 2-4), pediatric participants < 40 kg but ≥ 10 kg are to be instructed to drink at least 1 liter of fluids per day.

For pediatric participants who weigh < 10 kg, administer 250 mL of IV fluid on bempegaldesleukin dosing days (Day 1 of each cycle). For the next 3 days after administration of bempegaldesleukin (Days 2-4), participants < 10 kg are to be instructed to drink at least 500 mL of fluids per day.

Table 7.1.1.1-1: Hydration Guidelines for Adult and Pediatric Participants

	Adult & Pediatric ≥ 40 kg and Aged ≥ 12 Years	Pediatric ≥ 10 kg to < 40 kg	Pediatric < 10 kg
Day of infusion (IV)	1000 mL	500 mL	250 mL
Days 2-4 (oral)	2000 mL per day	1000 mL per day	500 mL per day

Abbreviation: IV = intravenous; kg = kilograms; mL = milliliters.

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

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

7.1.2 Nivolumab Dosing

Within a specified dosing schema, there will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 18 days from the previous dose during Q3W (± 3 days) 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 receive nivolumab as an approximately 30-minute (± 5 minutes) infusion on Day 1 of each treatment cycle Q3W (± 3 days) until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years of treatment, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

For weight-based dosing, use body weight for dosing calculations. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the baseline weight or the weight used to calculate the previous dose. Round all doses to the nearest milligram per institutional standard.

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. In the event that bempegaldesleukin is permanently discontinued due to toxicities, see Section 8.1.1.

Nivolumab injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL), is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. When the dose is based on participant weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP), or 5% Dextrose Injection, USP, to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 360 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets and glass bottles.

When bempegaldesleukin and nivolumab are to be administered on the same day, bempegaldesleukin should be administered first, followed by nivolumab.

7.2 Method of Treatment Assignment

Before the study is initiated at an investigative site, each user will receive login information and directions on how to access the Interactive Response Technology (IRT). Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers will not be reassigned. An IRT will be employed to manage participant dosing (either age/weight-based or flat to weight-based dosing). The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth

7.3 Blinding

Not applicable because this is an open-label study; however, the specific treatment to be taken by a participant will be assigned using an IRT. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

7.4 Dosage Modification

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 for AE Criteria for

Delay, Resumption, and Discontinuation of both drugs and Table 7.4.1-2 for bempegaldesleukin-specific criteria).

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. I-O 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 I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity.

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

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

In Oct-2020, the nivolumab AE grading criteria and algorithms were updated to CTCAE v5, and the AE criteria for delaying, resuming, and discontinuation of nivolumab and bempegaldesleukin are available in Table 7.4.1-1.

- SARS-CoV-2 infection either confirmed or suspected, requires delay of nivolumab and bempegaldesleukin study treatment. Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**:
  - 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen),
  - 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications),
  - 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and**
  - 4) consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

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.

All study treatment must be delayed at the same time. Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, gastrointestinal, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, renal toxicity, and myocarditis. The algorithms recommended for use are included in Appendix 5.

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.

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 delayed, both delayed)

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	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 delayed, both delayed)

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).
	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 or bempegaldesleukin therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of nivolumab or bempegaldesleukin.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)

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 replacement or other medical management, participant may not require discontinuation of nivolumab or bempegaldesleukin.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
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 ≤ 10% body surface area.
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if encephalitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis (ie, infection, tumor-related), if myelitis is not drug-related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	
	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Neurological (other than GBS, MG, encephalitis, or myelitis; for CVA/TIA, see bempegaldesleukin-specific criteria in Table 7.4.1-2)	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue	
Other Clinical AEs			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-related AE (not listed above, see	Grade 2 non-skin AE, except fatigue	Nivolumab: Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
bempegaldesleukin-specific criteria in Table 7.4.1-2 for further guidance)			
	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	
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

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)

Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			responding to supplementation/appropriate management within 72 hours of their onset.
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity Reaction or Infusion Reaction	Grade 3 or 4	Permanently discontinue	See Section 7.4.6 (Treatment of Bempegaldesleukin-Related or Nivolumab-Related Infusion Reactions).

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

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)

Bempegaldesleukin-specific Drug-related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Serum Creatinine Increased (transient, non-inflammatory)	Grade 2, 3, or 4	Delay dose*	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 5)
Other Drug-related AE (not listed in Table 7.4.1-1)	Persistent Grade 2 toxicity except fatigue and asthenia	Delay dose*	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 5.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; CVA = cerebrovascular accident; MRI = magnetic resonance imaging; TIA = transient ischemic attack

*If dosing of one drug is delayed, then dosing of both drugs is delayed.

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

These recommendations are for Cycle 1 only and are not intended to serve as rigid guidelines or to replace clinical judgment. Subsequent cycles should follow standard Hepatic Adverse Event Management Algorithm (Appendix 5).

Rule out alternative etiologies. Consider imaging if obstruction is suspected. If there is a noninflammatory 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 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 5]):

Discontinue bempegaldesleukin + nivolumab

1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper over at least 1 month

Consult gastroenterologist

Consider adding noncorticosteroid 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 5])

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 1 month
- Consult gastroenterologist
- If no improvement in > 3–5 days, worsens or rebounds, add noncorticosteroid immunosuppressive medication

Please refer to Section 8.1 for discontinuation criteria.

7.4.2 Monitoring and Management of Elevated Hepatic Transaminases

Elevated hepatic transaminases are an overlapping toxicity that can occur for both bempegaldesleukin and nivolumab. The elevations in hepatic transaminases associated with bempegaldesleukin typically occur at the time of peak active cytokine concentration in the blood (Days 4-8) and are often accompanied by other IL-2 mediated AEs such as flu-like symptoms, rash, or pruritus. The transient elevations in hepatic transaminases are usually asymptomatic, mild or moderate in severity, not associated with increased total bilirubin and alkaline phosphatase, resolve spontaneously without treatment, and predominantly occur in Cycle 1 and Cycle 2; the transaminase elevations are considered to occur in the context of IL-2 mediated AEs. For transaminase elevations occurring in Cycle 1 consistent with a cytokine-related effect without alternative etiologies, follow the Cycle 1 hepatic adverse event management guideline (Section 7.4.1.1).

Hepatic events, including elevated liver function tests, have also been observed for nivolumab. Most cases were of low or moderate severity. Higher-grade abnormalities are concerning for immune-mediated hepatitis and typically occur with a later onset (median time to onset of 3.3 months). Immune-mediated hepatitis generally results in a quick rise in liver function tests and responds to corticosteroids or immune-modulating agents. For transaminase elevations occurring in Cycle 2 onwards potentially involving an immune-mediated mechanism, follow the immune-mediated hepatic adverse event management guidelines in the nivolumab IB or product labeling for appropriate management.[127]

7.4.3 Monitoring and Management of Eosinophilia

7.4.3.1 Bempegaldesleukin-induced Eosinophilia

Frequent and significant eosinophilia has been observed in participants receiving bempegaldesleukin, primarily starting at Cycle 2, with levels plateauing after Cycle 3, consistent with the known pharmacodynamic effect of IL-2 therapy. The eosinophilia pattern demonstrates a cyclic waxing and waning pattern whereby eosinophil levels peak approximately 7 days after each infusion and wane before the participant's next infusion.

Absolute eosinophil count (AEC) should be closely monitored per protocol. If the study participant is suspected to have eosinophilic disorder (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous systems) with AEC at or above the 5000/μL (5×10^9/L) level, delaying bempegaldesleukin treatment may be considered while evaluating and treating the participant as clinically indicated.

7.4.3.2 Eosinophilic Disorders

Isolated cases of hypereosinophilic syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. If there is clinical concern for an eosinophilic disorder, the investigator is encouraged to contact the Medical Monitor.

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

7.4.4 Monitoring and Management of Adrenal Insufficiency and Hypophysitis

Adrenal insufficiency and hypophysitis have been observed in participants receiving nivolumab. Consider prompt evaluation when participants have signs or symptoms of hypophysitis or adrenal insufficiency, which includes levels of early-morning adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone (TSH), and free thyroxine (fT4). Co-management with an endocrinologist is recommended for participants with preexisting adrenal insufficiency.

7.4.5 Management Algorithms for Immune-mediated Adverse Events and Cytokine-Release Syndrome

7.4.5.1 Management Algorithms for Immune-mediated Adverse Events Associated with Immuno-oncology Agents

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 I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms (see 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

A management algorithm for possible signs and symptoms of CVA and cytokine-release syndrome for participants treated with bempegaldesleukin in combination with a checkpoint inhibitor is provided in Appendix 6 and Appendix 14, respectively.

Management algorithms for AEs associated with I-O agents are presented in Appendix 5.

For pediatric participants, dosages should be provided by kg or in accordance with institutional standards.

7.4.5.2 Management Algorithm for Cytokine-Release Syndrome

Cytokine-release syndrome 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 Sponsor. An algorithm for the management of CRS is provided in Appendix 14.

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

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, arthralgia, myalgia, hypotension, hypertension, bronchospasm, or other hypersensitivity/allergic-like reactions.

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

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

- For pediatric participants, dosages should be provided by kg or in accordance with institutional standards.
- 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 pediatric dose equivalent (or equivalent drug class) and/or acetaminophen/paracetamol 325 to 1000 mg (or pediatric dose equivalent) at least 30 minutes before subsequent infusions. Subsequent infusions may be administered at a reduced rate (ie, 50% of the original 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):

- **For pediatric participants, dosages should be provided by kg or in accordance with institutional standards.**
- Stop the bempegaldesleukin or nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV or pediatric dose equivalent (or equivalent drug class) and/or acetaminophen/paracetamol 325 to 1000 mg (or pediatric dose equivalent); 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 (or pediatric dose equivalent), 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 pediatric dose equivalent (or equivalent drug class) and/or acetaminophen/paracetamol 325 to 1000 mg (or pediatric dose equivalent) should be

administered at least 30 minutes before the infusion. If necessary, corticosteroids (up to 25 mg of methylprednisolone or pediatric dose equivalent [or equivalent drug class]) may be used. Subsequent infusions may be administered at a reduced rate (ie, 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):

- **For pediatric participants, dosages should be provided by kg or in accordance with institutional standards.**
- 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 (or pediatric equivalent) for IM administration or 0.1 to 0.25 mg of a 1:10,000 solution (or pediatric equivalent) injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or pediatric dose equivalent (or equivalent drug class), 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 IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

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

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

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

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.

The date and time of start and end of infusion and the exact amount given at each infusion will be recorded. In case the treatment has to be interrupted during an infusion and the dosing is not resumed, the medical personnel should evaluate the percentage of dose received by the participant and document it in the participant record.

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

Any reason for noncompliance should also be documented.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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

- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella) during treatment and until 150 days post last dose.
- Low-dose acetylsalicylic acid (approximately 81 mg/day) should not be combined with LMWH or DOAC due to an increased risk of hemorrhage (except as stated in Section 7.7.4.1).
- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.5)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of the tumor). Participants may receive focal radiation therapy for palliation.
- 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.

7.7.2 Palliative Therapy

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted and must be clearly documented in the study record. Participants receiving palliative radiation to target lesions require reimaging post radiation and prior to initiation of drug therapy.

7.7.3 Prior and Concomitant Medications

Recording of prior medications should include prior cancer treatments: previous immunotherapy, chemotherapy, targeted therapy, radiation, over-the-counter (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.

Premedications 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.

7.7.3.1 COVID-19 Vaccination

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

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

If a participant is already in the study, the full vaccination series is allowable. Study dose administration may be delayed until the biologic impact of the vaccine is stabilized, as determined by the Investigator. The appropriate information should be captured to assess any potential vaccine-related adverse events.

There does not need to be a minimum duration between the last administration of IP and administration of COVID-19 vaccine; however, if possible, overlap of administration should be avoided (A 2-day gap is recommended, but a 7-day gap is preferable).

[redacted]

7.7.3.2 Effect of Bempegaldesleukin on Pharmacokinetics of Concomitant Medications

Bempegaldesleukin causes transient increases in circulating cytokines lasting for about 1 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 drug-metabolizing enzymes and drug transporters. Consequently, treatment with bempegaldesleukin may lead to a temporary decrease in clearance of drugs that are substrates of these Phase I and Phase II drug metabolizing enzymes, or drug transporters. Where indicated based on decreased tolerability or the occurrence

of AEs related to a concomitant drug, reduce the dosage of the concomitant drug during Days 3 to 8 of each cycle of bempegaldesleukin.

7.7.4 Other Restrictions and Precautions

7.7.4.1 Restricted Treatments

Participants with a condition requiring systemic treatment with either corticosteroids (> 0.12 mg/kg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids and adrenal replacement steroid doses > 0.12 mg/kg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

Participants with a history of a venous or arterial thromboembolic event must be receiving a stable regimen of therapeutic anticoagulation (preferably LMWH or DOAC). Unless there is a new medical contraindication observed after Cycle 1 Day 1, a participant with a history of a venous or arterial thromboembolic event must be maintained on therapeutic anticoagulation throughout the participant's time on study treatment.

Anticoagulation options include the following:

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

If anticoagulation is being newly introduced or adjusted, the investigator may consider consulting the Medical Monitor for guidance.

7.7.4.2 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 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 < 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 acquisition manual.

Gentle hydration before and after IV contrast should follow local SOC. 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.

7.7.4.3 Blood Pressure Precautions

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 (eg, beta-blockers, calcium 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 stepwise 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.

7.7.4.4 Volume of Blood

Blood sample collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual to meet pediatric institutional guidelines for maximum daily and monthly blood draw limits.

7.7.5 Permitted Therapy

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 antihistamines 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 in the absence of active autoimmune disease. 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.

Direct effects of immune treatment on tumor may produce neurologic AEs, collectively termed "tumor flare," depending on the location and usually associated with radiographic changes (see

Section 5.4.2). Treatment with high-dose steroids should be implemented immediately to control inflammation and edema in addition to any other indicated therapy. In most cases, improvement is fairly rapid; tapering of steroids should be guided by neurologic effects but often may be tapered more quickly than advised for immune-mediated effects on normal tissues. Contact with BMS Medical Monitor is recommended.

7.8 Treatment After the End of the Study

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

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: (a) the study is terminated due to safety concerns; (b) the development of the combination 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.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Treatment

Participants MUST discontinue IP (and non-IP 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 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 BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Confirmed disease progression or investigator-assessed clinical progression as specified in Section 9.1.2 (with exceptions noted in Section 8.1.2).
- Toxicity as specified above and in Section 9.2.
- Maximal clinical benefit as assessed by investigator.
- Pregnancy.

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

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

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

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

8.1.1 Nivolumab and Bempegaldesleukin Discontinuation Criteria

Bempegaldesleukin and nivolumab treatment must be permanently discontinued per criteria in Table 7.4.1-1 and Table 7.4.1-2. Discontinue nivolumab and bempegaldesleukin for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents substantial clinical risk to the participant with continued nivolumab and bempegaldesleukin dosing.

Participants meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s). However, per investigator assessment, treatment with nivolumab or bempegaldesleukin may continue if the toxicities listed below are considered related to bempegaldesleukin or to nivolumab only and once the criteria to resume are met (Section 7.4.5).

- 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/or 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 AEs 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 reinitiating 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 Treatment Beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[142,155]

Participants treated with nivolumab ± bempegaldesleukin will be permitted to continue nivolumab ± bempegaldesleukin treatment beyond initial disease-appropriate defined progressive disease, assessed by the investigator, up to a maximum of 2 years from date of first dose as long as they meet the following criteria:

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

Participants may continue receiving study drug until confirmation of progression. Section 9.1.2 outlines the criteria used to assess tumor response for each tumor type under study. If the follow-up radiographic and/or histological assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined.

Radiographic and histological assessments/scans should continue in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and radiographic assessments/scans should be submitted to the central imaging vendor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

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

Radiographic Assessment of Further Progression

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

Study treatment should be discontinued permanently upon documentation of further progression. The decision to discontinue treatment beyond progression should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

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

8.1.3 Post-study Treatment Study Follow-up

In this study, objective response rate is a key endpoint. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

The Sponsor may request that survival data be collected on all treated participants outside of the protocol defined window (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.

Additional subsequent cancer therapy details, such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy, will be collected.

8.2 Discontinuation From the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed 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.

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

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

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

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary 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) IB.[127]

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

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo BICR at any time. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA045-020 Imaging Manual provided by the central imaging vendor.

Additional imaging that may demonstrate tumor response or progression (eg, scans performed at unscheduled time points and/or at an outside institution, radiographs demonstrating unequivocal evidence of disease progression) should be collected for tumor assessments and submitted to the central imaging vendor.

9.1.2 Method of Measurement

9.1.2.1 Ewing Sarcoma, Rhabdomyosarcoma, and Other Solid Tumors

Contrast-enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/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 (see Appendix 8). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response.

If a participant has a contraindication for CT IV contrast, then a contrast-enhanced MRI of the chest, 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 MRI of chest, 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 Positron Emission Tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care and is a

modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

9.1.2.2 Neuroblastoma

Along with imaging described in Section 9.1.2.1, MIBG scintigraphy should be performed for participants with MIBG-avid tumors, according to revised INRC.[156] Tumor response will be assessed by the investigator using the revised INRC (see Appendix 9). Confirmation of response after initial assessment of PR and CR is not required.

9.1.2.3 Non-Hodgkin Lymphoma

Participants with [^{18}F] fluorodeoxyglucose (FDG)-avid NHL should be followed with FDG PET-CT or PET-MRI of the skull base to mid-thigh and other known/suspected sites of disease.

Participants with FDG non-avid NHL should be followed with contrast-enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease.

The International Pediatric Non-Hodgkin Lymphoma Response Criteria (see Appendix 10).[157] Confirmation of response after initial assessment of PR and CR is not required.

9.1.2.4 Glioma, Medulloblastoma, Ependymoma, and Other CNS Tumors

Brain MRI without and with gadolinium contrast should be performed as outlined in Section 2 (Schedule of Activities). Participants who are unable (due to existent medical condition, ie, pacemaker or implantable cardioverter-defibrillator device) or unwilling to have a contrast-enhanced MRI of the brain at baseline are excluded from the study. Participants who become unable to undergo MRI imaging after the start of participation in the study may continue in the study for assessment of OS as long as there is no safety issue that would require monitoring by MRI. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response.

For participants with medulloblastoma and miscellaneous seeding CNS tumors, RAPNO criteria will be used to assess tumor response and will include cerebrospinal fluid (CSF) analysis where clinically indicated (see Appendix 11).[158]

For participants with glioma, ependymoma, and miscellaneous non-seeding CNS tumors, RANO criteria will be used to assess tumor response (See Appendix 11).[159]

9.1.2.5 Leukemia

Cerebrospinal fluid and bone marrow aspirate with buccal swab will be collected as clinically indicated, along with complete blood counts for platelets and neutrophils as outlined in the Schedule of Activities (Section 2), the clinical safety laboratory assessments (Table 9.4.6-1) [redacted]. A bone marrow biopsy/aspirate should be performed as clinically indicated if relapse is suspected.

[redacted]

Response assessment will be assessed using Modified NCCN Criteria for acute lymphoblastic leukemia or Modified Cheson et al International Working Group criteria for acute myeloid leukemia (see Appendix 12).

9.1.3 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Sites should not change the schedule of imaging due to a dose delay. Changes in tumor measurements and tumor responses should be assessed by the same investigator or designee using the applicable criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using applicable criteria. A BOR of SD requires a minimum of 56 days on study from date of first dose to the date of the first imaging assessment.

9.1.4 Patient-reported Outcomes

The evaluation of patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's and/or caregiver's perspective and offer insights into participant experience that may not be captured through physician reporting.

Given the evidence that clinicians underreport symptomatic AEs, selected items from the PRO-CTCAE (including the pediatric and caregiver version) will be used to enhance the assessment of symptomatic AEs in the trial. AEs will be selected based on the known clinical profile of the treatments being included in the trial, clinical judgment, and the experience of the study team members. Participants will be asked to complete the PROs version of the CTCAE (PRO-CTCAE; adults aged ≥18 years), Pediatric PRO-CTCAE (Ped-PRO-CTCAE; children aged ≥7 to <18 years), or Caregiver PRO-CTCAE (Ped-PRO-CTCAE [Caregiver]) (children aged <7 years, or older participants with a cognitive impairment which would limit their ability to complete a PRO) at designated study visits. The age-related version of the PRO-CTCAE completed at the start of the trial should be used throughout the treatment period. When possible, participants should complete the PRO measures prior to any other assessments or study procedures when they are being administered during study visits. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or Sponsor's representative.

The corresponding age version of the PRO-CTCAE will be provided in the participant's preferred language, if available. This questionnaire may be administered electronically on a weekly basis during the first 3 cycles of treatment, every cycle from Cycles 4 through 8, every other cycle (starting at Cycle 10) while on treatment, and at end of treatment in Part B only.

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

Appendix 1 in the Investigator's Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

All nonserious AEs (not only those deemed to be treatment related), with the exception of nonserious AEs related to SARS-CoV-2 infection, should be collected continuously during the treatment period and for a minimum of 150 days following discontinuation of study treatment.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, for a minimum of 150 days of discontinuation of dosing. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

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 150 days following discontinuation of dosing.

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 CRF 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 AESI 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 are provided in Appendix 6.

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

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

Every AE must be assessed by the investigator with regard to whether it is considered immune mediated. For AEs that 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 9.2.8), 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 8.3).

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 IB and will notify the Institutional Review Boards/Independent Ethics Committees, 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 SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

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

A pregnancy test does not need to be performed on women who are postmenopausal. A definition of postmenopausal 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.

If the investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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 ICF 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 partner(s) without the use of a condom during and at least for 5 half-lives after study product administration, 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 ICF for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Immune-mediated Adverse Events

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory 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.

Additional information may also be collected on IMAEs. A list of relevant AE terms will be maintained by the Medical Surveillance Team/Drug Safety Committee or equivalent.

9.2.7 Additional Information Collected for Adverse Events Primarily Related to Bempegaldesleukin

Additional information may also be collected on select AEs primarily related to bempegaldesleukin (eg, capillary leak syndrome and cytokine-release syndrome). A list of relevant AE terms will be maintained by the Medical Surveillance Team/Drug Safety Committee or equivalent.

9.2.8 Adverse Events of Special Interest

CVA (any grade) is considered an AESI and should be assessed for seriousness using the standard seriousness definition. However, all CVA events are required to follow the timelines for SAE reporting (eg, 24 hours). CVA management guidelines are provided in Appendix 6.

9.2.9 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 vs low hemoglobin value).

9.2.10 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (pDILI) event. All occurrences

of pDILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

pDILI is defined as:

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

AND

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

AND

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

9.2.11 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, 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 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 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. 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.

Pulse oximetry will also be included at baseline only.

9.4.3 Electrocardiograms

All participants will have 12-lead ECG done during Screening, Treatment, and in Long-term Follow-up 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 Activities (Section 2). 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 WOCBP according to the Schedule of Activities. A negative pregnancy test result must be obtained within 24 hours prior to the administration of the study drug(s).

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

If a female participant becomes pregnant, administration of the study drug(s) must be discontinued.

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

9.4.6 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Table 9.4.6-1: Clinical Safety Laboratory Assessments

Hematology – Complete Blood Count	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) or serum urea Glucose	Albumin Sodium Potassium Chloride Calcium Phosphorus Creatinine kinase TSH, free T3, and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Lipase and/or amylase
Serology - only if clinically indicated based on medical history and risk factors	
Hepatitis B/C (HBsAG, HCV antibody or HCV RNA) - screening only (Testing for HIV-1 and HIV-2 must be performed where mandated by local requirements)	

Table 9.4.6-1: Clinical Safety Laboratory Assessments

Other Analyses
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of hCG). Urine or serum.
Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55
Urinalysis - screening only and as clinically indicated.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CK = creatinine kinase; FSH = follicle stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; HBsAG = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

9.4.7 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.

9.5 Pharmacokinetics

9.5.1 Pharmacokinetics and Immunogenicity Assessments

PK and immunogenicity assessment data will be collected from study participants assigned to the nivolumab + bempegaldesleukin arms in both Parts A and B at the time points indicated in Table 9.5.1-1.

All time points are relative to the start of the first study drug administration. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. All predose samples should be collected within 24 hours before the start of any dose infusion. Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion.

Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual. For participants < 26 kg or those who require blood draw volume modifications, sample collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual to meet pediatric institutional guidelines for maximum daily and monthly blood draw limits.

Serum PK samples will be analyzed for nivolumab by a validated ligand-binding assay. Plasma PK samples will be analyzed for NKTR-214-RC (bempegaldesleukin-related molecules; mixture of compounds containing IL-2 independent of PEG conjugation status) and total PEG (mixture of compounds containing PEG independent of conjugation status to IL-2) by validated ligand-binding

assays as well as NKTR-214-AC (active bempegaldesleukin-related molecules; mixture of 2-PEG-IL-2, 1-PEG-IL-2, and free IL-2) by a qualified ligand-binding assay.

Validated methods to detect anti-nivolumab, anti-NKTR-214, anti-PEG, and anti-IL-2 ADA (anti-drug antibodies) will be used to analyze the immunogenicity samples. Immunogenicity sample testing will be done in tiers per the 2019 FDA guidance.[160] Samples will be first tested with screening electrochemiluminescence assays (ECLAs). Putative positive samples for anti-nivolumab, anti-NKTR-214, or anti-IL-2 ADA will then be analyzed in competition ECLA assays to confirm positivity. Confirmed anti-NKTR-214 ADA positive samples will be tested further in a PEG immuno-competition assay to determine the antibody specificity of the reactivity to the PEG or non-PEG (IL-2, linker) moiety of the NKTR-214. Confirmed positive samples from anti-nivolumab, anti-NKTR-214, and anti-IL-2 ADA assays will then be tested to obtain a titer. Samples confirmed to be positive for anti-nivolumab, anti-NKTR-214, and anti-IL-2 ADA will also be tested for neutralizing activity for IL-2 and nivolumab using validated cell-based assays.

Blood samples designated for assessments (eg, immunogenicity, PK[redacted]) from the same collection time point may be used interchangeably for analyses, if required (eg, insufficient volume for complete assessment, to follow-up on suspected immunogenicity-related AE, etc.). For pediatric participants, local standards for volumes of blood based on body weight that may be drawn within a specific time period should be followed. In order to obtain the samples required for safety, PK, [redacted] evaluations specified at a time point, blood volumes for safety laboratory analysis should be minimized through the use of pediatric sample tubes, if possible. In the case that, despite using these measures, the blood volumes required in the Schedule of Activities for a given time point will exceed those recommended in the laboratory manual, the sponsor should be contacted for further instructions on which blood tests can be omitted or modified to meet volume requirements. These omitted/modified tests will likely be [redacted] pharmacokinetic assessments since all required safety assessments must be performed.

Additionally, residual blood samples will be archived and may be used for potential exploratory analysis (eg, analysis of drug-ADA immune complexes, exploratory PK) and or for additional method purposes (eg, cross-validation, ADA/PK selectivity, cut point, etc.).

For all PK blood samples, the date and actual time collected must be recorded. For participants whose only peripheral access is via a venous access device or peripherally inserted central catheter, refer to the Laboratory Manual for the proper technique to ensure undiluted whole blood for PK assessments.

Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling - Bempegaldesleukin Combined with Nivolumab (Parts A and B)

Study Day of Sample Collection (1 cycle = 3 weeks)[a,b]	Event	Time (Relative to Start of Bempegaldesleukin Infusion) Hr:Min	Bempegaldesleukin PK Plasma Sample	Bempegaldesleukin IMG Serum Sample	Nivolumab PK Serum Sample	Nivolumab IMG Serum Sample
Cycle 1 Day 1	Predose[c]	00:00	X	X	X	X
	EOI[d]	00:30	X			
		04:00[e]	X			
Cycle 1 Day 3[f]		48:00[f]	X			
Cycle 1 Day 5[g]		96:00[g]	X			
Cycle 1 Day 8[h]		168:00[h]	X			
Cycle 2 Day 1	Predose[c]	00:00	X	X	X	X
Cycle 5 Day 1	Predose[c]	00:00	X	X	X	X
	EOI[d]	00:30	X			
Cycle 5 Day 3[f]		48:00[f]	X			
Cycle 5 Day 5[g]		96:00[g]	X			
Cycle 11 Day 1	Predose[c]	00:00	X	X	X	X
Cycle 17 Day 1	Predose[c]	00:00	X	X	X	X
Cycle 23 Day 1	Predose[c]	00:00	X	X	X	X
Cycle 29 Day 1	Predose[c]	00:00	X	X	X	X
Follow-up Visit 1				X	X	X
Follow-up Visit 2				X	X	X

Abbreviations: EOI = end of infusion; IMG = immunogenicity; IV = intravenous; PK = pharmacokinetic.

[a] If a participant permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow up visits.

[b] For participants < 26 kg or those who require blood draw volume modifications, sample collection volumes will be appropriately reduced per guidelines outlined in the laboratory manual.

[c] All predose samples should be collected within 24 hours before the start of any dose infusion.

[d] EOI=End of Infusion. This sample should be taken immediately after the completion of the bempegaldesleukin administration and flush. EOI samples may not be collected from the same IV access as drug was administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[e] Sample can be collected ± 1 hour but is preferred as close to 04:00 hours as is clinically feasible.

[f] Samples can be collected ± 3 hours. If participants are dosed on Thursday, Day 3 sample can be collected on Day 2 (Friday). If participants are dosed on a Friday, Day 3 sample can be collected on Day 4 (Monday).

[g] Day 5 sample can be collected ± 1 day.

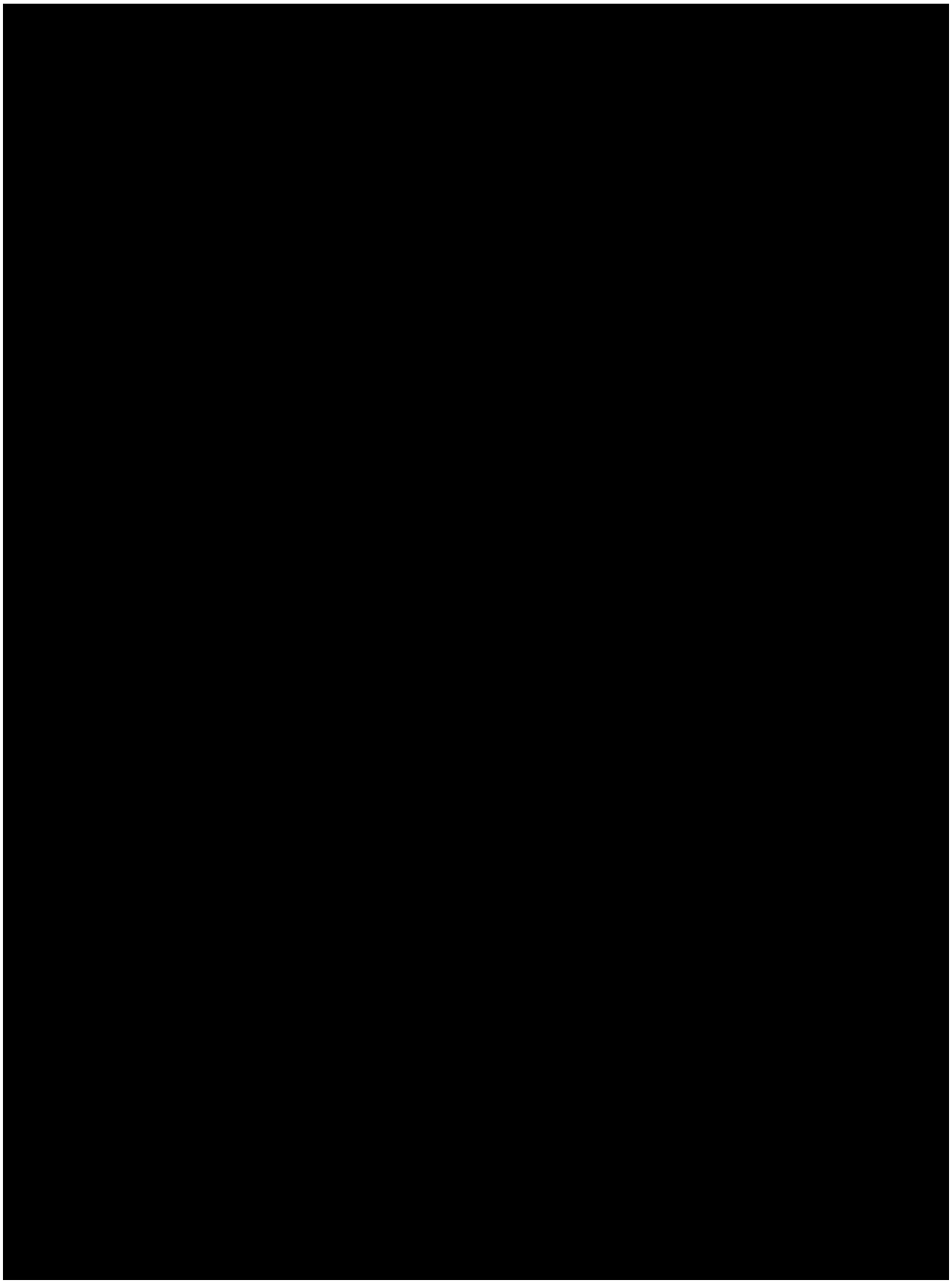
[h] Day 8 samples can be collected on Day 7.

[redacted]

9.7 Pharmacogenomics

Not applicable.

[redacted]



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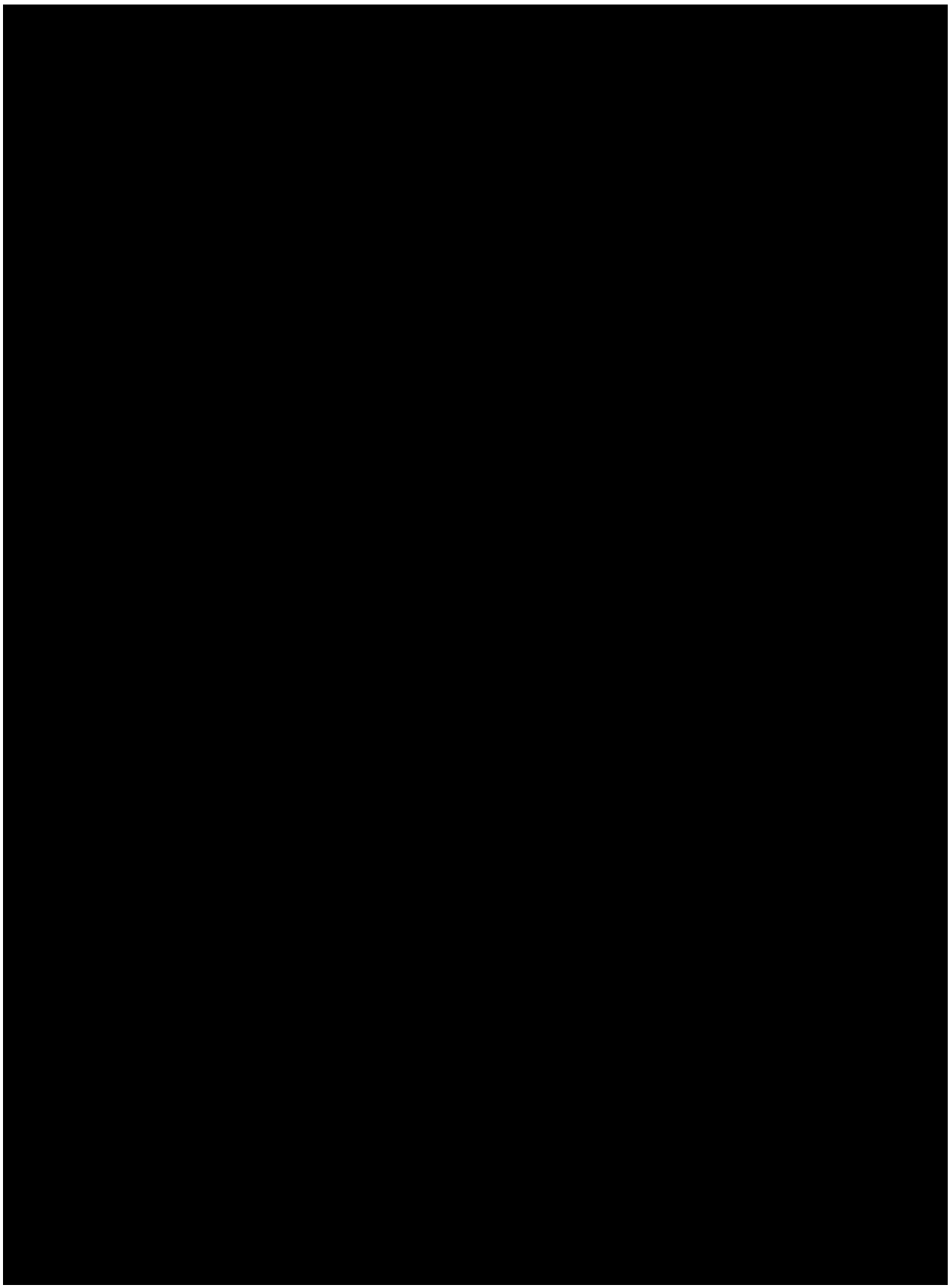
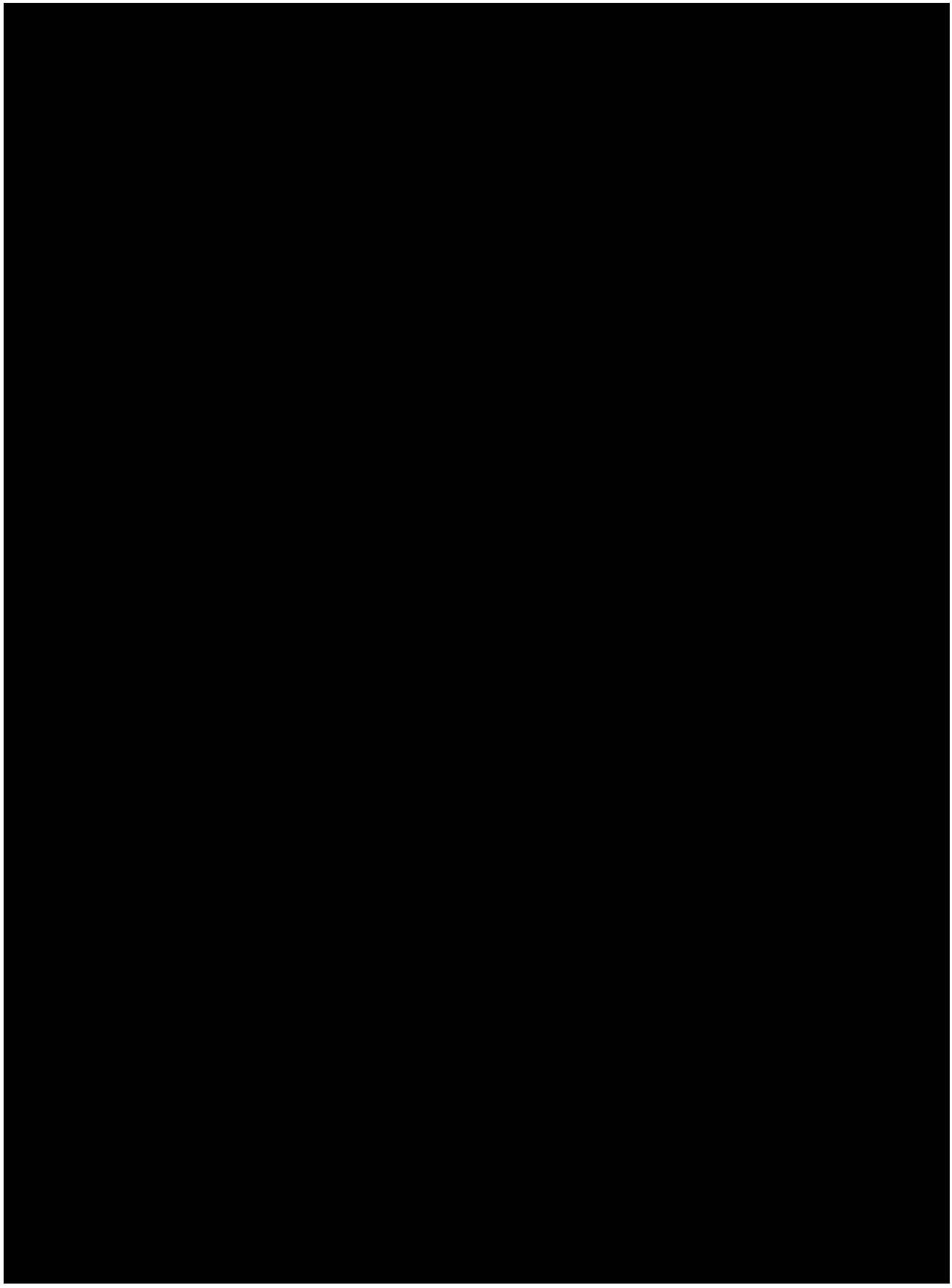
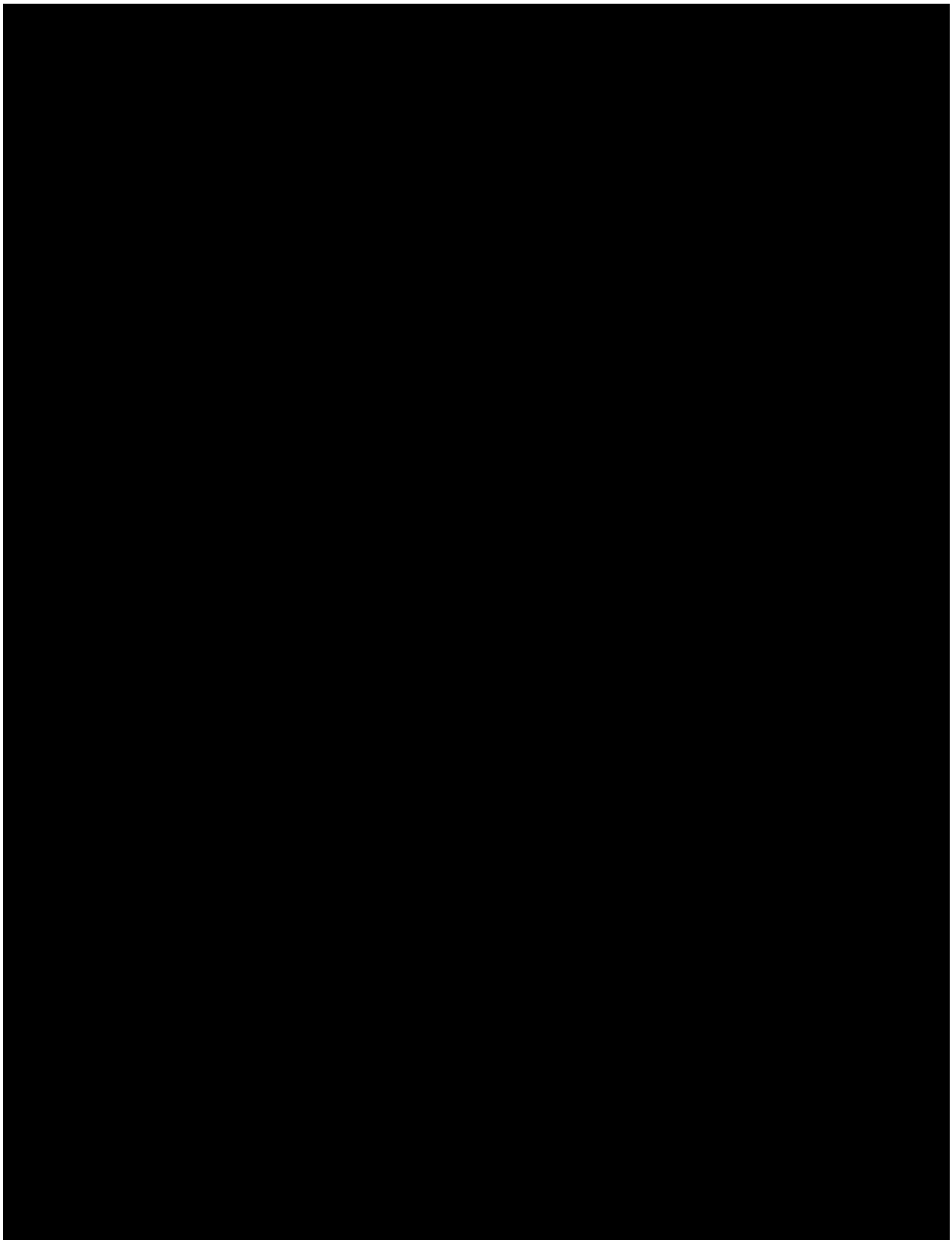






9.9 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of Part A (Phase 1 bempegaldesleukin in combination with nivolumab) is not based on statistical considerations, and it depends on the number of observed DLTs.

For Part B (Phase 2), the Simon 3-stage variant design will enroll an initial 9 participants per tumor cohort, and any cohort in which at least 1 response is observed may enroll up to 7 additional participants. If 2 or more responses in the first 16 participants are observed, an additional 8 participants (total 24) can be accrued to an individual cohort. A cohort in which at least 3 responses are observed would be considered to warrant further clinical development. This design assumes that a true response rate of 5% or less would not be of clinical interest and a true response rate of at least 20% would be of clinical interest. If the true response rate is 5%, the rule described above will identify it of sufficient activity for further study with a probability of 0.08 (type I error), and the study will have an average sample size of 12.9 (per tumor cohort using Simon 3-stage variant design) with 84% probability of early termination. If the true response rate is 20%, the rule described above will identify it of sufficient activity for further study with a probability of 0.77 (power against the alternative hypothesis ORR = 0.20), and the study will have an average sample size of 21.5 per tumor cohort using Simon 3-stage variant design with 20% probability of early termination.

Table 10.1-1: Dose Expansion Cohorts: Characteristics of the Simon 3-stage Variant Design

ORR	Probability of Early Stopping at Stage 1	Probability of Early Stopping at Stage 2	Probability of Early Stopping (Cumulative)	Probability to Conclude Efficacy
5%	63%	21%	84%	8%
20%	13%	6%	20%	77%

Abbreviation: ORR = objective response rate.

Inference for ORR will be based on the actual number of participants treated and evaluable in each cohort, using adjusted 95% CI based on the Atkinson and Brown method.[163] The design parameters are presented in Table 10.1-1. For the miscellaneous solid tumor cohort and the miscellaneous CNS tumor cohort, the Simon 3-stage variant design will not be applied and can accrue up to the maximum of 24 participants. If a participant with melanoma becomes eligible for enrollment after accruing the maximum of 24 participants in the miscellaneous solid tumor cohort, then they will be allowed to enroll in the trial.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent. This is the dataset for disposition.
Treated	All enrolled participants who received at least 1 dose of any study drug. This is the dataset for safety evaluation.
Response-evaluable participants	All treated participants with measurable disease at a baseline tumor assessment (source: eCRF).
PK-evaluable participants	All treated participants with at least 1 PK concentration measurement post-treatment.
Immunogenicity-evaluable participants	Bempegaldesleukin, nivolumab ADA-evaluable participants: all treated participants with baseline and at least 1 post-baseline bempegaldesleukin, nivolumab immunogenicity assessment.

Abbreviations: ADA = anti-drug antibody; eCRF =electronic case report form; PK = pharmacokinetic.

10.3 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary Endpoint (Part B)/Tertiary (Part A)	
ORR is defined as the number of participants whose BOR is confirmed CR or PR divided by all participants with the same disease. BOR is defined as the best response designation, as determined by investigators, recorded between the date of first dose and the date of objectively documented progression per imaging criteria (or blood and/or bone marrow assessment for leukemia) or the date of subsequent therapy, whichever occurs first. All available response designations will contribute to the BOR assessment. The following criteria will be used: • RECIST 1.1 for solid tumors • RANO/RAPNO for CNS tumors • International Pediatric Non-Hodgkin Lymphoma Response Criteria for NHL • Revised INRC for neuroblastoma • Modified NCCN Criteria for acute lymphoblastic leukemia • Modified Cheson et al International Working Group criteria for acute myeloid leukemia.	ORR and corresponding 2-sided adjusted 95% CI by the Atkinson and Brown method will be provided for participants from Part 2 by tumor type (if applicable). Response from participants from Part 1 will only be listed. ORR will be reported first on response-evaluable participants and repeated on all treated participants.
Tertiary Endpoint (Part A and Part B)	
DOR is computed for all treated participants with a BOR of CR or PR and is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.	Median DOR using the Kaplan-Meier method and corresponding 2-sided 95% CI may be reported for participants from Part 2 by tumor type (if appropriate). DOR will be reported first on all response-evaluable participants and then on all treated participants.
Secondary Endpoint (Part B)/Tertiary Endpoint (Part A)	
PFS is defined as the time from first dose to the date of the first documented tumor progression or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of death. Participants who did not have disease progression or die will be censored at the date of last evaluable tumor assessment. PFS rate at 24 weeks is defined as the probability to be alive and progression free after 24 weeks.	Median PFS will be estimated using the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) for treated participants from Part B by tumor type (if appropriate). The PFS rate will be estimated by the Kaplan-Meier method and corresponding 95% CI will be derived based on Greenwood formula for treated participants from Part B by tumor type (if appropriate). Analysis will only be conducted if the sample size exceeds 15 participants in the cohort.

Endpoint	Statistical Analysis Methods
Secondary Endpoint (Part B)	
OS is defined as the time between the date of first dose and the date of death. A participant who has not died will be censored at the last known alive date. OS will be followed continuously while participants are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study drug. OS rate at 1, 2, and 3 years is defined as the probability to be alive after 1, 2, and 3 years.	Median OS will be estimated using the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology using log-log transformation) for treated participants from Part 2 by tumor type (if appropriate). The OS rate will be estimated by the Kaplan-Meier method, and corresponding 95% CI will be derived based on Greenwood formula for treated participants from Part 2 by tumor type (if appropriate). Analysis will only be conducted if the sample size exceeds 15 participants in the cohort.

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; INRC = International Neuroblastoma Response Criteria; NCCN = National Comprehensive Cancer Network; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RAPNO = Response Assessment in Pediatric Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors.

The primary efficacy analyses will be performed on the response-evaluable population and repeated on the treated population for the final analysis. Details on censoring scheme on time-to-event endpoints such as OS, PFS, and DOR will be described in the SAP. Efficacy analysis will be performed by each tumor type separately; however, treated participants in the safety lead-in period (Part A) who meet the inclusion criteria for the corresponding cohort and who were treated at the same dose level as Part B will also be included in the tumor cohort analysis.

10.3.2 Safety Analyses

All safety analyses for will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Primary Endpoint (Part A)/Secondary Endpoint (Part B)	
Incidence of DLTs, AEs including IMAEs and AESI, SAEs, drug-related AEs, AEs leading to discontinuation, and death AEs will be graded according to CTCAE v5.0 Incidence of laboratory abnormalities Laboratory values will be graded according to CTCAE v5.0	DLT rate by dose level. Frequency distribution of treated participants with AE using the worst CTCAE grade. Participants will only be counted (1) once at the PT level, (2) once at the System Organ Class level, and (3) once in the "Total participant" row at their worst CTCAE grade, regardless of System Organ Class or PT. By cohort. Laboratory shift table using the worst CTCAE grade per participant by cohort.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events version 5; DLT = dose-limiting toxicity; IMAE = immune-mediated adverse event; PT = Preferred Term; SAE = serious adverse event.

10.3.3 Other Analyses

10.3.3.1 Pharmacokinetics

Endpoint	Statistical Analysis Methods
Primary Endpoint (Part A)	
PK parameters , such as peak, trough, and time-averaged concentration, CL, and Vd	Characterized by PPK models

Abbreviations: CL = clearance; PK = pharmacokinetic; PPK = population pharmacokinetics; Vd = volume of distribution.

PK data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of bempegaldesleukin and/or nivolumab and to determine measures of individual exposure (such as steady state peak, trough, and time-averaged concentration). Model-predicted exposures may be used for exposure-response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure-response analyses will be reported separately.

10.3.3.2 Immunogenicity Analyses

Immunogenicity will be reported for positive status of ADA for anti-nivolumab/anti-IL-2/anti-NKTR-214/anti-PEG (such as persistent positive, other positive, only last sample positive, baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable. Effect of immunogenicity on safety/efficacy and PK may be explored.

10.3.3.3 Other Exploratory Analyses

PK, [redacted] patient-reported outcomes, [redacted] analyses will be described in the SAP finalized before database lock.

10.3.4 Interim Analyses

The SAP will further describe the planned interim analyses. The expansion phase of this study employs a 3-stage variant design framework. Therefore, there will be interim analyses planned when the required number of response evaluable participants in a cohort have available tumor data to take a decision and no later than 6 months after the start of the treatment of the last response evaluable participants of the current stage. The interim analyses will be reviewed by the DMC. No formal inferences requiring any adjustment to statistical significance level will be performed.

11 REFERENCES

1 Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21(4):541-50.

2 Geoerger B, Zwaan CM, Marshall LV, et al. Atezolizumab for children and young adults with previously treated solid tumours, non-Hodgkin lymphoma, and Hodgkin lymphoma (iMATRIX): a multicentre phase 1-2 study. Lancet Oncol 2020;21(1):134-44.

3 Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21(1):121-133.

4 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67(1):7-30.

5 Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. Lancet 2004;364(9451):2097-105.

6 Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol 2017;18(6):719-31.

7 Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, et al. Cancer in children and adolescents in Europe: Developments over 20 years and future challenges. Eur J Cancer 2006;42(13):2183-90.

8 Spix C, Pastore G, Sankila R, et al. Neuroblastoma incidence and survival in European children (1978-1997): Report from the Automated Childhood Cancer Information System project. EurJ Cancer 2006;42:2081-91.

9 Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. Ann Oncol 2012;23(9):2464-9.

10 Scurr M, Judson I. How to treat the Ewing's family of sarcomas in adult patients. Oncologist 2006;11(1):65-72.

11 Rickel K, Fang F, Tao J. Molecular genetics of osteosarcoma. Bone 2017;102:69-79.

12 Englund A, Glimelius I, Rostgaard K, et al. Hodgkin lymphoma in children, adolescents and young adults - a comparative study of clinical presentation and treatment outcome. Acta Oncol 2018;57(2):276-82.

13 Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 2012;123(4):465-72.

[14] Indini A, Brecht I, Del Vecchio M, et al. Cutaneous melanoma in adolescents and young adults. Pediatr Blood Cancer 2018;65(11):e27292.

[15] Krebsregister Saarland Cancer Registry. Available from: http://www.krebsregister.saarland.de/datenbank/datenbank.html. Accessed 15-Nov-2017.

[16] North Rhine-Westphalia Cancer Registry. Available from: http://www.krebsregister.nrw.de/index.php?id=3. Accessed 15-Nov-2017.

[17] Niedersachsen Cancer Registry. Available from: http://www.krebsregister-niedersachsen.de/. Accessed 15-Nov-2017.

[18] Office for National Statistics. Cancer Registration Statistics, England, 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland. Accessed 15-Nov-2017.

[19] Registre National des Tumeurs Solides de l'Enfant. Repartition par groups diagnostiques et annees des tumeurs solides de l'enfant en France 2000-2006. Available from: https://rnce.inserm.fr/index.php/en/. Accessed 15-Nov-2017.

[20] Cancer Registry of the Republic of Slovenia. Available from: https://www.onko-i.si/rrs/. Accessed 15-Nov-2017.

[21] Latvian Cancer Registry 2016. Available from: https://www.spkc.gov.lv/lv/statistikaun-petijumi/statistika/veselibas-aprupes-statistika1/get/nid/14. Accessed 15-Nov-2017.

[22] Lithuanian Cancer Registry 2012. Available from: http://www.nvi.lt/index.php?page_id=3261&lang=lt. Accessed 15-Nov-2017.

[23] Netherlands Cancer Registry. Available from: http://www.cijfersoverkanker.nl/selecties/dataset_1/img5a09e372ebf8d. Accessed 15-Nov-2017.

[24] The Surveillance, Epidemiology, and End Results (SEER) Carcinoma Statistics Review 2000-2005. Available from: https://seer.cancer.gov/explorer/application.html. Accessed 07-Mar-2008.

[25] Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28(15):2625-34.

[26] Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomarkers Prev 2014;23(12):2716-36.

[27] Xu JQ, Murphy SL, Kochanek KD, et al. Deaths: final data for 2016. Natl Vital Stat Rep 2018;67(5):1-76.

[28] Cohn SL, Pearson ADJ, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol 2009;27(2):289-97.

[29] Matthay KK, Perez C, Seeger RC, et al. Successful treatment of stage III neuroblastoma based on prospective biologic staging: a Children's Cancer Group study. J Clin Oncol 1998;16(4):1256-64.

[30] Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010;363(14):1324-34.

[31] Cheung NKV, Cheung IY, Kushner BH, et al. Murine anti-GD2 monoclonal antibody 3F8 combined with granulocyte-macrophage colony-stimulating factor and 13-cis-retinoic acid in high-risk patients with stage 4 neuroblastoma in first remission. J Clin Oncol 2012;30(26):3264-70.

[32] Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HRNBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19(12):1617-29.

[33] Huh WW, Skapek SX. Childhood rhabdomyosarcoma: new insight on biology and treatment. Curr Oncol Rep 2010;12:402-10.

[34] Fletcher CDM, Bridge JA, Hogendoorm PCW, Mertens F, editors. WHO classification of tumours of soft tissue and bone. Lyon, France: IARC Press; 2013.

[35] Shern JF, Chen L, Chmielecki J, et al. Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov 2014;4(2):216-31.

[36] Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma—a report from the IRSG. Int J Radiat Oncol Biol Phys 2001;51(3):718-28.

[37] Stevens MCG. Treatment for childhood rhabdomyosarcoma: the cost of cure. Lancet Oncol 2005;6(2):77-84.

[38] Donaldson SS, Anderson JR. Rhabdomyosarcoma: many similarities, a few philosophical differences. J Clin Oncol 2005;23(12):2586-7.

[39] Rodeberg DA, Anderson JR, Arndt CA, et al. Comparison of outcomes based on treatment algorithms for rhabdomyosarcoma of the bladder/prostate: combined results from the Children's Oncology Group, German Cooperative Soft Tissue Sarcoma Study, Italian Cooperative Group, and International Society of Pediatric Oncology Malignant Mesenchymal Tumors Committee. Int J Cancer 2011;128(5):1232-9.

[40] Pappo AS, Anderson JR, Crist WM, et al. Survival after relapse in children and adolescents with rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. J Clin Oncol 1999;17(11):3487-93.

[41] Mazzoleni S, Bisogno G, Garaventa A, et al. Outcomes and prognostic factors after recurrence in children and adolescents with nonmetastatic rhabdomyosarcoma. Cancer 2005;104(1):183-90.

[42] Goldsby R, Burke C, Nagarajan R, et al. Second solid malignancies among children, adolescents, and young adults diagnosed with malignant bone tumors after 1976: follow-up of a Children's Oncology Group cohort. Cancer 2008;113(9):2597-604.

[43] Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. J Pediatr Hematol Oncol 2008;30(6):425-30.

[44] Cotterill SJ Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 2000;18(17):3108-14.

[45] Gaspar N, Hawkins DS, Dirksen U, et al. Ewing sarcoma: current management and future approaches through collaboration. J Clin Oncol 2015;33(27):3036-46.

[46] Aldrink JH, Heaton TE, Dasgupta R, et al. Update on Wilms tumor. J Pediatr Surg 2019;54(3):390-7.

[47] D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study. Cancer 1989;64(2):349-60.

[48] Jereb B, Burgers JM, Tournade MF, et al. Radiotherapy in the SIOP (International Society of Pediatric Oncology) nephroblastoma studies: a review. Med Pediatr Oncol 1994;22(4):221-7.

[49] Green DM. The treatment of stages I-IV favorable histology Wilms' tumor. J Clin Oncol 2004;22(8):1366-72.

[50] Davidoff AM. Wilms' tumor. Adv Pediatr 2012;59(1):247-67.

[51] Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000;27(3):443-54.

[52] Szychot E, Apps J, Pritchard-Jones K. Wilms' tumor: biology, diagnosis and treatment. Transl Pediatr 2014;3(1):12-24.

[53] Pritchard-Jones K. Controversies and advances in the management of Wilms' tumour. Arch Dis Child 2002;87(3):241-4.

[54] Green DM, Breslow NE, Beckwith JB, et al. Effect of duration of treatment on treatment outcome and cost of treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 1998;16(12):3744-51.

[55] Malogolowkin M, Cotton CA, Green DM, et al. Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. Pediatr Blood Cancer 2008;50(2):236-41.

[56] Reinhard H, Schmidt A, Furtwängler R, et al. Outcome of relapses of nephroblastoma in patients registered in the SIOP/GPOH trials and studies. Oncol Rep 2008;20(2):463-7. initial Pediatric Study Plan (iPSP) NKTR-214/Nivolumab/Ipilimumab BMS-986321/BMS-936558/BMS-734016 Nektar Therapeutics.

[57] Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. Br J Ophthalmol 2009;93(1):21-3.

[58] Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. Nat Rev Dis Primers 2015;1:15021.

[59] Gregersen PA, Urbak SF, Funding M, et al. Danish retinoblastoma patients 1943-2013 - genetic testing and clinical implications. Acta Oncol 2016;55(4):412-7.

[60] Aerts I, Lumbroso-Le Rouic L, Gauthier-Villars M, et al. Retinoblastoma. Orphanet J Rare Dis 2006;1:31.

[61] Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer 2008;112(2):416-32.

[62] Ostrom QT, Gittleman H, Fulop J et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol 2015;17(suppl 4):iv1-iv66.

[63] Woehrer A, Hackl M, Waldhör T, et al. Relative survival of patients with non-malignant central nervous system tumours: a descriptive study by the Austrian Brain Tumour Registry. Br J Cancer 2014;110(2):286-96.

[64] Jones C, Karajannis MA, Jones DTW, et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. Neuro Oncol 2017;19(2):153-61.

[65] Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol 2011;13(3):317-23.

[66] Kram DE, Henderson JJ, Baig M, et al. Embryonal tumors of the central nervous system in children: the era of targeted therapeutics. Bioengineering (Basel) 2018;5(4):78.

[67] Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol 2016;17(4):484-95.

[68] Frühwald MC, Biegel JA, Bourdeaut F, et al. Atypical teratoid/rhabdoid tumors-current concepts, advances in biology, and potential future therapies. Neuro Oncol 2016;18(6):764-78.

[69] Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131(6):803-20.

[70] Witt H, Mack SC, Ryzhova M, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell 2011;20(2):143-57.

[71] Pajtler K, Witt H, Sill M, et al. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. Cancer Cell 2015;27(5):728-43.

[72] Jaglowski SM, Linden E, Termuhlen AM, et al. Lymphoma in adolescents and young adults. Semin Oncol 2009;36(5):381-418.

[73] Galardy PJ, Bedekovics T, Hermiston ML. Targeting childhood, adolescent and young adult non-Hodgkin lymphoma: therapeutic horizons. Br J Haematol 2016;173(4):625-36.

[74] Percy CL, Smith MA, Linet M, et al. Lymphomas and reticuloendothelial neoplasms. In: Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR, editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. NIH Pub. No. 99-4649. Bethesda, MD: National Cancer Institute; 1999. pp. 35-50.

[75] Hochberg J, Waxman IM, Kelly KM, et al. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. Br J Haematol 2009;144(1):24-40.

[76] Sandlund JT. Should adolescents with NHL be treated as old children or young adults? Hematology Am Soc Hematol Educ Program 2007;2007(1):297-303.

[77] Reiter A, Klapper W. Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. Br J Haematol 2008;142(3):329-47.

[78] Lenz G, Wright GW, Tolga Emre NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A 2008;105(36):13520-5.

[79] Wright G, Tan B, Rosenwald A, et al. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 2003;100(17):9991-6.

[80] Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346(25):1937-47.

[81] Deffenbacher KE, Iqbal J, Sanger W, et al. Molecular distinctions between pediatric and adult mature B-cell non-Hodgkin lymphomas identified through genomic profiling. Blood 2012;119(16):3757-66.

[82] Miles RR, Raphael M, McCarthy K, et al. Pediatric diffuse large B-cell lymphoma demonstrates a high proliferation index, frequent c-Myc protein expression, and a high incidence of germinal center subtype: Report of the French-American-British (FAB) international study group. Pediatr Blood Cancer 2008;51(3):369-74.

[83] Oschlies I, Klapper W, Zimmermann M, et al. Diffuse large B-cell lymphoma in pediatric patients belongs predominantly to the germinal-center type B-cell lymphomas: a clinicopathologic analysis of cases included in the German BFM (Berlin-Frankfurt-Munster) Multicenter Trial. Blood 2006;107(10):4047-52.

[84] Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med 1996;334(19):1238-48.

[85] Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol 2005;131(1):39-49.

[86] Agrawal R, Wang J. Pediatric follicular lymphoma: a rare clinicopathologic entity. Arch Pathol Lab Med 2009;133(1):142-46.

[87] Howlader N, Morton LM, Feuer EJ, et al. Contributions of subtypes of non-Hodgkin lymphoma to mortality trends. Cancer Epidemiol Biomarkers Prev 2016;25(1):174-9.

[88] Meadows AT, Sposto R, Jenkin RD, et al. Similar efficacy of 6 and 18 months of therapy with four drugs (COMP) for localized non-Hodgkin's lymphoma of children: a report from the Childrens Cancer Study Group. J Clin Oncol 1989;7(1):92-9.

[89] Reiter A, Schrappe M, Parwaresch R, et al. Non-Hodgkin's lymphomas of childhood and adolescence: results of a treatment stratified for biologic subtypes and stage—a report of the Berlin-Frankfurt-Münster Group. J Clin Oncol 1995;13(2):359-72.

[90] Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood 2007;109(7):2773-80.

[91] Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109(7):2736-43.

[92] Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. Blood 2000;95(2):416-21.

[93] Sandlund JT. Non-Hodgkin lymphoma in children. Curr Hematol Malig Rep 2015;10(3):237-43.

[94] Pinkerton R. Continuing challenges in childhood non-Hodgkin's lymphoma. Br J Haematol 2005;130(4):480-8.

[95] Philip T, Hartmann O, Pinkerton R, et al. Curability of relapsed childhood B-cell non-Hodgkin's lymphoma after intensive first line therapy: a report from the Société Française d'Oncologie Pédiatrique. Blood 1993;81(8):2003-6.

[96] American Cancer Society. Special section: cancer in children and adolescents. Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society, 2014. pp. 25-42.

[97] Noone AM, Howlader N, Krapcho M, et al, editors. SEER Cancer Statistics Review, 1975-2015. Bethesda, MD: National Cancer Institute; 2017. Available from: https://seer.cancer.gov/csr/1975_2015/. Updated 10-Sep-2018. Accessed 27-Jul-2020.

[98] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.

[99] Möricke A, Zimmermann M, Reiter A, et al. Prognostic impact of age in children and adolescents with acute lymphoblastic leukemia: data from the trials ALL-BFM 86, 90, and 95. Klin Padiatr 2005;217(6):310-20.

[100] Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62(1):61-73.

[101] Haydu JE, Ferrando AA. Early T-cell precursor acute lymphoblastic leukaemia. Curr Opin Hematol 2013;20(4):369-73.

[102] Gerr H, Zimmermann M, Schrappe M, et al. Acute leukaemias of ambiguous lineage in children: characterization, prognosis and therapy recommendations. Br J Haematol 2010;149(1):84-92.

[103] Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med 2012;366(15):1371-81.

[104] Borowitz MJ, Devidas M, Hunger SP, et al. Children's Oncology Group. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 2008;111(12):5477-85.

[105] Locatelli F, Schrappe M, Bernardo ME, et al. How I treat relapsed childhood acute lymphoblastic leukemia. Blood 2012;120(14):2807-16.

[106] Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010;376(9757):2009-17.

[107] Brentjens RJ, Curran KJ. Novel cellular therapies for leukemia: CAR-modified T cells targeted to the CD19 antigen. Hematology Am Soc Hematol Educ Program 2012;2012:143-51.

[108] Hoffman LM, Gore L. Blinatumomab, a Bi-Specific Anti-CD19/CD3 BiTE(®) antibody for the treatment of acute lymphoblastic leukemia: perspectives and current pediatric applications. Front Oncol 2014;4:63.

[109] Kreitman RJ, Pastan I. Antibody fusion proteins: anti-CD22 recombinant immunotoxin moxetumomab pasudotox. Clin Cancer Res 2011;17(20):6398-405.

[110] Rasche M, Zimmermann M, Borschel L, et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia 2018;32(10):2167-77.

[111] Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: a European study. Pediatr Blood Cancer 2018;65(6):e26974.

[112] Austin MT, Xing Y, Hayes-Jordan AA, et al. Melanoma incidence rises for children and adolescents: an epidemiologic review of pediatric melanoma in the United States. J Pediatr Surg 2013;48(11):2207-13.

[113] Wechsler J, Bastuji-Garin S, Spatz A, et al. Reliability of the histopathologic diagnosis of malignant melanoma in childhood. Arch Dermatol 2002;138(5):625-8.

[114] Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 2005;23(21):4735-41.

[115] Longo MI, Lázaro P, Bueno C, et al. Fluorodeoxyglucose-positron emission tomography imaging versus sentinel node biopsy in the primary staging of melanoma patients. Dermatol Surg 2003;29(3):245-8.

[116] Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. Ann Surg Oncol 2001;8(2):101-8.

[117] Harris MN, Shapiro RL, Roses DF. Malignant melanoma. Primary surgical management (excision and node dissection) based on pathology and staging. Cancer 1995;75(2 Suppl):715-25.

[118] Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. Clin Dermatol 2009;27:529-36.

[119] Saiyed FK, Hamilton EC, Austin MT. Pediatric melanoma: incidence, treatment, and prognosis. Pediatric Health Med Ther 2017;8:39-45.

[120] National Comprehensive Cancer Network. Guidelines for patients 2018: melanoma. Available from: https://www.nccn.org/patients/guidelines/melanoma/. Accessed 04-Sep-2018.

[121] Rodriguez-Galindo C, Pappo AS, Kaste SC, et al. Brain metastases in children with melanoma. Cancer 1997;79(12):2440-5.

[122] Hayes FA, Green AA. Malignant melanoma in childhood: clinical course and response to chemotherapy. J Clin Oncol 1984;2(11):1229-34.

[123] Pappo AS. Melanoma in children and adolescents. Eur J Cancer 2003;39(18):2651-61.

[124] Boddie AW Jr, Cangir A. Adjuvant and neoadjuvant chemotherapy with dacarbazine in high-risk childhood melanoma. Cancer 1987;60(8):1720-3.

[125] Ipilimumab [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

[126] Ipilimumab [Summary of Product Characteristics]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

[127] BMS-936558 (Nivolumab) Investigator Brochure, Version No. 19. Bristol-Myers Squibb Company; 2020. Document Control No. [redacted]

[128] Rose K, Kummer H. A new ethical challenge for institutional review boards (IRBs)/ethics committees (ECs) in the assessment of pediatric clinical trials. Children (Basel) 2015;2(2):198-210.

[129] Charych DH, Hoch U, Langowski JL, et al. NKTR-214, an engineered cytokine with biased IL2 receptor binding, increased tumor exposure, and marked efficacy in mouse tumor models. Clin Cancer Res 2016;22(3):680-90.

[130] Charych DH, Rubas W, Dixit V, et al. Immune memory in nonclinical models after treatment with NKTR-214, an engineered cytokine biased towards expansion of CD8+ T cells in tumor. Poster presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO); 2016 Jun 3-7; Chicago, IL.

[131] Parisi G, Saco JD, Salazar FB, et al. Persistence of adoptively transferred T cells with a kinetically engineered IL-2 receptor agonist. Nat Commun. 2020;11:660.

[132] Sharma M, Khong H, Fa'ak F. Bempegaldesleukin selectively depletes intratumoral Tregs and potentiates T cell-mediated cancer therapy. Nat Commun 2020;11:661.

[133] Bentebibel SE, Hurwitz ME, Bernatchez C, et al. A first-in-human study and biomarker analysis of NKTR-214, a novel IL2Raf-biased cytokine, in patients with advanced or metastatic solid tumors. Cancer Discov. 2019;9:711–21.

[134] Diab A, Tannir N, Cho D, et al. Pivot 02: preliminary safety, efficacy and biomarker results from the Phase 1/2 study of CD 122 biased agonist NKTR 214 plus nivolumab in patients with locally advanced/metastatic solid tumors. Paper presented at the Society for Immunotherapy of Cancer Annual Meeting; 2017 Nov 10-12; National Harbor, MD.

[135] Diab A, Tannir NM, Bentebibel SE, et al. Bempegaldesleukin (NKTR-214) plus nivolumab in patients with advanced solid tumors: phase I dose-escalation study of safety, efficacy, and immune activation (PIVOT-02). Cancer Discov 2020;10:1158-1173.

[136] Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol 2003;21:807-39.

[137] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6(10):715-27.

[138] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3(11):991-8.

[139] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[140] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027-34.

[141] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 2007;8(3):239-45.

[142] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

[143] Diab A, Hurwitz ME, Cho DC, et al. NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: preliminary Phase 1/2 results of PIVOT. Abstract #3006. Presented at Annual Meeting of the American Society of Clinical Oncology; 2018 Jun 1-5; Chicago, IL.

[144] Diab A, Puzanov I, Maio, M. Clinical activity of BEMPEG plus NIVO in previously untreated patients with metastatic melanoma: updated results from the Phase 1/2 PIVOT-02 study. Paper presented at Annual Meeting of the Society for Immunotherapy of Cancer (SITC); 2019 Nov 6-10; National Harbor, MD.

[145] Siefker-Radtke AO, Fishman M, Balar V, et al. NKTR-214 + nivolumab in first-line advanced/metastatic urothelial carcinoma (mUC): updated results from PIVOT-02. Presented at Annual Meeting of the American Society of Clinical Oncology Genitourinary Cancers Symposium; 2019 Feb 14-16; San Francisco, CA.

[146] Tolaney S, Baldini C, Spira A, et al. Clinical activity of BEMPEG plus NIVO observed in metastatic TNBC: preliminary results from the TNBC cohort of the Ph1/2 PIVOT-02 study.

Poster presented at the 2019 CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference; 2019 Sep 25-28; Paris, France.

147 Bempegaldesleukin (NKTR-214) Investigator Brochure, Edition 8.0. Nektar Therapeutics; 2020. Document Control No. [redacted]

148 Chen TT. Optimal three-stage designs for phase II cancer clinical trials. Stat Med 1997;16(23):2701-11.

149 Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med 1995;14:357–79.

150 Schadendorf D, et al. Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). Presented at the 2016 Annual Meeting of the European Association of Dermato-Oncology; 2016 Aug 31-Sep 3; Vienna, Austria.

151 Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation at the American Association for Cancer Research (AACR) Annual Meeting; 2017 Apr 1-5; Washington, DC, USA.

152 Felip Font E, Gettinger SN, Burgio MA, et al. Three-year follow-up from Checkmate 017/057: nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster 1301PD. Poster discussion presentation at the European Society of Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain.

153 Herbst RS, Garon E, Kim DW, et al. KEYNOTE-010: durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. Poster presentation at the World Conference on Lung Cancer; 2016 Dec 4-7; Vienna, Austria.

154 Spigel DR, McLeod M, Hussein MA, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Oral presentation at the European Society of Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain.

155 Nishino M, Tirumani SH, Ramaiya NH, et al. Cancer immunotherapy and immune-related response assessment: the role of radiologists in the new arena of cancer treatment. Eur J Radiol 2015;84(7):1259-68.

156 Park JR, Bagatell R, Cohn SL, et al. Revisions to the International Neuroblastoma Response Criteria: a consensus statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 2017;35(22):2580-7.

157 Sandlund JT, Guillerman RP, Perkins SL, et al. International pediatric non-Hodgkin lymphoma response criteria. J Clin Oncol 2015;33(18):2106-11.

158 Warren KE, Vezina G, Poussaint TY, et al. Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from the Response Assessment in Pediatruc Neuro-Oncology committee. Neuro Oncol 2018;20:13-23.

[159] Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. Clin Oncol 2010;28(11):1963-72.

[160] US Food and Drug Administration. Immunogenicity Testing of Therapeutic Protein Products Developing and Validating Assays for Anti-Drug Antibody Detection Guidance for Industry FDA-2009-D-0539. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug. Accessed 9-Sept-2020.

[redacted]

[163] Atkinson EN, Brown BW. Confidence limits for probability of response in multistage Phase II clinical trials. Biometrics 1985;41(3):741-4.

[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ABC	activated B-cell-like
AC	active cytokines
ACE	angiotensin-converting enzyme
ADA	anti-drug antibody
AE	adverse event
AEC	absolute eosinophil count
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ART	antiretroviral therapy
AST	aspartate aminotransferase
AT/RT	atypical teratoid rhabdoid tumor
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BTLA	B- and T-lymphocyte attenuator
Cavgss	steady state average concentration
CBC	complete blood count
CI	confidence interval
Cmaxss	maximum concentration at steady state
CMV	cytomegalovirus
CNS	central nervous system
COG	Children's Oncology Group
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal carcinoma

Term	Definition
CrCL	creatinine clearance
CRS	Cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CVA	cerebrovascular accident
DIPG	diffuse intrinsic pontine glioma
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulation
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECLA	Electrochemiluminescence assay
eCRF	electronic case report form
EFS	event-free survival
EOI	end of infusion
EOT	end of treatment
EPE	Essential Protocol Elements
ET	embryonal CNS tumor
EU	European Union
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
[redacted]	
FL	follicular lymphoma
FSH	follicle-stimulating hormone

Term	Definition
fT3	free triiodothyronine
fT4	free thyroxine
GCB	germinal center B cell-like
GEP	gene expression profiling
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HGG	high-grade glioma
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HR	hazard ratio
IB	Investigator Brochure
ICF	informed consent form
ICOS	inducible T-cell co-stimulator
IFN-γ	interferon gamma
[redacted]	
IL	interleukin
IL-2	interleukin-2
IL-2Rαβγ	interleukin-2 receptor alpha beta gamma
IL-2Rβγ	interleukin-2 receptor beta gamma
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	Investigational Medicinal Product
INR	international normalized ratio
INRC	International Neuroblastoma Response Criteria
I-O	immuno-oncology
IP	Investigational Product
IRS	Intergroup Rhabdomyosarcoma Study

Term	Definition
IRT	Interactive Response Technology
IV	intravenous
[redacted]	
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
MGMT	O6-methylguanylmethyltransferase
MIBG	metaiodobenzylguanidine
MMT	Malignant Mesenchymal Tumor
MR	mixed response
MRI	magnetic resonance imaging
[redacted]	
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NKTR-214	bempegaldesleukin
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over the counter
PD-1	programmed cell death protein 1
pDILI	potential drug-induced liver injury
PD-L1	programmed death-ligand 1
PEDS	pediatric
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival

Term	Definition
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	Preferred Term
Q2W	every 2 weeks
Q3W	every 3 weeks
QTcF	QT interval corrected using Fridericia's correction formula
[redacted]	
RANO	Response Assessment in Neuro-Oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RC	related cytokines
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human IL-2
RMS	rhabdomyosarcoma
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
sAG	surface antigen
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SEER	Surveillance, Epidemiology, and End Results Program
SHH	Sonic hedgehog
SIOP	Société Internationale d'Oncologie Pédiatrique
SOC	standard of care
SSC	study steering committee
STS	Soft-tissue Sarcoma Committee

Term	Definition
SUSAR	suspected, unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TIA	transient ischemic attack
TIL	tumor-infiltrating lymphocyte
Tim-3	T-cell immunoglobulin mucin 3
[redacted]	
TME	tumor microenvironment
[redacted]	
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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 eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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. 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 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.

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 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 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 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, 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, 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 must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

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

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

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

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

refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, 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 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 AND PUBLICATIONS

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

- External Principal Investigator designated at protocol development
- Participant recruitment
- Involvement in trial design
- Other criteria (as determined by the study team)

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.

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 (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: 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 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic 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

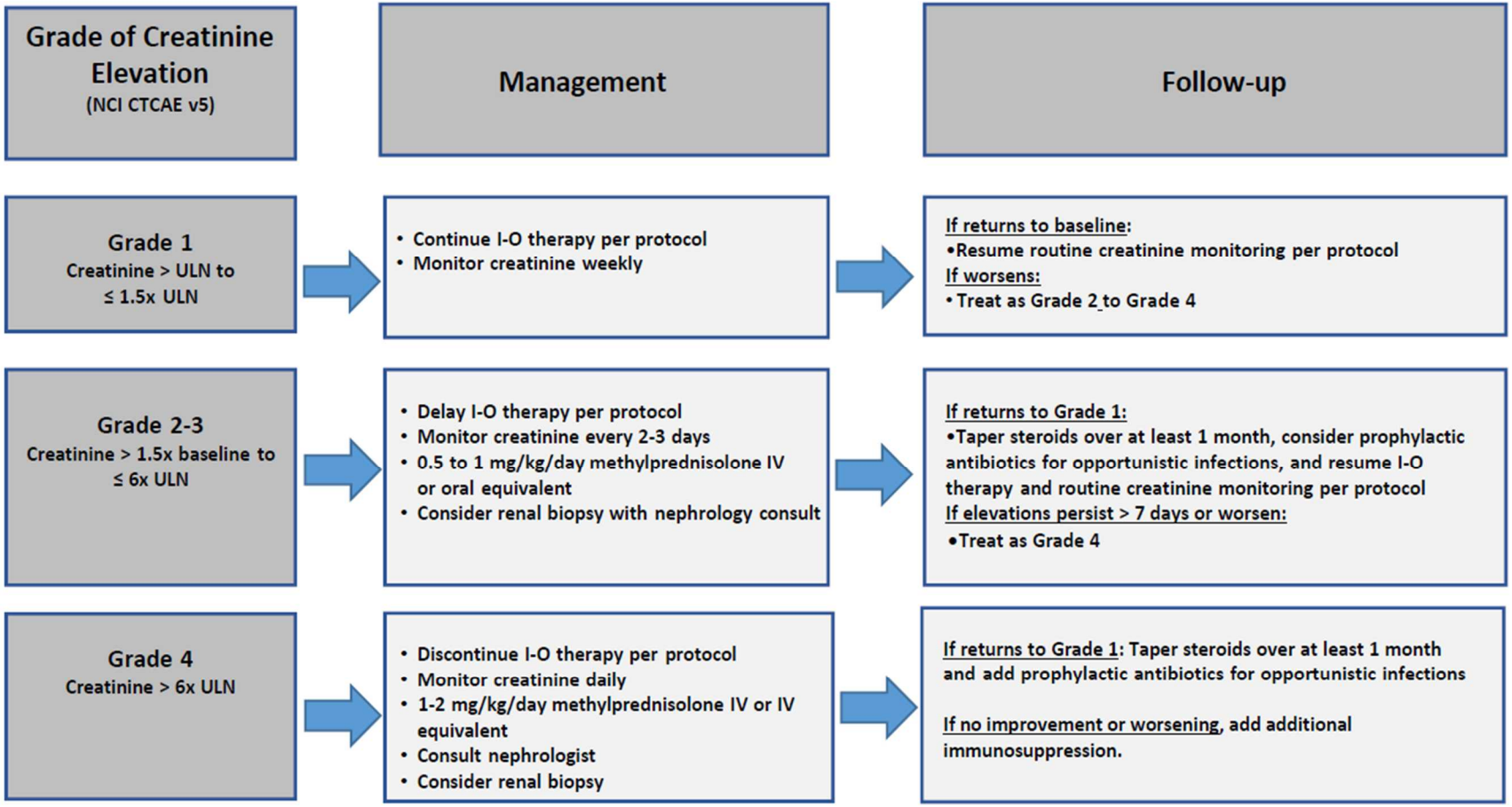
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

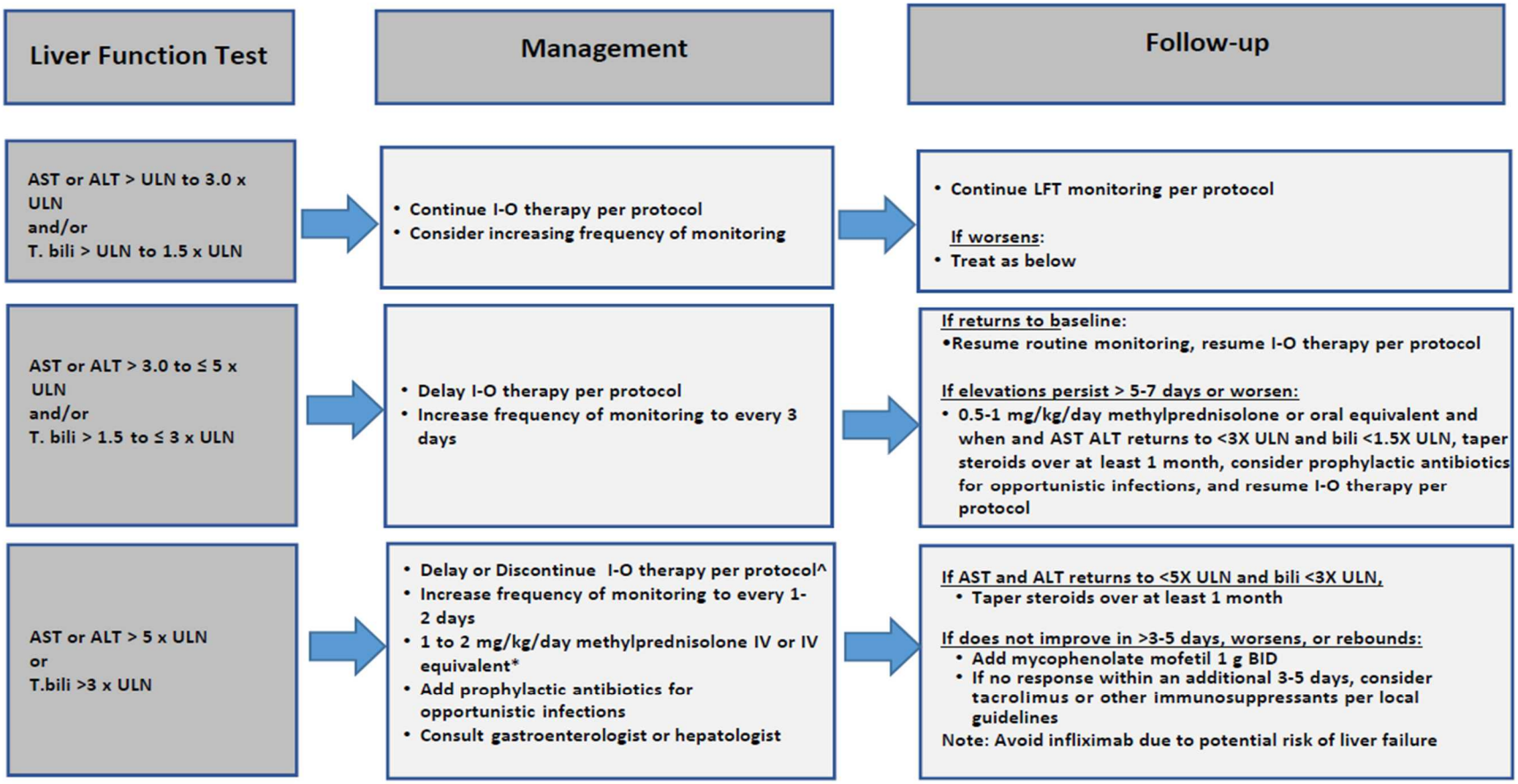
Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms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

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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

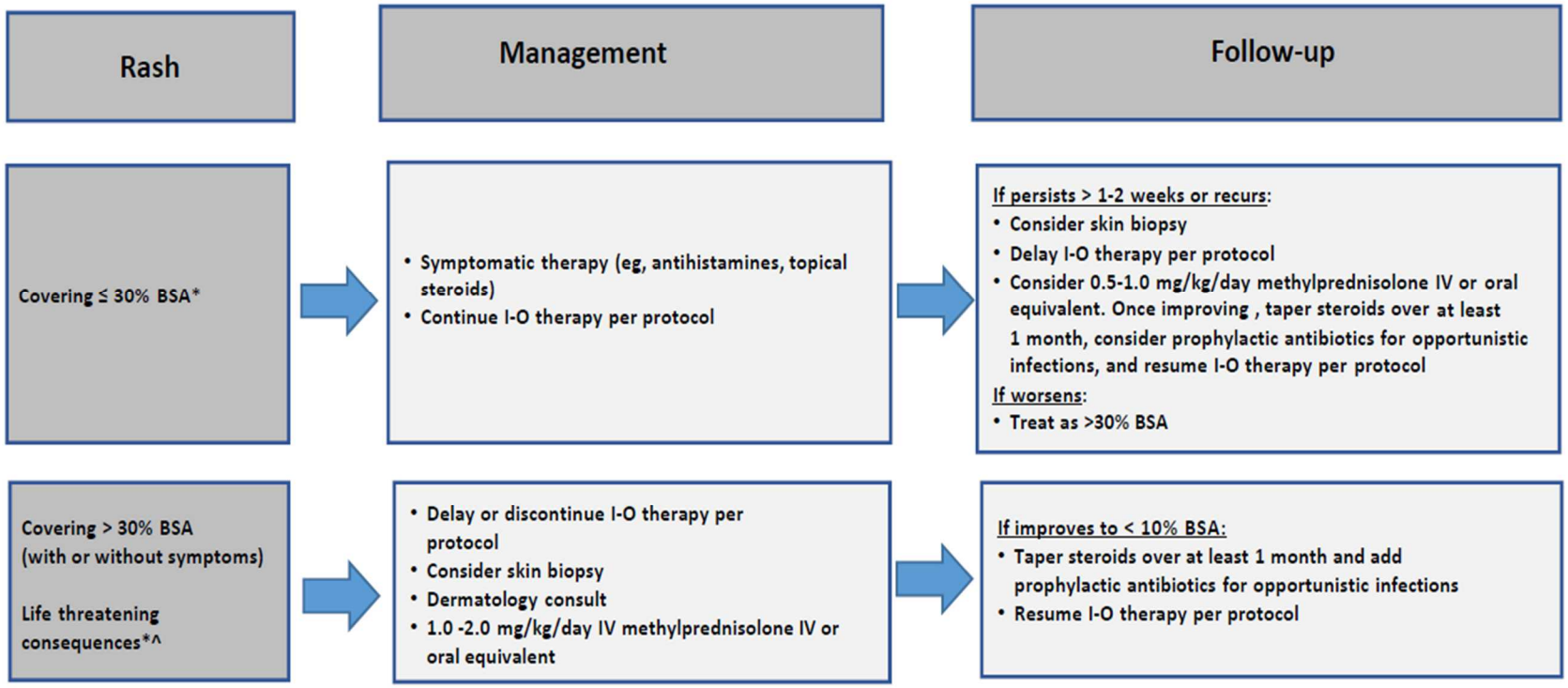
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated;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

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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

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

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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

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

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

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

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Myocarditis Adverse Event Management Algorithm

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

Myocarditis	Management	Follow-up

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

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

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

28-Sep-2020

APPENDIX 6 CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM FOR THE COMBINATION OF BEMPEGALDESLEUKIN WITH CHECKPOINT INHIBITORS

The table below provides a management algorithm for possible signs/symptoms of CVA for patients treated with the combination of bempegaldesleukin with a checkpoint inhibitor. This general guideline constitutes guidance to the Investigator and may be supplemented by clinical judgment of the Investigator and/or discussions with the Medical Monitor representing the Sponsor.

CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM **This guideline pertains to all participants receiving bempegaldesleukin 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. Perform neurological imaging with diffusion-weighted imaging (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).[a]
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 7 KARNOFSKY AND LANSKY CRITERIA

STATUS		STATUS
KARNOFSKY	**LANSKY**	**KARNOFSKY or LANSKY**
Normal, no complaints	Fully active, normal	100
Able to carry on normal activities; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity	90
Normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly	80
Cares for self. Unable to carry on normal activity or to do active work	Substantial restriction of, and less time spent, in play activity	70
Requires occasional assistance, but able to care for most of his needs	Out of bed, but minimal active play; keeps busy with quiet activities	60
Requires considerable assistance and frequent medical care	Gets dressed, but inactive much of day; no active play, able to participate in quiet play	50
Disabled. Requires special care and assistance	Mostly in bed; participates in some quiet activities	40
Severely disabled. Hospitalization indicated though death non imminent	In bed; needs assistance even for quiet play	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	Often sleeping; play limited to passive activities	20
Moribund	No play; does not get out of bed	10

APPENDIX 8 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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable.

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
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

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 = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

1 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 9 REVISED INTERNATIONAL NEUROBLASTOMA RESPONSE CRITERIA

Table 1: Primary (Soft Tissue) Tumor Response[a]

Response[b]	Anatomic + MIBG (FDG+PET)[c] Imaging
CR	< 10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site
PR	≥ 30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved
PD	> 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension[d]
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

Source: Park JR, Bagatell R, Cohn SL, et al. Revision to the International Neuroblastoma Response Criteria: A Consensus Statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587.

Abbreviations: CR = complete response; FDG = [^{18}F]fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; PD = progressive disease; PET = positron emission tomography; PR = partial response; SD = stable disease.

[a] Not for use in assessment of metastatic sites.

[b] In participants with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both sites unless biopsy proves one to be ganglioneuroma. In participants with multifocal nonadrenal disease, the largest tumor will be considered the primary tumor, and additional lesions will be assessed as metastatic sites unless biopsy proven to be ganglioneuroma.

[c] Used for MIBG-nonavid tumors.

[d] Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

Table 2: Tumor Response at Metastatic Soft Tissue and Bone Sites

Response	Anatomic + MIBG (FDG+PET)[a] Imaging
CR	Resolution of all sites of disease, defined as: • Nonprimary target and nontarget lesions measure < 10 mm AND • Lymph nodes identified as target lesions decrease to a short axis < 10 mm AND • MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely
PR	≥ 30% decrease in sum of diameters[b] of nonprimary target lesions compared with baseline AND all of the following: • Nontarget lesions may be stable or smaller in size AND • No new lesions AND • ≥ 50% reduction in MIBG absolute bone score (relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET–avid bone lesions[c,d]
PD	Any of the following: • Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma • Any new bone site that is MIBG avid • A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions • Relative MIBG score ≥ 1.2[d]
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions

Source: Park JR, Bagatell R, Cohn SL, et al. Revision to the International Neuroblastoma Response Criteria: A Consensus Statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587.

Abbreviations: CR = complete response; CT = computed tomography; FDG = [^{18}F]fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; SD = stable disease.

[a] Used for MIBG-nonavid tumors

[b] Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases. Masses of conglomerate nondiscrete lymph nodes will be measured using longest diameter.

[c] For participants with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[d] Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (eg, Curie or International Society of Pediatric Oncology European Neuroblastoma) must be used at all assessment time points. MIBG single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT may be used for scoring purposes, but the same imaging methodology should be used for all evaluations.

Table 3: Bone Marrow Metastasis Response[a]

Response	Cytology[b]/Histology[c]
CR	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement
PD	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration on reassessment OR • Bone marrow with tumor infiltration that increases by > 2-fold and has > 20% tumor infiltration on reassessment
MD	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0 to ≤ 5% tumor infiltration on reassessment OR • Bone marrow with no tumor infiltration that has ≤ 5% tumor infiltration on reassessment OR • Bone marrow with > 20% tumor infiltration that has > 0 to ≤ 5% tumor infiltration on reassessment
SD	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria

Source: Park JR, Bagatell R, Cohn SL, et al. Revision to the International Neuroblastoma Response Criteria: A Consensus Statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587; Burchill SA, Beiske k, Shimada H, et al. Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma: On behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer 2017;123:1095-1105.

Abbreviations: CR = complete response; MD = minimal disease; PD = progressive disease; SD = stable disease.

NOTE. In the case of discrepant results between aspirations or core biopsies from 2 or more sites taken at the same time, the highest infiltration result should be reported using the criteria in this table.

[a] Response will be compared with baseline disease evaluations before enrollment in a clinical trial or, for newly diagnosed participants, with baseline at specific times during therapy (ie, at diagnosis and before start of therapy, before specific phases of therapy such as induction, high-dose chemotherapy with stem-cell rescue consolidation, or postconsolidation immunotherapy).

[b] Accompanied by immunocytology (recommended, not mandatory).

[c] Accompanied by immunohistochemistry (IHC); specific recommendations included in Burchill et al:
IHC of multiple sections (> 3 sections) from all bone marrow biopsies using a minimum of 2 antibodies; to minimize cost, 3 sections might be placed on a single slide with each antibody. The quality of any immunohistological analysis should be monitored by simultaneous processing of a positive control sample. Relevant controls can be sections from multi-tissue blocks including the adrenal gland or other neuroendocrine tissues; an ideal control would have areas of positive and negative cells. A bone marrow biopsy is regarded as negative for tumor in the

absence of neuroblastoma cell nests detected by hematoxylin and eosin staining and IHC, using a minimum of 2 antibodies to analyze at least 3 sections. A case should only be confirmed as negative after the assessment of all available sections.

Table 4: Determination of Overall Response

Response	Cytology/Histology
CR	All components meet criteria for CR
PR	PR in at least 1 component and all other components are either CR, MD[a] (bone marrow), PR (soft tissue or bone), or NI[b]; no component with PD
MR	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	SD in one component with no better than SD or NI[b] in any other component; no component with PD
PR	Any component with PD

Source: Park JR, Bagatell R, Cohn SL, et al. Revision to the International Neuroblastoma Response Criteria: A Consensus Statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587.

Abbreviations: CR = complete response; MD = minimal disease; MR = minor response; NI = not involved; PD = progressive disease; PR = partial response; SD = stable disease.

[a] For bone marrow assessment only.

[b] Site not involved at study entry and remains uninvolved.

APPENDIX 10 INTERNATIONAL PEDIATRIC NON-HODGKIN LYMPHOMA RESPONSE CRITERIA

Table 1: International Pediatric NHL Response Criteria

Criterion	Definition
CR	• Disappearance of all disease (three designations) • CT or MRI reveals no residual disease or new lesions • Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as supporting data [Table 2]) • BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])
CRb	• Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as supporting data [Table 2]), with no new lesions by imaging examination • BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2]) • No new and/or progressive disease elsewhere
CRu	• Residual mass is negative by FDG-PET; no new lesions by imaging examination • BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2]) • No new and/or progressive disease elsewhere
PR	• 50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); • No new lesion and/or no PD; • Morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); • However, there should be 50% reduction in percentage of lymphoma cells
MR	• Decrease in SPD > 25% but < 50% on CT or MRI; no new lesion and/or no PD; • Morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); • However, there should be 25% to 50% reduction in percentage of lymphoma cells
NR	• For those who do not meet CR, PR, MR, or PD criteria
PD	• For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM or CSF

Source: Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 2015;33:2106-2111.

Abbreviations: BM = bone marrow; CR = complete response; CRb = complete response biopsy negative; CRu = complete response unconfirmed; CT = computed tomography; FDG = [^{18}F]fluorodeoxyglucose; MR = minor response; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NR = no response; PD = progressive disease; PET = positron emission tomography; PR = partial response; SPD = sum of product of greatest perpendicular diameters.

Table 2: Supporting International Pediatric NHL Response Criteria Data

Criterion	Definition
BM involvement	Currently defined by morphologic evidence of lymphoma cells; this applies to any histologic subtype; type and degree of BM involvement should be specified[a]
BMm	BM positive by morphology (specify percentage of lymphoma cells)
BMi	BM positive by immunophenotypic methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
BMc	BM positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
BMmol	BM positive by molecular techniques
CNS involvement	
CSF status	CSF positivity is based on morphologic evidence of lymphoma cells; CSF should be considered positive when any number of blasts is detected; CSF may be unknown; as with BM, type of CSF involvement should be described whenever possible
CSFm	CSF positive by morphology (specify No. of blasts/µL)
CSFi	CSF positive by immunophenotype methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
CSFc	CSF positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
CSFmol	CSF positive by molecular techniques
RM	
RMm	Tumor detected by standard morphologic evaluation
RMi	Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometric analysis)
RMc	Tumor detected by cytogenetic or FISH analysis
RMmol	Tumor detected by molecular techniques

Source: Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 2015;33:2106-2111.

Abbreviations: BM = bone marrow; FISH = fluorescent in situ hybridization; NHL = non-Hodgkin lymphoma; PB = peripheral blood; RM = residual mass.

[a] Same approach should be used for PB involvement (ie, PBm, PBi, PBc, PBmol).

APPENDIX 11 RESPONSE ASSESSMENT IN NEURO-ONCOLOGY(RANO)/PEDIATRIC NEURO-ONCOLOGY (RAPNO)

Table 1: Summary of RAPNO Response Criteria In Medulloblastoma and Leptomeningeal Seeding Tumors

Response	CR	PR	SD	PD
Criteria	**Must meet ALL criteria**	**Must meet ALL criteria**	**Must meet ALL criteria**	**Must meet ANY criteria**
MRI-brain	Complete disappearance of all disease (enhancing and non-enhancing, measurable and nonmeasurable) for a minimum of 4 weeks; no new lesions	≥50% decrease (compared with baseline) in the sum of the products of perpendicular diameters of all (up to 4) measurable lesions sustained for at least 4 weeks; no progression of nonmeasurable disease	Does not meet criteria for CR, PR, or PD	≥25% increase (compared with smallest measurement at any time point) in the sum of the products of perpendicular diameters of all measurable lesions; significant progression of nonmeasurable disease not attributed to prior therapy; any new tumor (any new lesions suspected to be treatment related should be confirmed by biopsy)
MRI-spine	Complete disappearance of all disease (enhancing and non-enhancing, measurable and nonmeasurable) for a minimum of 4 weeks; no new lesions	≥50% decrease (compared with baseline) in the sum of the products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks; no progression of nonmeasurable disease. If negative at baseline, must remain negative	Does not meet criteria for CR, PR, or PD	≥25% increase (compared with smallest tumor measurement at any time point) in the sum of the products of perpendicular diameters of all (up to 4) measurable lesions; significant progression of nonmeasurable disease not attributed to prior therapy; any new tumor (any new lesions suspected to be treatment related should be confirmed by biopsy)
CSF cytology	If tumor cells are present at baseline, must be negative × 2 (sampling at least 2 weeks apart)	If absent (negative) at baseline, must remain absent. If present at baseline, can be present or absent	If absent at baseline, must remain absent. If present at baseline, can be present or absent	Previously absent tumor cells in CSF now present (positive)

Table 1: Summary of RAPNO Response Criteria In Medulloblastoma and Leptomeningeal Seeding Tumors

Response	CR	PR	SD	PD
Criteria	**Must meet ALL criteria**	**Must meet ALL criteria**	**Must meet ALL criteria**	**Must meet ANY criteria**
Neurologic exam[a]	Stable or improving	Stable or improving	Stable or improving	Clinical deterioration not attributable to other causes
Steroid use	Off steroids or physiologic replacement doses only	Stable or less than baseline dose	Stable or less than baseline dose	
Extra-CNS disease	If positive at any time point, must be reevaluated and have no evidence of disease	No new sites of disease	No new sites of disease	New sites of disease
Serum or CSF AFP, βhCG (if obtained, eg, germ cell tumors)	Must be within normal range for age			A previously negative (normal) assessment becomes positive

Source: Warren KE, Vezina G, Poussaint TY, et al. Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from Response Assessment in Pediatric Neuro-Oncology committee. Neuro Oncol 2018;20:13-23.

Abbreviations: AFP, alpha-fetoprotein; βhCG, beta human chorionic gonadotropin; CNS = central nervous system; CR = complete response; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If it is unclear that the participant has disease progression, it may be a reasonable option to keep the participant on study until subsequent assessments (eg, MRI, CSF cytology) confirm progression. If subsequent testing confirms progression, the date of progression should be backdated to the onset of neurologic deterioration.

Table 2: RANO Criteria for Time-point Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
CR	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; participants must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Participants with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
PR	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Participants with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
SD	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
PD	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids (Stable doses of corticosteroids include participants not on corticosteroids); significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[a] not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Source: Wen PY, Macdonald DR, Reardon DA, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol 2010;28:1963-72.

Abbreviations: CR = complete response; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Stable doses of corticosteroids include patients not on corticosteroids.

Table 3: RANO Criteria for Determining First Progression Depending on Time after Radiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of radiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor or histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of radiotherapy.
Progressive disease ≥ 12 weeks after completion of radiotherapy	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first post radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For participants receiving antiangiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the participant on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Source: Wen PY, Macdonald DR, Reardon DA, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol 2010;28:1963-72.

Abbreviation: FLAIR = fluid-attenuated inversion recovery.

Table 4: RANO Assessment of Best Overall Response

Best Overall Response	Criteria
CR	CR observed in assessments ≥ 4 weeks apart per RANO
PR	PR observed in assessments ≥ 4 weeks apart per RANO
SD Note: To qualify for SD there must be a minimum on-treatment period of 6 weeks.)	SD observed and does not qualify for CR or PR or Suspected PD followed with histologic results not confirming PD, and no CR, PR or SD observed
Not Evaluable (NE)	Insufficient data to determine disease progression or response
PD	No CR, PR, or SD prior to PD

Source: Wen PY, Macdonald DR, Reardon DA, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol 2010;28:1963-72.

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

APPENDIX 12 RESPONSE TO THERAPY FOR HEMATOLOGICAL MALIGNANCIES

The assessment of the response to therapy in the bone marrow and cerebrospinal fluid (CSF) is solely based on cytological criteria.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Bone marrow status categories:

M1: Representative bone marrow aspirate with <5% lymphoblasts, satisfactory cellularity and signs of regenerating normal hematopoiesis

M2: Bone marrow with ≥ 5% and < 25% of lymphoblastic leukemic blasts irrespective of the cellular content

M3: Bone marrow with ≥ 25% of lymphoblastic leukemic blasts irrespective of the cellular content These criteria were modified from the National Comprehensive Cancer Network Criteria especially with respect to hematopoietic regeneration (platelets 50,000/μL and not 100,000/μL and absolute neutrophil count (ANC) > 500/μL and not 1000/μL). Since this mostly affects platelet regeneration, we distinguish between complete response without platelet recovery (CRp) and complete response with incomplete hematological recovery (CRi), in which respectively platelet regeneration or both platelet and ANC regeneration are below the level of recovery required for complete respone (CR) designation. Moreover, the categories of partial response (PR) and stable disease (SD) were defined.

Table 1: Response to Therapy for Acute Lymphoblastic Leukemia

Category	Definition
Non-representative bone marrow	Markedly reduced cellularity despite signs of regeneration in the peripheral blood and differential count of nucleated cells in the marrow largely corresponding to that in the peripheral blood. It should be repeated particularly when therapeutic decisions are taken based on the results.
Complete response (CR)	Attainment of M1 bone marrow status, or <1% by flow or molecular testing, with no evidence of circulating blasts or extra-medullary disease (No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement) and with recovery of peripheral counts (ANC >0.50 x 10^9/L (500/μL) and platelet count > 50 x 10^9/L (50,000/μL), transfusion independent). The detection of leukemic cells below the threshold of cytological detection using molecular or flow cytometric methods is compatible with the definition of CR. No recurrence for 4 weeks.
Complete response without platelet recovery (CRp)	Meets all criteria for CR except platelet count (≤ 50 x 10^9/L [50,000/μL])

Table 1: Response to Therapy for Acute Lymphoblastic Leukemia

Category	Definition
Complete response with incomplete hematological recovery (CRi)	Meets all criteria for CR except platelet count or ANC (ANC $\leq 0.50 \times 10^9$/L [500/μL]) and/or insufficient recovery of platelets ($\leq 50 \times 10^9$/L [50,000/μL])
Partial response (PR)	For participants with an M2 marrow already at study entry, greater than 50% relative reduction (with a minimum of 10% absolute reduction) in the bone marrow aspirate leukemic cell count, irrespective of recovery of the peripheral blood counts.
Non-response or stable disease (SD)	Stable disease is present when the participant fails to qualify for CR, CRp, CRi, PR, or PD.
Treatment Failure	
Progressive disease (PD)	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extra-medullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets
Refractory disease	Any participant not achieving CR, CRp or CRi after 1 or 2 cycles and does not meeting criteria for progressive disease.
Molecular reappearance	A reconversion after minimal residual disease (MRD) negativity to reproducible MRD positivity. A reconfirmation is strongly recommended. This finding does not fulfill the conditions for the definition of subsequent relapse
Relapse	Reappearance of blasts in blood or bone marrow (> 5%; M2 or greater) or >1% with previous/supportive molecular findings, or in any extramedullary site after a CR.

Source (Adapted from): (1) Pediatric Acute Lymphoblastic Leukemia Version 12.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN.org; 25-Nov-2019; (2) Acute Lymphoblastic Leukemia Version 1.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN.org; 15-Jan-2020.

Abbreviations: ANC = absolute neutrophil count; CNS = central nervous system; CR = complete response; CRi = complete response with incomplete hematological recovery; CRp = complete response without platelet recovery; MRD = minimal residual disease; PD = progressive disease; PR = partial response; SD = stable disease.

Classification of Central Nervous System (CNS) status:

- CNS-1: No lymphoblasts in CSF regardless of white blood cell (WBC) count.
- CNS-2: WBC < 5/mcL in CSF with presence of lymphoblasts.
- CNS-3: WBC ≥ 5/mcL in CSF with presence of lymphoblasts or, for pediatric participants, the clinical symptoms of cranial nerve palsy (if not explained by extracranial tumor), clinical spinal cord compression, or isolated intracerebral mass.

- If the participant has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥ 5/mcL in CSF with blasts, then compare the CSF WBC/red blood cell (RBC) ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, thente classification is CNS-3; if not, then it is CNS-2.

Table 2: Response Criteria for CNS Disease in Acute Lymphoblastic Leukemia

Category	Definition
Remission	Achievement of CNS-1 status in a participant with CNS-2 or CNS-3 status at diagnosis
Relapse	New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation. For pediatric participants, new development of CNS-2 status on 2 consecutive lumbar punctures (between 2 to 4 weeks apart) with confirmation by immunophenotyping or other molecular testing methods.

Source (Adapted from): (1) Pediatric Acute Lymphoblastic Leukemia Version 12.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN.org; 25-Nov-2019; (2) Acute Lymphoblastic Leukemia Version 1.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN.org; 15-Jan-2020.

Abbreviations: CNS = central nervous system.

ACUTE MYELOID LEUKEMIA (AML)

Table 3: Response to Therapy for Acute Myeloid Leukemia

Category	Definition
Complete remission/response (CR)[a]	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1 x 10^9/L (1000/μL); platelet count > 80 x 10^9/L (80,000/μL); independence of transfusions for a minimum of 1 week. No duration of response is required for CR.
CR with incomplete recovery (CRi)[b]	All CR criteria except for residual neutropenia (< 1 x 10^9/L [1000/μL]) or thrombocytopenia (< 80 x 10^9/L [80,000/μL]). No duration of response is required for CR.
Morphologic leukemia-free state	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extra-medullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%. A value of ≤5% blasts may also be considered a PR if Auer rods are present. No duration of response is required for PR
Cytogenetic CR (CRc)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Stable Disease (SD)	A subject who has no CR/CRi/PR nor has progressive disease for a period of at least 2 months should be considered SD
Treatment Failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes participants surviving ≥ 7 days after completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination (this should be stated by bone marrow examination < day 42 and at the end of intensification courses)
Progressive disease (PD)	Increase of at least 25% in the absolute number of circulating leukemic cells, development of new sites of extra-medullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets
Refractory disease	Any participant not achieving CR, CRi after one or two cycles and not meeting criteria for progressive disease

Table 3: Response to Therapy for Acute Myeloid Leukemia

Category	Definition
Molecular reappearance	A reconversion after minimal residual disease (MRD) negativity to reproducible MRD positivity. A reconfirmation is strongly recommended. This finding does not fulfill the conditions for the definition of subsequent relapse
Relapse[c]	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease
Early Death	
Death in aplasia	Death occurring ≥ 7 days after completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia (< day 42)
Death from indeterminate cause	
Early bleeding/leukostasis	Deaths occurring before completion of therapy, or < 7 days after its completion; or deaths occurring ≥ 7 days after completion of initial therapy with no blasts in the blood, but no bone marrow examination available (< day 42)

Sources (Adapted from): (1) Cheson BD, Bennett JM, Kopecky KJ, et al. Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-4649; (2) Creutzig U, Kaspers GJ. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2004;22(16):3432-3433; (3) Creutzig U, van den Heuvel-Eibrink MM, Gibson B, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendation from an international expert panel. Blood 2012:120:3187-3205.

Abbreviations: CR = complete response/remission; CRc = cytogenetic response/remission; CRi = complete response/remission with incomplete recovery; MRD = minimal residual disease; PD = progressive disease; PR = partial remission; RD = resistant disease; SD = stable disease.

Note: Definitions of response criteria are based primarily on those given by Cheson et al. and amended by Creutzig and Kaspers.

[a] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeating examination after 5-7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[b] The criterion of CRi is of value in protocols that use intensified induction or double-induction strategies, in which hematologic recovery is not awaited but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi participants. Some participants may not achieve complete hematologic recovery, even with longer observation times. As treatment courses should be very condensed (with minimal delay) in pediatric participants, treatment is continued, even without complete platelet recovery. Therefore, the recommended cut-off value for platelets indicating CR is 80 x 10^9/L.

[c] In participants with low blast percentages (5 % to 10 %), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a participant who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

APPENDIX 13 COUNTRY SPECIFIC AMENDMENTS

Country/Location Requirement	Section	Country-specific language
Any countries where exclusion of HIV positive participants is locally mandated	Section 2 Schedule of Activities Table 2-1: Screen Procedural Outline (CA045020) Laboratory Tests	Add "HIV" to the list of laboratory tests
	Section 6.2 Exclusion Criteria, Exclusion criterion 1) j)	Standard language in exclusion criteria add: "Countries where exclusion of HIV positive participants is locally mandated."
France	Table 7.4.1-1 Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Bempegaldesleukin (if one delayed, both delayed)	In the Event of Grade 4 hyperthyroidism and hypothyroidism
	Section 7.7.4.4 Volume of Blood	Based on Ethical considerations for clinical trials on medicinal products conducted with minors (Revision 1, 18-Sep-2017), the volume of each sample must not exceed 1% of the total blood volume at any single time and the total volume of blood sample must not exceed 3% of the total blood volume over a period of 4 weeks.[1]
Germany	Section 9.2.1 Time Period and Frequency for Collecting AE and SAE information and Appendix 3	All SAEs will be recorded and reported to Sponsor or designee immediately, without undue delay.

References:

1 Ethical considerations for clinical trials on medicinal products conducted with minors. Revision 1, 18 September 2017. Available from URL: https://ec.europa.eu/health/sites/default/files/files/eudralex/vo-10/2017_09_18_ethical_consid_ct_with_monors.pdf. Accessed 03-Jun-2021.

APPENDIX 14 CYTOKINE RELEASE SYNDROME - PEDIATRIC ADAPTED MANAGEMENT ALGORITHM

The following treatment management guidelines are provided for general guidance. These guidelines should not be a substitute for a more individualized, tailored approach to managing a patient experiencing cytokine release syndrome (CRS).

CRS Management Measures/Algorithm

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:

- Grade 1 (Fever with or without constitutional symptoms) supportive care as per institutional guidelines.
- Grade 2 (Hypotension responding to fluids, hypoxia responding to < 40% O2). Inpatient monitoring with fluid management, oxygen supportive care, and management of isolated symptoms based on institutional practices.
- Monitor for persistent or worsening clinical condition after initial treatment of CRS and evaluate for other contributing conditions. It is particularly important to reassess the patient for coexisting infections, and cardiac, pulmonary, thromboembolic and other complications.

Grading Assessment per CTCAE v.5.0		**Treatment Measures Recommended**
Grade 3 CRS	• Hypotension managed with one pressor • Hypoxia requiring >40% O2	• Vasopressor support per institutional guidelines should be considered if the hypotension is refractory to 20 ml/kg 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- dexamethasone 0.2 mg/kg Q 6 hrs or 12 hrs for subjects <50 kg. Dexamethasone 10 mg Q 6 or 12 hrs for subjects > 50kg. Alternatively, methylprednisolone 1-2 mg/kg/d divided Q6 hrs • For severe CRS cases that require simultaneously aggressive management of hypotension, oxygenation and cardiac telemetry, consult Intensivist for ICU evaluation. Consider anti-IL-6 (tocolizumab)