Official Title of Study:

A Phase 1/2 Study of the Combination of Lirilumab (Anti-KIR) Plus Nivolumab (Anti-PD-1) or Lirilumab Plus Nivolumab and Ipilimumab in Advanced Refractory Solid Tumors

NCT Number: NCT01714739

Document Date (Date in which document was last revised): May 8, 2018

Protocol Number: CA223001
IND Number: 115,879
EUDRACT Number 2016-001359-36
Date: 11-Jun-2012
Revised Date: 08-May-2018

Clinical Protocol CA223001

A Phase 1/2 Study of the Combination of Lirilumab (Anti-KIR) Plus Nivolumab (Anti-PD-1) or Lirilumab Plus Nivolumab and Ipilimumab in Advanced Refractory Solid Tumors

Revised Protocol Number: 12

Incorporates Administrative Letters 04 & 05

Study Director

[redacted]

Telephone (office): [redacted]
Fax: [redacted]

Medical Monitor

[redacted]

Telephone (office): [redacted]
Fax: [redacted]

24-hr Emergency Telephone Number

[redacted]

Bristol-Myers Squibb Research and Development
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium
Route 206 & Province Line Road
Lawrenceville, NJ 08543

Replace all previous version(s) of the protocol with this revised protocol, and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 12	08-May-2018	The primary purpose of this revised protocol is to close the future enrollment in Part 3 and Part 5 and removal of Part 4 and Part 6 from the protocol study design. Additional revisions based on the lack of clear evidence of clinical benefit will include removal of overall survival visits for all subjects, additional subjects entering treatment beyond progression, retreatment at the time of disease progression as well as select sample collection and study visits.
Administrative Letter 05	30-Aug-2017	Medical Monitor update
Administrative Letter 04	30-May-2017	Medical Monitor and Study Director update
Revised Protocol 11	28-Feb-2017	Incorporates Amendment 15
Amendment 15	28-Feb-2017	Updated the cohort size and subject allocation for the Signal Detection Cohort Expansion (Part 4) and the cohort size, randomization scheme, treatment regimen, and inclusion criteria for the Signal Detection in Squamous Cell Carcinoma of the Head and Neck (SCCHN) with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5). Throughout the protocol, administrative changes, clarifications and typographical corrections, and updates for consistency were made.
Revised Protocol 10	12-Dec-2016	Incorporates Amendment 13
Amendment 13	12-Dec-2016	Indicated that the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) have both completed enrollment and are not applicable starting with Amendment 13 and all subsequent amendments and that their specific eligibility criteria are not applicable. Added 4 new study parts: • The SCCHN Randomized Cohorts (Part 3) • The Signal Detection Cohort Expansion (Part 4) • The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) • The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6) Updated for all new cohorts listed above, including updates to study rationale, background, safety text, eligibility criteria, study objectives, study design, discontinuation criteria, and statistical analyses. Added that enrollment for the SCCHN Cohort Expansion (Part 2) will stop when the SCCHN Randomized Cohorts (Part 3) open. Clarified that subjects on nivolumab will be allowed to continue study therapy after initial investigator-assessed Response Evaluation Criteria in Solid Tumors version 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Aligned applicable text to current Bristol-Myers Squibb (BMS) standards. Aligned introductory and product development background sections to current Investigator's Brochures. Updated relevant text from the Dose Escalation and Cohort Expansion (Part 1; completed) and The SCCHN Cohort Expansion (Part 2; completed) per recent clarification that lirilumab dosing should begin 30 minutes after dosing of nivolumab and moved order of infusion text into Section 4.1, Study Treatments. Added new headings or reorganized sections of text related to the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion

Document	Date of Issue	Summary of Change
		(Part 2; completed) for clarification. Removed sentence stating subjects who have received nivolumab are not eligible to enroll (maintained exclusion for subjects in any prior clinical study with ipilimumab or nivolumab). Clarified that biopsy sites no longer need to be distinct from evaluable lesions. Clarified which parts of the study may have an interim analysis done. Added "and suggest preliminary signs of clinical activity" to the hypothesis. For all study parts, Vz will be used instead of Vss. Throughout the protocol, administrative changes, clarifications and typographical corrections, and updates for consistency were made.
Revised Protocol 09	29-Jul-2016	Incorporated Amendment 12
Amendment 12	29-Jul-2016	Added 150-day follow-up
Revised Protocol 08	22-Jul-2016	Incorporates Amendment 11
Amendment 11	22-Jul-2016	Updated statistical language for SCCHN Expansion Cohort (Part 2), Updated WOCBP, Updated management algorithms in Appendix 3.
Revised Protocol 07	12-Apr-2016	Incorporates Amendment 10
Amendment 10	12-Apr-2016	Added European Union Drug Regulating Authorities Clinical Trials (EUDRACT) Number, updated protocol title, added BMS Belgium address, updated objectives, updated hepatitis language, moved male condoms and spermicide to Less Effective Methods of Contraception, updated Table 5.7d, updated statistical sections, updated Appendix 1.
Revised Protocol 06	11-Jan-2016	Incorporates Amendment 09
Amendment 09	11-Jan-2016	Correction to Inclusion Criteria (Target Population) numbering/lettering.
Revised Protocol 05	02-Nov-2015	Incorporates Amendment 07
Amendment 07	02-Nov-2015	The purpose of this amendment is to add additional subjects to the SCCHN cohort in order to further explore the safety and efficacy of the compound. Some administrative corrections were also updated.
Revised Protocol 04	24-Jul-2014	Incorporates Amendment 06
Amendment 06	24-Jul-2014	Updated inclusion and exclusion criteria, clarification of diagnostic imaging scan criteria and collection timelines, and addition of pharmacokinetic anti-killer cell immunoglobulin-like receptors (KIR), pharmacokinetic anti-programmed cell death 1 (PD-1), anti-drug-antibody (ADA) anti-KIR, and ADA anti-PD-1 collection points.
Revised Protocol 03	06-Feb-2014	Incorporates Amendment 05
Amendment 05	06-Feb-2014	Updated safety information for nivolumab and lirilumab. In the dose escalation cohorts, increased the number of subjects that may be enrolled at each Dose Level from 12 to 15 in order to obtain additional data. Additional tumor types of SCCHN and hepatocellular carcinoma added to dose cohort expansions. The colorectal cancer cohort was modified to enroll only subjects with non-microsatellite-instability-high tumors. Gehan 2-stage approach for efficacy assessment of these tumor types added. Cohort expansions of ovarian and renal cell carcinoma deleted. Expanded the biomarker collection to the head and neck dose cohort expansion. Inclusion criteria for all cohort expansions updated. Increased number of subjects in non-small cell lung cancer and melanoma cohorts.

Document	Date of Issue	Summary of Change
		Updates to vital sign assessments, clarifications of efficacy criteria, and ADA endpoints were added. Rationale for circulating tumor DNA analysis and assessment schedule added.
Revised Protocol 02	08-Apr-2013	Incorporates Amendment 04
Amendment 04	08-Apr-2013	Updated generic drug names to lirilumab for BMS-986015 and nivolumab for BMS-936558. Revised contraception requirements for Appendix 1. New laboratory requirements for after Cycle 1 Day 1.
Revised Protocol 01	04-Sep-2012	Incorporates Amendment 03
Amendment 03	04-Sep-2012	Revised dose escalation design 3 + 3 + 3. Revised permanent discontinuation criteria (Section 4.9.4). Revised eligibility to require subjects to have normal thyroid function and at least 1 prior therapy in the advanced/metastatic setting.
Original Protocol	11-Jun-2012	Not applicable.

OVERALL RATIONALE FOR REVISED PROTOCOL 12:

The primary purpose of this revised protocol is to close the future enrollment in Part 3 and Part 5 and removal of Part 4 and Part 6 from the protocol study design. At the time of Amendment 13, preliminary data from an initial cohort of subjects in this study suggested a signal of potential efficacy (ORR of 24% [7/29]) in recurrent or metastatic SCCHN subjects with disease progression on or after platinum-based therapy. Subsequent efficacy analysis of additional SCCHN subjects treated with the combination of lirilumab and nivolumab did not demonstrate a differential efficacy signal as compared to nivolumab monotherapy treatment in a similar population of SCCHN subjects. Therefore, with Revised Protocol 12, enrollment in Parts 3 and 5 is closing and Parts 4 and 6 are removed from the protocol. As the combination of lirilumab and nivolumab continues to be well tolerated, individual subjects who continue to have clinical benefit with the combination of lirilumab and nivolumab without an increase in adverse events will be permitted to remain on study treatment until protocol-specified discontinuation criteria are met.

Additional revisions based on the lack of a differential efficacy signal will include removal of overall survival visits for all subjects, additional subjects entering treatment beyond progression, retreatment at the time of disease progression as well as select sample collection and study visits. Subjects will be permitted up to a maximum of 2 years of treatment as specified in the individual study parts.

Sections in the synopsis have been updated to align with the protocol section changes listed below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12

Section Number & Title	Description of Change	Brief Rationale
Section 1.2.3, The Signal Detection Cohort Expansion (Part 4); Section 1.2.5, The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); Section 1.3.1.3, Primary Objective for the Signal Detection Cohort Expansion (Part 4); Section 1.3.1.5, Primary Objective for the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); Section 1.3.2.3, Secondary Objectives for the Signal Detection Cohort Expansion (Part 4); Section 1.3.2.5, Secondary Objectives for the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); [redacted]	Existing text under these sections is now replaced with a statement "Removed with Revised protocol 12" as Part 4 and Part 6 are no longer part of this study.	Existing text under these sections is removed to reflect the modified protocol design for the removal of Part 4 and Part 6 after implementation of this revised protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] Section 3.1.4, The Signal Detection Cohort Expansion (Part 4); Section 3.1.6, The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); Section 5.1.3, The Signal Detection Cohort Expansion (Part 4); Section 8.1.5, The Signal Detection Cohort Expansion (Part 4); Section 8.1.7, The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); Section 8.3.1.3, The Signal Detection Cohort Expansion (Part 4); Section 8.3.1.5, The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); Section 8.3.2.3, The Signal Detection Cohort Expansion (Part 4); Section 8.3.2.5, The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6); [redacted] Section 8.4.7, Outcomes Research Analyses		
Section 1.4.4, Lirilumab: Clinical Pharmacology and Safety	Section has been updated for number of subjects and also clarified most common related AEs.	The updates were made to align with the current Lirilumab Investigator Brochure.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.4.13.2, Rationale for Schedule, Dose, and Tumor Types for the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) and the Signal Detection Cohort Expansion (Part 4 - removed): Flat Doses; Section 1.4.16, Rationale for Use of Blood and Tumor Tissue in Biomarker Studies; Section 3.5.1, Treatment Beyond Disease Progression; Section 4.1, Study Treatments; Section 4.3, Selection and Timing of Dose for Each Subject; Section 4.4, Blinding/Unblinding; Section 4.9.5, Guidelines for Permanent Discontinuation; Section 5.3.1, Microsatellite Instability Testing; Section 5.4, Efficacy Assessments; [redacted] Section 8.3, Endpoint Definitions; Section 8.4.4, Pharmacokinetic Analyses	These sections have been updated to remove the text related to Part 4 and Part 6.	Related text for Part 4 and Part 6 under these sections are removed to reflect the modified protocol design for the removal of Part 4 and Part 6 after implementation of this revised protocol.
Section 1.4.19, Rationale for Two Year Duration of Treatment	New section added.	New text added to provide the rationale for limiting treatment duration for all study parts in the study.
Section 1.5, Overall Risk/Benefit Assessment	Modified the text under this section to reflect the closing of Part 3 and Part 5 enrollment and removal of Part 4 and Part 6 from the protocol.	Existing text in this section is updated to reflect the modified protocol design for closing future enrollment in Part 3 and Part 5 and removal of Part 4 and Part 6 after implementation of this revised protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1, Study Design and Duration; Figure 3.1 1: Overall Study Design for All Study Arms (Study CA223001)	Modified the text under this section to reflect the closing of Part 3 and Part 5 enrollment and removal of Part 4 and Part 6 from the protocol. Study Schema was updated.	Existing text and figure (study design) in this section is updated to reflect the modified protocol design for closing future enrollments in Part 3 and Part 5 and removal of Part 4 and Part 6 after implementation of this revised protocol.
Section 3.1.1, The Dose Escalation and Cohort Expansion (Part 1; Completed); Section 3.1.2, The SCCHN Cohort Expansion (Part 2; Completed); Section 3.1.5, The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)	Text regarding retreatment at the time of disease progression during the follow-up periods was removed.	Revision was made to remove the retreatment option based on the lack of a differential efficacy signal.
Section 3.1.1, The Dose Escalation and Cohort Expansion (Part 1; Completed); Figure 3.1.1-1: Study Period Schematic for the Dose Escalation and Cohort Expansion (Part 1; Completed); Section 3.1.2, The SCCHN Cohort Expansion (Part 2; Completed); Figure 3.1.2 1: Study Period Schematic for Part 2 (Completed); Section 3.1.3, The SCCHN Randomized Cohorts (Part 3 closed to enrollment); Figure 3.1.3-2: Study Period Schematic for the SCCHN Randomized Cohorts (Part 3); Section 3.1.5, The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment); Figure 3.1.5 2: Study Period Schematic for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5); Section 3.7, Post-treatment Study Follow-up	Added a statement to indicate that survival follow-up no longer applicable after implementation of this revised protocol 12.	Revision was made to remove the overall survival visits for all subjects based on the lack of a differential efficacy signal.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.5.1, Treatment Beyond Disease Progression	Added statement: "With Revised Protocol 12, no additional subjects are permitted to enter Treatment Beyond Disease progression. At the time of initial progressive disease, subjects will be required to discontinue study treatment and enter clinical follow-up"	The statement was added to reflect the modified protocol design upon approval of this revised protocol.
Section 5.3 Safety Assessments; Tables Table 5.1.1 2: On-treatment Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001); Table 5.1.1 3: Follow-up Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001); Table 5.1.2 2: On-treatment Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001); Table 5.1.2 3: Follow-up Procedural Outline the SCCHN Randomized Cohorts (Part 3-closed to enrollment) (CA223001); Table 5.1.4 2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001); Table 5.1.4 3: Follow-up Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)	Added clarification statement indicating non-serious AEs will also be collected until the start of subsequent anti-cancer therapy.	The statement was added to discontinue AE collection at the start of subsequent anti-cancer therapy.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.6, Biomarker Assessments; Table 5.7.3.3 4: Biomarker Assessment Schedule: the SCCHN Cohort Expansion (Part 2; completed); [redacted] Table 5.7.3.3 7: Pharmacokinetics, Immunogenicity, and Biomarker Assessment Schedule: the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed for enrollment) and in the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)	Added statement that no further biomarker samples are to be collected upon implementation of this revised protocol 12.	The statement was added to reflect the modified protocol design upon approval of this revised protocol.
Section 5.7.3.3, Pharmacokinetics, Immunogenicity (Anti-drug antibodies) and Biomarker Assessment Schedules; Table 5.7.3.3 4: Biomarker Assessment Schedule: the SCCHN Cohort Expansion (Part 2; completed); [redacted] Table 5.7.3.3 7: Pharmacokinetics, Immunogenicity, and Biomarker Assessment Schedule: the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed for enrollment) and in the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)	Added statement "PK and ADA samples will continue to be collected but will not be analyzed except as clinically indicated in specific cases such as Grade 3/4 toxicity, infusion reactions, etc."	Clarification statement was added.
Section 5.8, Outcomes Research Assessments	Added statement that no additional quality of life questionnaire (QLQ) are to be collected upon	The statement was added to reflect the modified protocol design upon approval of this revised protocol.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
	implementation of this revised protocol 12.	

SYNOPSIS

Clinical Protocol CA223001

Title of Study: Protocol CA223001: A Phase 1/2 Study of the Combination of Lirilumab (Anti-KIR) Plus Nivolumab (Anti-PD-1) or Lirilumab Plus Nivolumab and Ipilimumab in Advanced Refractory Solid Tumors

Investigational Product(s), Dose and Mode of Administration, and Duration of Treatment with Investigational Product(s): Subjects will receive intravenous (IV) doses of lirilumab (BMS-986015) every 4 weeks (Q4W), nivolumab (BMS-936558) every 2 weeks (Q2W), ipilimumab (BMS-734016) every 6 weeks (Q6W), and/or placebo for lirilumab Q4W until the end of the defined treatment period for the applicable study part.

Study Phase: 1/2

Research Hypothesis:

Please note that the Dose Escalation and Cohort Expansion (Part 1) and the Squamous Cell Carcinoma of the Head and Neck (SCCHN) Cohort Expansion (Part 2) have both completed enrollment and not applicable starting with Amendment 13 and all subsequent amendments or revised protocols. For preliminary safety and efficacy results, see Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment" of the protocol body. With Revised Protocol 12, Parts 3 and 5 are closed to enrollment and Parts 4 and 6 are removed.

- **The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)**: It is anticipated that the combination of anti-killer cell immunoglobulin-like receptors (KIR) antibody (lirilumab) and anti-programmed cell death 1 (anti-PD-1) antibody (nivolumab) will demonstrate adequate safety and tolerability at pharmacologically relevant doses and suggest preliminary signs of clinical activity so as to permit further clinical testing.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)**: It is anticipated that treatment with nivolumab alone or in combination with lirilumab will lead to clinically meaningful tumor reductions, as measured by objective response rate (ORR), in subjects with platinum-refractory recurrent or metastatic SCCHN who are programmed cell death ligand 1-positive (PD-L1+) (PD-L1+ is defined as PD-L1 expressed in ≥ 1% of tumor cells).
- **The Signal Detection Cohort Expansion (Part 4)**: Removed with Revised Protocol 12.
- **The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)**: It is anticipated that the triplet regimen of anti-KIR antibody (lirilumab), anti-PD-1 antibody (nivolumab), and anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody (ipilimumab) to treat subjects with platinum-refractory recurrent or metastatic SCCHN will demonstrate adequate safety and tolerability at pharmacologically relevant doses for further clinical testing.
- **The Signal Detection in Previously Untreated Metastatic Melanoma (MEL) with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)**: Removed with Revised Protocol 12.

Primary Objective:

- **The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed):** To assess the safety and tolerability of lirilumab given in combination with nivolumab and to identify dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of the combination in subjects with advanced (metastatic and/or unresectable) solid tumors. To assess the safety and preliminary anti-tumor activity of the combination of lirilumab and nivolumab in subjects with advanced solid tumors.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):** To estimate the ORR of lirilumab given in combination with nivolumab in subjects with recurrent or metastatic SCCHN that has relapsed or progressed within 6 months of the last dose of a platinum-containing therapy and whose tumors express PD-L1.
- **The Signal Detection Cohort Expansion (Part 4):** Removed with Revised Protocol 12.
- **The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment):** To assess the safety and preliminary anti-tumor activity of the combination of lirilumab with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.
- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6):** Removed with revised Protocol 12.

Secondary Objective(s):

- **The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)**
  - To characterize the pharmacokinetics (PK) of lirilumab and nivolumab when co-administered.
  - To monitor immunogenicity of lirilumab and nivolumab when administered as combination therapy.
  - To assess the pharmacodynamic effect in tumor tissue on tumor-infiltrating lymphocyte (TIL) subsets from MEL and SCCHN subjects treated with lirilumab given in combination with nivolumab.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)**
  - To estimate disease control rate (DCR), duration of response (DOR), and time to response of lirilumab given in combination with nivolumab.
  - To assess depth of response of lirilumab given in combination with nivolumab and of nivolumab monotherapy.
  - To assess the overall survival (OS) of lirilumab given in combination with nivolumab and nivolumab monotherapy.
  - To assess the progression-free survival (PFS) of lirilumab given in combination with nivolumab and nivolumab monotherapy.
  - To estimate the ORR by investigator assessment of lirilumab given in combination with nivolumab and nivolumab monotherapy.
  - To assess the safety of lirilumab given in combination with nivolumab in subjects with SCCHN.
- **The Signal Detection Cohort Expansion (Part 4)**

  Removed with Revised Protocol 12
- **The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)**
  - To estimate DOR of lirilumab given in combination with nivolumab and ipilimumab.
  - To assess depth of response of lirilumab given in combination with nivolumab and ipilimumab.
  - To characterize the PK and immunogenicity of lirilumab in combination with nivolumab and ipilimumab.
  - To investigate the immunomodulatory properties of lirilumab in combination with nivolumab and ipilimumab, and to evaluate potential baseline and on-treatment biomarkers in peripheral blood and tumor for association with efficacy in subjects with platinum-refractory recurrent or metastatic SCCHN.
  - To explore biomarkers of lirilumab in combination with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.
- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)**

  Removed with Revised Protocol 12.

[redacted]

- **Primary Endpoints:**
- **The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed):**
  - The primary endpoints are safety measures (the Dose Escalation and Cohort Expansion [Part 1] the SCCHN Cohort Expansion [Part 2]), and assessment of preliminary anti-tumor activity (for the SCCHN Cohort Expansion [Part 2]).
    - For the SCCHN Cohort Expansion (Part 2), assessment of preliminary anti-tumor activity will be based on using immune-mediated Response Evaluation Criteria in Solid Tumors (irRECIST) for the purposes of subject management. Timepoint tumor response evaluations will be recorded on the case report form (CRF) based on investigators' assessments using irRECIST criteria. Statistical analysis and reporting will be based primarily on RECIST v1.1 criteria.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):**
  - The primary endpoint is ORR in subjects randomized to lirilumab plus nivolumab.
    - Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, every 8 weeks (Q8W; ± 7 days) until Week 48, and then every 12 weeks (Q12W; ± 7 days) until progressive disease (PD) or treatment discontinuation, whichever occurs earlier.

- **The Signal Detection Cohort Expansion (Part 4):**

  Removed with Revised Protocol 12.

  The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment):

  – The primary endpoints are safety measures and assessment of preliminary anti-tumor activity.

    ♦ The assessment of preliminary anti-tumor activity will be based on using RECIST v1.1. Timepoint tumor response evaluations will be recorded on the CRF based on investigators' assessments using RECIST v1.1 criteria. Statistical analysis and reporting will be based primarily on RECIST v1.1 criteria. Investigator-assessed BOR based on RECIST v1.1 will be listed.

- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6) :**

  Removed with revised Protocol 12.

- **Secondary Endpoints**:

- **The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed):**

  – The secondary endpoints are PK, anti-drug antibodies [ADAs], and biomarkers.

    ♦ The secondary endpoint of occurrence of specific ADAs to lirilumab and nivolumab will be determined from measurements on Weeks 1, 3, 5, 13, 17, 33, 49, 65, and 81; end of treatment; and all 3 clinical follow-up visits (please see Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4 in the protocol body).

    ♦ Biomarker endpoint measures will be taken from a minimum of 10 MEL cohort expansion subjects and a minimum of 10 SCCHN (the Dose Escalation and Dose Expansion [Part 1; completed]) cohort expansion subjects or other additional subjects included in the biomarker analysis data sets.

    ♦ Biomarker endpoint measures will be taken from a minimum of 15 subjects in the SCCHN Cohort Expansion (Part 2) or other additional subjects included in the biomarker analysis data sets.

- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):**

  – The secondary endpoints are DCR, DOR, time to response, depth of response, OS, PFS, ORR by investigator assessment, and safety measures.

    ♦ Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, Q8W (± 7 days) until Week 48, and then Q12W (± 7 days) until PD or treatment discontinuation, whichever occurs earlier.

- **The Signal Detection Cohort Expansion (Part 4):**

  – Removed with revised Protocol 12.

- **The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment):**

  – The secondary endpoints are DOR, depth of response, PK, ADAs, immunomodulatory properties, and biomarkers.

    ♦ Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, Q8W (± 7 days) for 1 year (48 weeks), and then Q12W (± 7 days) until PD or treatment discontinuation, whichever occurs earlier.

    ♦ The secondary endpoint of occurrence of specific ADAs to lirilumab, nivolumab, and ipilimumab, will be determined from measurements specified in Table 5.7.3.3-7 of the protocol body).

    ♦ Biomarker endpoint measures will be included from all subjects in the biomarker analysis data sets.

- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6):**

  Removed with revised Protocol 12.

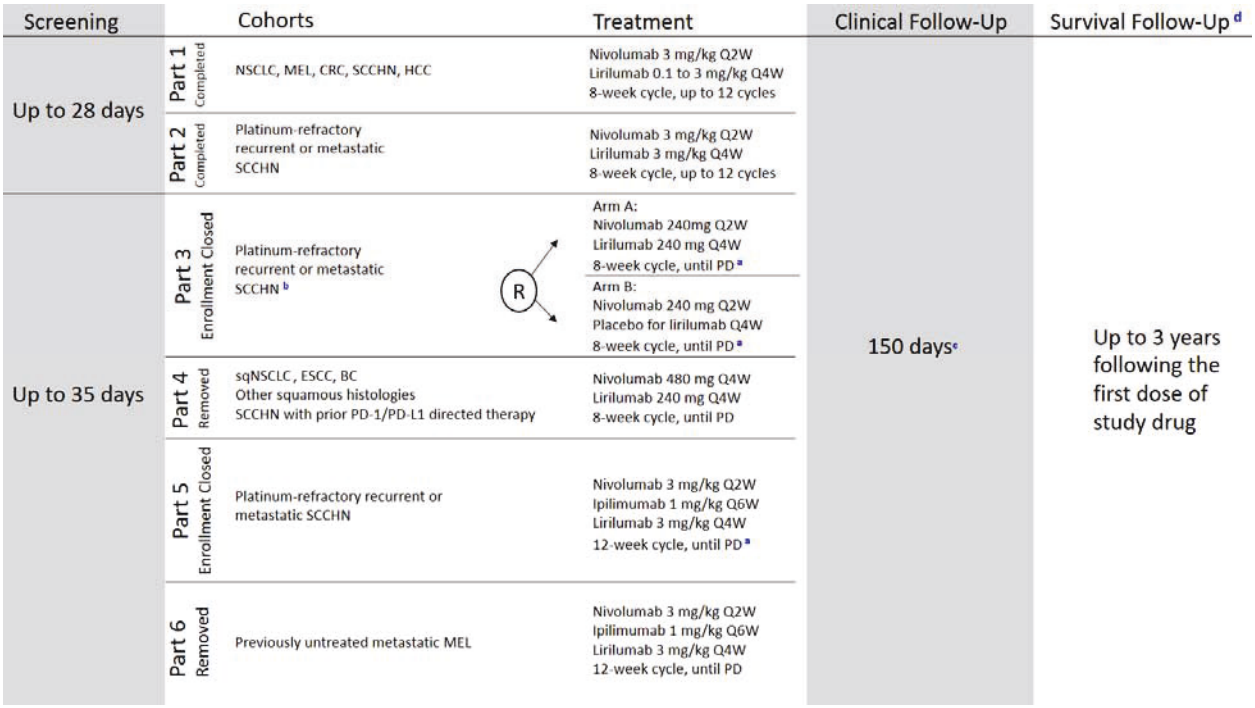
Study Design:

This is a Phase 1/2 study that will be conducted in 6 parts.

- Part 1 (completed): The Dose Escalation and Cohort Expansion of the study will consist of a dose escalation assessment of the safety and tolerability of lirilumab administered in combination with nivolumab in subjects with advanced solid tumors and 5 cohort expansions at either the MTD, maximum administered dose (MAD), or at an alternative dose as determined by the investigators and the Sponsor.
- Part 2 (completed): The SCCHN Cohort Expansion will be an additional cohort expansion at Dose Level 4 in subjects with platinum-refractory recurrent or metastatic SCCHN. The SCCHN Cohort Expansion (Part 2) of this study will close to enrollment as the SCCHN Randomized Cohorts (Part 3) open.
- Part 3 (closed to enrollment): The SCCHN Randomized Cohorts will involve a single-blinded, randomized cohort expansion of lirilumab in combination with nivolumab vs nivolumab monotherapy in subjects with platinum-refractory recurrent or metastatic SCCHN who are PD-L1+.
- Part 4 (removed): The Signal Detection Cohort Expansion will be an additional cohort expansion of nivolumab and lirilumab at a flat dose in subjects with sqNSCLC, ESCC, BC, and other squamous histologies (including squamous cell cancers of the skin, cervix, vulva, vagina, penis, anorectal, and of unknown primary site) and in subjects with SCCHN who have received prior PD-1/PD-L1 directed therapy.
- Part 5 (closed to enrollment): The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination will be an open-label safety and signal detection cohort with a triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.
- Part 6 (removed): The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination will be a safety and signal detection cohort with a first-line triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with previously untreated metastatic MEL.

Subjects will not be allowed to crossover between any parts or allowed to crossover to other Bristol-Myers Squibb studies, including CA209714 and CA209651 for SCCHN.

Figure 1: Overall Study Design for All Study Arms (CA223001)



[a] Treatment period is until PD, treatment discontinuation, or a maximum of up to 2 years of treatment as specified in the individual study parts, whichever occurs earlier.

[b] Subjects must have PD-L1+ tumors. PD-L1+ is defined as PD-L1 expressed in >1% of tumor cells.

[c] 150 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 150 days after last dose.

[d] No longer required with Revised Protocol 12.

CRC=colorectal cancer; HCC=hepatocellular carcinoma; R=randomization.

In all parts, subjects will complete up to 4 study periods: Screening (up to 28 days for the Dose Escalation and Cohort Expansion [Part 1; completed] and the SCCHN Cohort Expansion [Part 2; completed] and up to 35 days for all other study parts), Treatment (as defined below), Clinical follow-up (150 days), Survival follow-up (up to 3 years following the first dose of study drug). Survival follow-up is no longer required with Revised Protocol 12 and no further visits should be conducted.

The treatment period will last until PD, treatment discontinuation or a maximum of up to 2 years of treatment, as specified in the individual study parts whichever occurs earliest. For subjects receiving lirilumab and nivolumab combination therapy in the Dose Escalation and Cohort Expansion (Part 1; completed), the SCCHN Cohort Expansion (Part 2; completed), and the SCCHN Randomized Cohorts (Part 3; Arm A only), each 8-week treatment cycle is composed of 4 doses of nivolumab and 2 doses of lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each 8-week treatment cycle, and lirilumab will be administered on Days 1 and 29 of each 8-week treatment cycle. For subjects receiving nivolumab monotherapy (Arm B of the SCCHN Randomized Cohorts [Part 3] only), each 8-week treatment cycle is composed of 4 doses of nivolumab and 2 doses of placebo for lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each 8-week treatment cycle, and placebo for lirilumab will be administered on Days 1 and 29 of each 8-week treatment cycle. For subjects receiving lirilumab in combination with nivolumab and ipilimumab in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), nivolumab will be administered Q2W, ipilimumab will be administered Q6W, and lirilumab will be administered Q4W in each 12-week cycle.

Safety lead-in: Initially approximately 10 subjects will be enrolled in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5). Any findings will be discussed between the BMS Medical Monitor and investigators and an agreement will be reached as to whether a lower dose or an alternate dose schedule should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

Following each treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next 8 week cycle for all study parts except the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5], which is performed Q8W and completed before study therapy is continued. Treatment decisions related to subject management will be based exclusively on irRECIST for the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed) (see protocol body Section 1.4.14 for the rationale and Appendix 2 for definitions); with Amendment 13, all other study parts will use only RECIST v1.1 (see protocol body Sections 3.1.3, 3.1.4, 3.1.5, and 3.1.6 for details).

Subjects will generally be allowed to continue study therapy until the first occurrence of any of the following:

a) Achievement of irCR-confirmed (the Dose Escalation and Cohort Expansion [Part 1; completed] and the SCCHN Cohort Expansion [Part 2; completed]) or CR-confirmed the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5]).
b) Completion of a maximum of up to 2 years of the study treatment; 12 cycles in Parts 1, 2 and 3, and 8 cycles in Part 5.
c) irPD (the Dose Escalation and Cohort Expansion [Part 1; completed] and the SCCHN Cohort Expansion [Part 2; completed]) or PD confirmed or unconfirmed (the SCCHN Randomized Cohorts [Part 3], and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5],).
d) Clinical deterioration suggesting that no further benefit from treatment is likely.
e) Intolerability to therapy.
f) Meeting criteria for discontinuation of study therapy as outlined in protocol body Sections 3.5 and 4.9.5.

For all study parts, the subjects listed above will enter the clinical follow-up period, with visits scheduled on Days 30, 60, 100, and 150 to monitor for adverse events (AE)s.

Survival follow-up is no longer required with Revised Protocol 12 and no further visits should be conducted.

The Dose Escalation (Part 1; Completed): A 3 + 3 + 3 design will be used to assess the safety of lirilumab given in combination with nivolumab. The dosages during dose escalation are provided in Table 1. The DLT observation period will last for 8 weeks or until the completion of Cycle 1, whichever is longer. Three subjects will be treated initially at each Dose Level. If 0 DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher Dose Level. If 1 of 3 subjects experiences a DLT, that cohort will be expanded to 6 subjects. If 1 of 6 subjects experiences a DLT, a new cohort of 3 subjects will be treated at the next higher Dose Level. If 2 of 6 DLT subjects experience a DLT, that cohort will be expanded to 9 subjects. If 2 of 3, 3 of 6, or 3 of 9 subjects experience DLTs within a cohort, then that Dose Level will be determined to have exceeded the MTD. If no MTD is reached through Cohort 4, then additional cohorts at 6 mg/kg lirilumab and 10 mg/kg lirilumab, given in combination with 3 mg/kg nivolumab, may be considered based on the aggregate safety experience during dose escalation and in consultation and agreement between investigators and Sponsor via a protocol amendment.

After determining the MTD, MAD, or completion of dose escalation without identifying the MTD and to further explore pharmacodynamic/biomarker objectives, 3 to 12 additional subjects may be enrolled in each Dose Level for a total of up to 15 subjects at any Dose Level (original 3 to 12 subjects from dose escalation plus additional subjects required to have a total cohort size of 15).

No intra-subject dose escalation or reduction is allowed. Subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same Dose Level. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled nivolumab doses through the 8-week observation period only if the 1 missed dose was secondary to non-

medical reasons. In addition, subjects with dosing delays of ≥ 3 weeks in Cycle 1 for non-DLT events will be considered not evaluable for making decisions on dose escalation and should be replaced.

Dose escalation will be based on the number of DLTs experienced during Cycle 1.

The initial 6 subjects at each Dose Level will have peripheral blood evaluations for pharmacodynamic markers.

Table 1: Dosages During Dose Escalation

Dose Level Number	Total Subjects[a]	Lirilumab (IV; mg/kg)	Nivolumab (IV; mg/kg)
1	n = approximately 3 to 15	0.1	3
2	n = approximately 3 to 15	0.3	3
3	n = approximately 3 to 15	1	3
4	n = approximately 3 to 15	3	3
Total	n = approximately 12 to 60		

[a] 3 to 12 subjects will be enrolled during dose escalation. Additional subjects may be added to each Dose Level after completion of the dose escalation period of the study for a total of up to 15 subjects per Dose Level.

All available clinical and laboratory data and the nature, time of onset, and time to resolution of DLTs observed during dose escalation will be reviewed to determine whether an alternative dose schedule should be examined after consultation between the investigators and the Sponsor, if needed. If agreed upon, the alternative schedule will be identified by a protocol amendment.

The Cohort Expansion (Part 1; Completed): The purpose of the cohort expansions is to gather additional safety, tolerability, preliminary efficacy, and pharmacodynamic information regarding the combination of lirilumab and nivolumab. Once the safety profile of all doses tested has been characterized and the MTD of combined administration of lirilumab and nivolumab has been defined, the cohort expansions will be initiated at the MTD, the MAD, or an alternate dose, if recommended by the investigators and the Sponsor. Treatment doses in the cohort expansion groups will not exceed the MAD. Five cohort expansions will be restricted to the tumor types listed in Table 2. The non-small cell lung cancer (NSCLC) and MEL cohorts, which have demonstrated activity with nivolumab monotherapy, will be used to assess increased activity of the combination therapy. The colorectal cancer (CRC), SCCHN, and hepatocellular carcinoma (HCC) cohorts will explore activity of the combination therapy in tumors with unknown or historically low responses to nivolumab monotherapy. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the cohort expansions. If the rate of DLTs exceeds 33%, then the findings will be discussed and further enrollment may be interrupted. If a cohort expansion is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower Dose Level.

In each of the NSCLC and MEL cohorts, approximately 35 subjects will be enrolled to allow for a more precise estimate of the ORR in these tumors following combination treatment. The sample size for the other 3 cohorts will be guided by the Gehan design. In order to determine if a target response rate (eg, 25% to 30%) is likely, an initial number of subjects (eg, 9) will be treated at first (Stage I) in a cohort, as outlined in Table 2. In the tumor cohort in which no responses are observed, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate and no more subjects will be enrolled in that cohort. Otherwise, in the cohorts in which at least 1 response among the Stage I subjects is observed, up to 9 additional subjects will be treated for a total of 18 subjects per tumor type, as guided by Table 3. In Stage I, approximately 9 subjects will be enrolled per tumor type. The number of subjects enrolled in Stage II per tumor cohort will be guided by the number of responders observed in Stage I and the required precision of the ORR estimate. This is summarized in Table 3 below, using a precision of 12% around the ORR point estimate.

Table 2: Tumor Types Eligible for Cohort Expansion

Tumor Type	Stage I Subjects	Stage II Subjects	Total Subjects
NSCLC	N/A	N/A	Approx. 35
MEL	N/A	N/A	Approx. 35
CRC	9	4 to 9	Approx. 9 to 18
SCCHN	9	4 to 9	Approx. 9 to 18
HCC	9	4 to 9	Approx. 9 to 18
Totals			Approx. 97 to 124

Approx. = approximately; N/A = not applicable.

The actual sample size per cohort in Stage II to achieve desired precision (standard error) of 12% for the ORR estimate, as guided by the Gehan design, depends on the number of responses observed in Stage I (see Table 3), assuming a target ORR of 25% to 30%.

Table 3: Cohort Expansion Sample Sizes by n of Responses in Stage I for CRC, SCCHN, and HCC Tumors

Stage I Number of Responses in the First 9 Subjects	Stage II n[a]	Total n/Cohort
0	0	9
1	4	13
2	8	17
3	9	18
4	8	17
5	5	14
6	0	9

[a] Based on 12% precision for the ORR estimates and a target ORR of 25% to 30%.

DLT: This section only applies to the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2), which have both completed enrollment and therefore this section and its subsections are not applicable starting with Amendment 13 and all subsequent amendments or revised protocols. For the purpose of guiding dose escalation, hepatic, non-hematologic, and hematologic DLTs will be defined separately (protocol body Section 4.8) and will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 56 days (8 weeks, through the completion of Cycle 1) of initiation of study drug in the Dose Escalation and Cohort Expansion (Part 1; completed). The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). For the purposes of subject management, DLTs will lead to dose interruption regardless of the cycle in which a DLT occurs (see protocol body Section 4.9.3 for specific guidelines).

The SCCHN Cohort Expansion (Part 2; Completed): To further explore emerging efficacy and safety data in subjects with SCCHN; an additional cohort of approximately 35 subjects will be treated at Dose Level 4 (see Table 1). The null hypothesis that the true ORR is 25% will be tested against a 1-sided alternative: ORR = 40%. The null hypothesis will be rejected if 12 or more responses are observed in 35 subjects. This design gives a 1-sided type I error

rate of 0.15 and a power of 0.81. See Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment" in the protocol body for preliminary safety and efficacy results.

The SCCHN Randomized Cohorts (Part 3 - closed to enrollment): This is a parallel study of lirilumab in combination with nivolumab vs nivolumab monotherapy in subjects with platinum-refractory recurrent or metastatic SCCHN. This will be a single-blind, placebo-controlled, randomized, expansion study. Patients will be tested for PD-L1 status and enrolled if PD-L1 is expressed in ≥ 1% of tumor cells. Randomization will occur within approximately 35 days after screening. A total of approximately 225 subjects will be randomized in a 2:1 ratio to the 2 treatment arms (Arm A [flat dose of 240 mg lirilumab Q4W and flat dose of 240 mg nivolumab Q2W] and Arm B [placebo for lirilumab Q4W and flat dose of 240 mg nivolumab Q2W monotherapy]). The treatment period will last until PD, treatment discontinuation, or a maximum of up to 12 cycles of treatment, whichever occurs earlier.

The Signal Detection Cohort Expansion (Part 4): Removed with Revised Protocol 12.

The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment): This is an open-label Phase 2, cohort expansion study of lirilumab in combination with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN. Enrollment will occur within approximately 35 days after screening. Approximately 40 subjects will be treated with nivolumab 3 mg/kg IV Q2W, ipilimumab 1 mg/kg IV Q6W, and lirilumab 3 mg/kg IV Q4W. The treatment period will last until PD, treatment discontinuation, or a maximum of up to 8 cycles of treatment, whichever occurs earlier.

The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6): Removed with revised Protocol 12.

Duration of Study: The screening period will last up to 28 days for the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed) and up to 35 days for all the other study parts. The treatment period will last up to a maximum of 2 years or until PD or treatment discontinuation, whichever occurs earlier. The clinical follow-up period will last 150 days. Survival follow-up is no longer required with Revised Protocol 12 and no further visits should be conducted. With revised protocol 12, the total time on study for any individual subject will not exceed approximately 2.5 years. The total duration of the study is expected to be 4.5 years from the time of the first visit of the first subject to the required clinical follow-up of the last subject enrolled.

Number of Subjects: Up to approximately 740 subjects will be dosed pending results from the various 2-stage design components of the study. Additional subjects may also be enrolled if necessary to ensure an adequate number of higher PD-L1 expressers.

Study Population:

The study population will include men and women who are more than 18 years old, have histologic confirmation of a solid malignancy that is advanced (metastatic and/or unresectable), have measurable disease, and meet all eligibility criteria. As of Protocol Amendment 13, subjects undergoing biopsy do not need to have a biopsy lesion that is distinct from an index lesion.

- **For the Dose Escalation (Part 1; Completed):** Subjects with any tumor type (with the exception of primary central nervous system tumors and hematologic malignancies) are eligible to enroll.
- **For the Cohort Expansion (Parts 1 and 2; Completed):** Subjects must have 1 of the following tumor types to be eligible: NSCLC; MEL, CRC, SCCHN, or HCC. All subjects will be given the option of undergoing pre-treatment, on-treatment, and post-treatment biopsies if they can be performed with acceptable clinical risk. For subjects with MEL and SCCHN, a minimum of 10 treated subjects in each cohort will be required to undergo pre-treatment and on-treatment biopsies during cohort expansion. Post-treatment biopsies (following completion of all study therapy) will be optional. In addition, optional biopsies may be obtained from subjects who have clinically meaningful events, such as response, disease progression, or AEs of interest. Consent for biopsies must be obtained. Biopsy sites for these subjects must be distinct from evaluable lesions and must not have been irradiated prior to entry.
- **For the SCCHN Cohort Expansion (Part 2; Completed) and the SCCHN Randomized Cohorts (Part 3 - closed to enrollment):** Subjects must have histologically confirmed platinum-refractory recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage 3/4 and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) and in the SCCHN Randomized Cohorts (Part 3) only must have tumors that are PD-L1+ on fresh biopsies by immunohistochemistry (IHC) testing performed by the central

laboratory during the screening period. For SCCHN Cohort Expansion (Part 2; completed) only, a minimum of 15 subjects will be required to undergo mandatory pre-treatment and on-treatment biopsies at acceptable clinical risk as judged by the investigator. For the SCCHN Randomized Cohorts (Part 3), all subjects **will be required to provide fresh biopsies at baseline and on-treatment** if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable.

- **For the Signal Detection Cohort Expansion (Part 4):** Removed with Revised Protocol 12.
- **For the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment):** Subjects must have histologically confirmed platinum-refractory metastatic or recurrent SCCHN (oral cavity, oropharynx, hypopharynx, and larynx). Subjects must have tumor progression or recurrence after prior platinum-containing systemic therapy for recurrent or metastatic disease. In addition, subjects who have progressed within 6 months of platinum-based therapy used as part of concurrent chemoradiation (definitive or adjuvant therapy) are also eligible. All subjects will be **required to provide fresh biopsies at baseline and on-treatment** if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable.
- **For the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6):** Removed with Revised Protocol 12.

Study Assessments:

- **Safety Outcome Measures**: AEs will be assessed continuously during the study and for 150 days after the last treatment or until the start of subsequent anti-cancer therapy.AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator. Safety evaluation will also be based on clinical laboratory tests collected to assess laboratory abnormalities as well as results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and imaging studies. Both AEs and laboratory tests will be graded using NCI CTCAE v4.0.
- **Efficacy Measures**: Disease assessment with computed tomography and/or magnetic resonance imaging, as appropriate, will be performed at baseline and Q8W until disease progression, at the completion of clinical follow-up, or until subjects withdraw from the study. Disease assessments at other timepoints may be performed if the investigator is concerned about tumor progression. Tumor responses will be derived for appropriate populations of subjects as defined by RECIST v1.1 (see protocol body Appendix 3) from tumor measurements. For the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed), investigator-assessed responses and treatment decisions related to subject management will be based on irRECIST (see protocol body Appendix 2); all other study parts will use only RECIST v1.1. Radiographic assessments may be submitted to the third-party radiology vendor for any part of the study. Tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis. Submission of radiographic scans to the third-party vendor is no longer required with Revised Protocol 12.
  - In Parts 1 and 2, changes in tumor measurements and tumor responses will be assessed by the investigator using irRECIST criteria. Investigators will also report the number and size of new lesions that appear while on-study. The timepoint tumor assessments will be reported on the CRF based on investigators' assessment using irRECIST criteria. The SCCHN Randomized Cohorts (Part 3), and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), however, will use only RECIST v1.1 for all assessments. Please refer to Appendix 3 for specifics of RECIST v1.1 and Appendix 2 for specifics of irRECIST criteria to be utilized in this study.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):**
  - The primary endpoint is ORR based on assessment in all subjects randomized to lirilumab plus nivolumab. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria. All randomized subjects will be monitored by radiographic assessment every 8 weeks (± 7 days) beginning from the first dose date until Week 48 and Q12W (± 7 days) thereafter until PD or treatment discontinuation (whichever occurs later), to determine changes in tumor size.
  - Secondary efficacy endpoints of the SCCHN Randomized Cohorts (Part 3) are DCR, DOR, time to response, depth of response, OS, PFS, ORR according to investigator-assessed response, and safety measures.
- **The Signal Detection Cohort Expansion (Part 4):**
  - Removed with Revised Protocol 12.

[redacted]

- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6):**
  - Removed with Revised Protocol 12.
- **PK Measures**: Serum samples for lirilumab, nivolumab, and/or ipilimumab PK assessments will be collected for all subjects in both dose escalation and cohort expansion. Detailed schedules of PK evaluation is provided in Section 5.7.3.3. PK of nivolumab, lirilumab, and ipilimumab will be derived from serum concentration vs time. The PK parameters to be assessed wherever feasible include: maximum observed concentration (Cmax), time of maximum observed concentration, area under the plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration, AUC from time zero extrapolated to infinite time, trough observed serum concentration, AUC in 1 dosing interval (AUC[TAU]), clearance, volume of distribution of the terminal phase, and half-life. Nivolumab, lirilumab, and ipilimumab end of infusion and trough (trough observed concentration) concentrations will be calculated at specified visits whenever feasible.
- **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):** Outcomes Research Assessments Measures: EQ-5D-3L, EORTC-QLQ-C30, EORTC-QLQ-H&N35, and healthcare resource utilization questionnaire. Removed with Revised Protocol 12.
- **Immunogenicity Measures**: Serum samples to evaluate development of positive ADA response to lirilumab and nivolumab will be collected from all subjects pre-dose at specified timepoints.

[redacted]

[redacted]

Statistical Methods:

- Sample Size Determination:
  - **The Dose Escalation and Cohort Expansion (Part 1; Completed):**
    - See Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment" of the protocol body for a summary of preliminary safety and efficacy results.
    - Dose Escalation: Because this is a Phase 1/2 dose escalation study, the sample size at each dose cannot be determined exactly, as it depends on the number of observed toxicities. Approximately between 3 and 12 subjects are expected to be treated during dose escalation in each Dose Level, and up to 15 subjects may be dosed at selected Dose Levels.
    - The Cohort Expansion: During cohort expansion, approximately 18 subjects are expected to be enrolled in each of the 3 unknown or low historic response cohort expansions and 35 subjects in each of the 2 cohorts with higher historic ORR and treated at the previously determined MTD, MAD, or at an alternative dose that is not to exceed the MAD.
    - CRC, SCCHN, and HCC Cohorts: The sample size for each cohort will be guided by a 2-stage Gehan design. In order to determine whether a target ORR is likely in a tumor cohort, approximately 9 subjects will be treated at Stage 1 in each tumor type, as outlined in Table 2. For a tumor type in which no responses are observed, it will be concluded that the true ORR is unlikely to be greater than or equal to the target ORR and no more subjects will be enrolled in these tumors. For tumor cohort(s) in which at least 1 response among the first approximately 9 subjects is observed, up to an additional 9 subjects will be enrolled as guided by Table 3. With approximately 9 subjects in Stage 1, there is no more than a 10% chance of declaring that there is no therapeutic effect when actually there is an effect. A total of up to approximately 18 subjects across the 2 stages per tumor will guarantee an estimate of the true ORR with 12% precision.
    - NSCLC and MEL Cohorts: A total of approximately 35 subjects will be enrolled per tumor cohort based on achieving a higher precision with a reasonable control on the type I error. In a cohort of approximately 35 subjects, if 12, 14, or 16 responses are observed, then the lower limit of the 1-sided 90% confidence interval (CI) for the ORR is 24%, 29%, or 34%, respectively. In addition, 19 responses would need to be observed in approximately 35 subjects so that the lower limit of the 1-sided 90% CI for the ORR is 42%. These calculations are based on the Clopper-Pearson method for exact CIs. If the true ORR in a tumor type is 45%, then with approximately 35 subjects in a cohort there is 96% chance of observing at least 10 responses, and 93% chance of observing at least 11 responses, and there is 7% chance of observing 10 or fewer responses (false negative rate). If the true ORR for a tumor is only 30% rather than 45%, then there is a 35% and 14% chance, respectively, that there will be at least 12 or at least 14 responses in approximately 35 subjects (false positive rate).
  - **The SCCHN Cohort Expansion (Part 2; Completed):** See Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment" of the protocol body for a summary of preliminary safety and efficacy results. A total of approximately 35 subjects will be enrolled in the SCCHN Expansion Cohort (Part 2; completed). The null hypothesis that the true ORR is 25% will be tested against a 1-sided alternative: ORR = 40%. The null hypothesis will be rejected if 12 or more responses are observed in 35 subjects. This design gives a 1-sided type 1 error rate of 0.15 and a power of 0.81.
  - **The SCCHN Randomized Cohorts (Part 3 - closed to enrollment):** The SCCHN Randomized Cohorts (Part 3) has a primary endpoint of ORR. Overall 2-sided alpha is set at 0.10. The final analysis of ORR will take place 6 months after last patient first treatment. A total of approximately 225 subjects will be enrolled if PD-L1 is expressed in ≥1% of tumor cells, and will be randomized in a 2:1 ratio to the 2 treatment arms, nivolumab combined with lirilumab (Arm A) and nivolumab monotherapy (Arm B), stratified by PD-L1+ ≥ 50% expression (yes/no) and prior treatment with cetuximab (yes/no). The sample size considers the

precision of the estimated ORR in Arm A. With 150 participants in Arm A, if 50 responses are observed, the estimated ORR will be 33% and the 90% CI will be [26%, 41%]. (Study CA209-041, 90% CI for nivolumab arm in PD-L1+ [9%, 25%].)

- **The Signal Detection Cohort Expansion (Part 4):** Removed with Revised Protocol 12.
- **The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment):** A total of 40 subjects will be enrolled in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5). With this sample size, the average width of the 2-sided 80% Clopper-Pearson CI for the ORR will be approximately 16% to 21% (assuming that the expected ORR in subjects with platinum-refractory recurrent or metastatic SCCHN is between 13% and 33%).
- **The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6):** Removed with Revised Protocol 12.

- **Statistical Analysis:**
  - **Safety:** All recorded AEs will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed. Summary tables will be presented on safety parameters for each treatment arm and/or tumor types, if applicable.
  - **PK:** Summary statistics will be tabulated for the PK parameters of lirilumab, nivolumab, and ipilimumab by dose and study day/week. For [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), summary tables will also be presented by each randomized treatment arm. To describe the dependency on dose of anti-KIR, scatter plots of Cmax and AUC(TAU) vs dose will be provided for each day measured. Dose proportionality of lirilumab when co-administered with nivolumab will be assessed based on a power model. Dose proportionality of lirilumab when co-administered with nivolumab, and of lirilumab when co-administered with nivolumab and ipilimumab will be assessed based on a power model.
  - **Immunogenicity Analyses**: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least 1 positive ADA at any timepoint will be provided by treatment for each analyte. The number (%) of subjects with the following anti-drug responses will be reported for each analyte if applicable, by dose, and overall: Baseline ADA Positive, ADA Positive (Persistent Positive, Only the Last Sample Positive), ADA Positive with Neutralizing Positive, and ADA Negative. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between trough concentrations of lirilumab (or nivolumab or ipilimumab) and corresponding ADA assessments may be explored.
  - **Efficacy Analyses**:
    - **The SCCHN Randomized Cohorts (Part 3) Primary Endpoints Analysis**: The primary endpoint of ORR will be analyzed for the SCCHN Randomized Cohorts (Part 3). Subjects will be enrolled if PD-L1 is expressed in ≥ 1% of tumor cells. CIs will be provided separately for each treatment arm using the Clopper-Pearson method.
  - **Secondary Endpoints Analysis:** Individual BOR, DOR, OS, and PFS will be listed using RECIST v1.1 criteria. Summary tables will be presented on efficacy endpoints for each treatment arm. The OS and PFS rates at specific timepoints and corresponding CI will be estimated by KM methodology depending on data availability. ORR, DOR and PFS analyses will include subjects in the cohort expansion phase and subjects in dose escalation matching those in cohort expansion by disease type and treatment. Individual changes in the tumor burden over time will be presented graphically within a disease type. The secondary endpoint of OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drug and every 3 months for up to 3 years following the first dose of study drug via in-person or phone contact after subjects discontinue the study drug. [redacted]

- The number and percentage of subjects in each category of BOR (CR, partial response [PR], stable disease [SD], PD, or unable to determine) will be presented by treatment arm and/or tumor types, if applicable. Finally, a waterfall plot showing the biggest reduction in the sum of target lesions will be produced for response-evaluable subjects.

– **Biomarker Analyses:** The pharmacodynamic effect on TILs and expression of tumor markers including PD-L1 [redacted] will be assessed by summary statistics, and investigated graphically to explore patterns of change. In addition, the correlation of TIL changes and tumor marker expression with measures of peripheral blood markers will be explored graphically and by appropriate statistics based on data availability.

[redacted]

– **Outcomes Research Analyses -** Removed with Revised Protocol 12.

– **Interim Analysis:**

- Data emerging from the unblinded parts of this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final lock of the study database. While the study is still ongoing, additional interim analyses may also be performed for administrative purposes or publications. In that case, analyses will only consist of listings, summaries, and graphs of the available data, and no formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use response-evaluable or all-treated populations depending on the purpose of the analysis.
- The Dose Escalation and Cohort Expansion (Part 1; completed) of the study is the dose-escalation study and includes expansion cohorts in specific tumor types. In the dose expansion portion of the Dose Escalation and Cohort Expansion (Part 1; completed), in order to assess if the target response rate is likely for tumor cohorts with unknown or low historic ORR, the tumor response will be initially based on the tumor measurements from the first approximately 9 subjects in each cohort to facilitate decisions on continuing enrollment in that tumor. If no responses are observed in approximately the first approximately 9 subjects with tumor measurements, enrollment in that tumor cohort will not continue. However, accrual to these tumor types may continue, while the Stage I response assessments are performed.

TABLE OF CONTENTS

[redacted]

1 INTRODUCTION AND STUDY RATIONALE

Lirilumab (BMS-986015) is a fully human monoclonal antibody that is designed to act as a checkpoint inhibitor by blocking the interaction between killer cell immunoglobulin-like receptor (KIR)2DL-1,-2,-3 inhibitory receptors and their ligands facilitating activation of natural killer (NK) cells and, potentially some subsets of T cells, ultimately leading to anti-tumor activity.

The Dose Escalation and Cohort Expansion (Part 1) and the squamous cell carcinoma of the head and neck (SCCHN) Cohort Expansion (Part 2) have both completed enrollment and are not applicable starting with Amendment 13 and all subsequent amendments. For preliminary safety and efficacy results, see Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment" of the protocol body.

At the time of Amendment 13, preliminary data from an initial cohort of subjects in Study CA223001 suggested a signal of potential efficacy in recurrent or metastatic SCCHN subjects with disease progression on or after platinum-based therapy. Specifically, preliminary data in 29 evaluable subjects treated with the combination of lirilumab plus nivolumab showed an objective response rate (ORR) of 24% (7/29) in the all-comer population and an ORR of 41% (7/17) in the programmed cell death ligand 1 positive (PD-L1+) population.[1] Whereas, nivolumab monotherapy, in a similar population of patients with previously treated SCCHN, showed an ORR of 13.1% (32/240) in all SCCHN subjects and an ORR of 17.0% (15/88) in subjects with ≥ 1% programmed cell death ligand 1 (PD-L1) expression.[2] Preliminary data also indicated the combination of lirilumab plus nivolumab is safe, with the addition of lirilumab to nivolumab adding little additional toxicity to that typically observed with nivolumab alone. Based on these results, the protocol was revised to add additional cohorts (Parts 3-6; see description in Section 3.1).

Subsequent efficacy analysis of additional recurrent or metastatic SCCHN subjects with disease progression on or after platinum-based therapy treated with the combination of lirilumab and nivolumab did not demonstrate a differential efficacy signal as compared to nivolumab monotherapy treatment in a similar population of SCCHN subjects. Based on the review of these data, Revised Protocol 12 will implement the following:

- Enrollment permanently closed in Part 3, a single-blinded, placebo-controlled, randomized cohort expansion of lirilumab in combination with nivolumab vs nivolumab monotherapy in subjects with platinum-refractory recurrent or metastatic SCCHN who are PD-L1+.
- Removal of Part 4, a signal detection cohort expansion of nivolumab and lirilumab at a flat dose in subjects with sqNSCLC, ESCC, BC, and other squamous histologies and in subjects with SCCHN who have received prior PD-1/PD-L1 directed therapy. No subjects were enrolled.
- Enrollment permanently closed in Part 5, a safety and signal detection with a triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.

- Removal of Part 6, a safety and signal detection with a triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with previously untreated metastatic melanoma. No subjects were enrolled.
- Removal of overall survival visits for all subjects, select sample collection and study visits, additional subjects entering treatment beyond progression and retreatment at the time of disease progression.
- All subjects will be permitted a maximum of up to 2 years of treatment as specified in the individual study parts.

Background of NK Cells and KIR in Inflamed Tumors

An analysis of the immune infiltration in a large cohort of head and neck tumors, integrating genetic data with RNA-seq–based deconvolution of immune cell populations and effector/regulatory molecules was done[3] and found that SCCHN is one of the most highly immune-infiltrated cancer types, and in fact, the most highly NK cell– and Treg-infiltrated cancer type. These tumors are poised to benefit from immunotherapy that includes Treg and NK checkpoint-targeted approaches that may have unique applicability in head and neck cancer.

Analysis of the levels of NK-cell infiltration in SCCHN showed that the $CD56^{bright}$ subpopulation is predominantly found in lymph nodes and peripheral blood and believed to be the likely precursor to $CD56^{dim}$ cells, which are far more cytotoxic and play a critical role in antitumor immunity.[4] Strikingly, SCCHN tumors had the numerically highest levels of infiltration with $CD56^{dim}$ NK cells, compared with other highly immune-infiltrated cancer types. $CD56^{dim}$ NK cells are inhibited by KIRs, which are absent on $CD56^{bright}$ NK cells. $CD56^{dim}$ NK-cell infiltration correlated strongly with overexpression of the KIR inhibitory receptor genes KIR2DL1 and KIR2DL3. These data suggest that SCCHN tumors are prime candidates for trials of anti-KIR antibodies.

It has been shown that there are high levels of immunoregulatory influence in SCCHNs, which harbor the highest levels of Treg infiltration and the highest Treg/CD8+ T-cell ratio across all cancers, suggesting that these tumors are poised to respond to immunotherapeutic modalities that relieve inhibitory pathways. Treg function and proliferation rely on a number of targetable pathways. CTLA-4 is highly constitutively expressed on Tregs. Its activation is necessary for Treg function and proliferation. CTLA-4 inhibitors have clearly been shown to promote antitumor immunity in MEL. Blockade of the CTLA-4 receptor on activated Tregs may therefore dampen the immunosuppressive function of these cells in head and neck tumors. A growing body of evidence suggests that CTLA-4 blockade does, in some contexts, repress Treg function and accumulation in the tumor microenvironment.

Analysis of immune-cell infiltration and levels of immune activation in other highly inflamed cancer types, namely MEL, prostate, kidney clear cell, cervical/endometrial, sqNSCLC, adeno NSCLC, breast, bladder, and thyroid[5] showed that the levels of $CD56^{bright}$ NK-cell infiltration was predominantly found in lymph nodes and peripheral blood and is believed to be the likely precursor to $CD56^{dim}$ cells, which are far more cytotoxic and play a critical role in antitumor immunity.

Taken together, these data reveal that inflamed tumors such as SCCHN and MEL are infiltrated with Tregs and KIR-overexpressing $CD56^{dim}$ NK cells, to a higher degree than other cancer types. These findings suggest these tumors possess an immune landscape that is poised to respond to immunotherapeutic approaches that block inhibitory signals to T cells and NK cells.

Background of Anti-KIR Antibody Lirilumab (BMS-986015)

Lirilumab binds specifically and with high affinity to subsets of KIRs (ie, KIR2DL1, -2, and -3 and KIR2DS1 and -2), thus preventing the interaction between KIR and HLA-C. Therefore NK-cell activation is determined by the balance of activating (positive) and inhibitory (negative) receptor stimulation. Tumor cells are able to evade innate immunity through the interaction of KIR with HLA-C. By blocking this interaction, lirilumab facilitates the activation of NK cells and subsequent killing of the tumor cell. Blockade of inhibitory KIR by lirilumab is, thus, a promising mechanism to promote killing of tumor cells by the innate immune system.

Lirilumab is being studied as a potential immunotherapy alone and in combination with other agents in subjects with various hematologic malignancies and solid tumors. A total of 550 subjects have been treated with lirilumab across 5 studies as of 13-Jul-2017 assessing safety, pharmacokinetics (PK), biomarker modulation, and clinical activity. The first (Study CA223003, IPH2102-101) is a monotherapy, dose-escalation, Phase 1 trial to determine the safety and maximum tolerated dose (MTD) of BMS-986015 (IPH2102) and is completed. The second (Study CA223004, IPH2102-201) is a double-blind, placebo-controlled, Phase 2 trial of lirilumab evaluating the relapse-free survival in subjects with AML in complete remission but ineligible for allogeneic transplant and is completed. One-third of subjects in this study received placebo. The third (Study CA223001), fourth (Study CA223002), and fifth (Study CA223028) are Phase 1 (or Phase 1/2) trials of lirilumab in combination with the anti-PD-1 antibody nivolumab (Study CA223001), the anti-CTLA-4 antibody ipilimumab (Study CA223002), and the Signaling Lymphocytic Activation Molecule Family Member 7 antibody elotuzumab (Study CA223028) were initiated to determine if coordinate modulation of the innate and adaptive immune systems results in greater clinical benefit. Study CA223002 was terminated early, Study CA223028 is completed and study CA223001 is ongoing.

The majority of adverse events (AEs) in these 5 trials were mild or moderate (Grade 1 or 2), self-limiting, and manageable. The most common related AEs in the monotherapy trials were asthenia, bronchitis, diarrhea, headache, fatigue, pruritus, and thrombocytopenia. The most common related AEs in the combination trials were fatigue, infusion-related reaction, pruritus, rash, nausea, chills, diarrhea, rash maculo-papular, and pyrexia. The data to date support a positive safety profile of lirilumab.

Background of Nivolumab: Mechanism of Action

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.[6] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the cluster of differentiation (CD) 28 family of T-cell co-stimulatory receptors, which also include CD28, CTLA-4, inducible T-cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[7] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-gamma (IFN-γ), and B-cell lymphoma-extra large. 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.[8] 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.

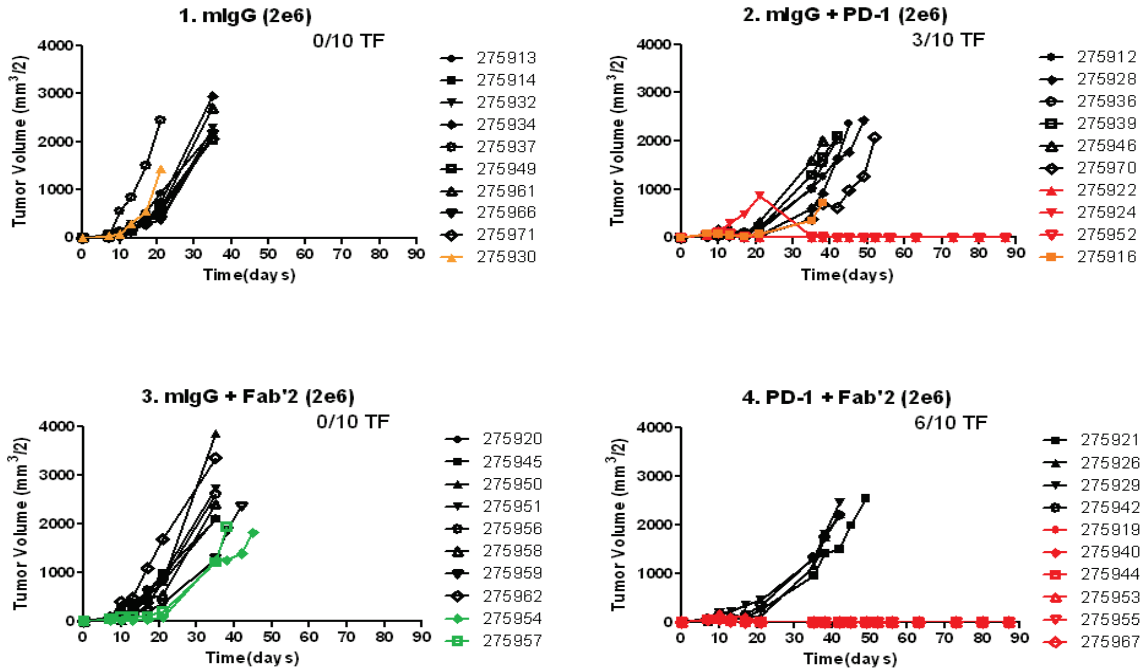
In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (concentration required for 50% efficacy [EC50]: 0.39 to 2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and programmed cell death ligand 2 (PD-L2) (concentration required for 50% inhibition [IC50] ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction. Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cell (PBMC), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner vs isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[9]

Pre-clinical Results Utilizing Murine Anti-PD-1 and Anti-KIR Antibodies

Pre-clinical studies tested the hypothesis that the combination of anti-KIR and anti-PD-1 would potentiate anti-tumor efficacy in a murine solid tumor model. Both nivolumab (human anti-PD-1 antibody) and lirilumab recognize only human sequences. Thus, a murine-specific PD-1 antibody and anti-Ly49 antibody, an F(ab)2 that recognizes Ly49C/I, which is the KIR homologue in mice, were used to test this hypothesis. Mice were injected with the syngeneic MC38 murine colon carcinoma cell line and, following the formation of palpable tumors, they were randomized to 1 of 4 cohorts to receive control IgG, anti-Ly49 antibody, anti-PD-1 antibody, or both antibodies. Mice treated with a control IgG antibody had rapid growth of tumors (upper left panel of Figure 1-1). Mice treated with anti-Ly49 antibody (lower left panel of Figure 1-1) did not differ significantly from control animals. Those treated with a murine anti-PD-1 antibody (upper right panel of Figure 1-1) showed latency in tumor progression, and 30% of mice continued to be free of tumor.

Those treated with both antibodies (lower right panel of Figure 1-1) also had latency in tumor progression and 60% of mice continued to be free of tumor.

Figure 1-1: Anti-PD-1 and Anti-Ly49C/I (5E6 F(ab')$_2$) in MC38 Murine Colon Carcinoma Model



Female C57BL/6 mice were injected subcutaneously with 2e6 (2×10^6) MC38 tumor cells. After randomization of animals, treatments began 7 days later. Mice were treated intraperitoneally on Days 7, 10, and 14 with control mAb, anti-PD-1, and/or anti-Ly49C/I (5E6 F[ab']2). Animals receiving anti-Ly49C/I (5E6 F[ab']2) were dosed additionally on Days 17, 21, and 24. Tumor measurements were taken twice weekly. Shown here are data from individual animals.

Fab = fragment antigen-binding; mAb = monoclonal antibody; mIgG = murine immunoglobulin; TF = tumor free.

These results provide pre-clinical evidence of the additive benefit of anti-KIR antibody to potentiate the efficacy of an anti-PD-1 antibody in a murine solid tumor model.

Clinical Experience with Lirilumab and Nivolumab Combination Treatment

As of 13-Jul-2017, a total of 322 subjects have been treated with the combination of lirilumab and nivolumab in the current study (Study CA223001). AEs evaluated as related to the combination of lirilumab and nivolumab were reported in 217 (67.4%) exposed subjects. The most common related AEs reported in > 10% subjects were fatigue, 62 (19.3%) subjects; and pruritus, 43 (13.4%) subjects; infusion-related reaction, 43 (13.4%) subjects each. Thirty-six (11.2%) subjects reported a related Grade 3 or 4 event. Lipase increased were reported in 5 (1.6%) subjects and amylase increased, aspartate aminotransferase increased, and infusion related reaction were reported in 4 (1.2%) subjects each. There were no related Grade 5 events reported. Fourteen (4.3%) subjects reported related events leading to study discontinuation. With continued enrollment and follow-up of treated subjects, no new safety signals have been identified.

At the time of Amendment 13, preliminary data from an initial cohort of subjects in Study CA223001 suggested a signal of potential efficacy in recurrent or metastatic SCCHN subjects with disease progression on or after platinum-based therapy. Specifically, preliminary data in 29 evaluable subjects treated with the combination of lirilumab plus nivolumab showed an ORR of 24% (7/29) in the all-comer population and an ORR of 41% (7/17) in the PD-L1+ population.[1] No responses (0/12) were observed in the PD-L1 negative population. To put into context nivolumab monotherapy in a similar population of patients with previously treated SCCHN (recently approved by the US FDA for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy) showed an ORR of 13.1% (32/240) in all SCCHN subjects and an ORR of 17.0% (15/88) in subjects with ≥ 1% PD-L1 expression.[2] Also of note, in 5 out of the 7 lirilumab plus nivolumab responders, the reduction in tumor burden was substantial, exceeding greater than 80%.[1] Responses appeared durable, with the median DOR not reached.

Subsequent efficacy analysis of additional SCCHN subjects treated with the combination of lirilumab and nivolumab did not demonstrate a differential efficacy signal as compared to nivolumab monotherapy treatment in a similar population of SCCHN subjects. Efficacy parameters analyzed included ORR regardless of tumor PD-L1 status, ORR in PD-L1+ population, median PFS and median duration of responses.

Background: Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 Ig superfamily that competes with CD28 for B7. CTLA-4-mediated signals are inhibitory and turn off T-cell-dependent immune responses.[10] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and non-human primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen-presenting cells, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

Background: Anti-KIR Antibody in Combination with Anti-CTLA-4 Antibodies

Pre-clinical studies tested the hypothesis that the combination of anti-KIR and anti-CTLA-4 antibodies would potentiate anti-tumor efficacy in a murine AML model. Both lirilumab and ipilimumab (human anti-CTLA-4 antibody) recognize only human receptors. Thus, a murine-specific anti-CTLA-4 antibody and anti-Ly49C/I (5E6 $F(ab')_2$) were used to test this hypothesis. Mice were infused with the murine leukemia C1498 cell line and randomized to 1 of 4 cohorts to receive control immunoglobulin (Ig)G antibody, anti-CTLA-4 monoclonal antibody, anti-Ly49C/I (5E6 $F(ab')_2$), or both anti-CTLA-4 monoclonal antibody and anti-Ly49C/I (5E6 $F(ab')_2$). Mice treated with control antibody had a median survival of 25.5 days. Mice treated with anti-CTLA-4 did not differ significantly from control animals (median 26.0 days, $P = 0.37$). Those treated with anti-Ly49C/I (5E6 $F(ab')_2$) had prolonged survival (median 27.0 days, $P = 0.016$). Those treated with both antibodies had further prolonged survival (median 29.5 days, $P < 0.001$). It is possible that the combination of the 2 antibodies has a more

potent effect than either alone. However, the difference in survival between anti-Ly49C/I (5E6 $F(ab')_2$) alone and both antibodies (27.0 days vs 29.5 days, respectively) did not reach statistical significance (P = 0.17). It is possible that a prolonged dosing schedule will yield more robust results, and that this combination of antibodies will be efficacious in other cancer models. These results provide pre-clinical evidence of the benefit of an anti-KIR antibody to potentiate the efficacy of an anti-CTLA-4 antibody in a murine AML model.[11]

Clinical Experience with Lirilumab and Ipilimumab Combination Treatment

CA223002 was primarily designed to evaluate the safety, tolerability, and MTD of lirilumab, an anti-KIR monoclonal antibody, when administered in combination with an approved dose of ipilimumab in subjects with select advanced tumors. The study was to be conducted in 2 parts, with a dose-escalation phase followed by a dose-expansion phase. During the dose-escalation phase, subjects received BMS-986015 (0.1, 0.3, 1, or 3 mg/kg) and ipilimumab (3 mg/kg) as Induction therapy (every 3 weeks [Q3W] for 4 doses) and then Maintenance therapy (every 12 weeks [Q12W] for 4 doses) for a total of up to 1.4 years of therapy.

During the conduct of the dose-escalation phase, the study was terminated for business reasons that were unrelated to any AEs associated with the use of lirilumab in this or any other ongoing clinical study. No further subjects were enrolled after termination of the study, but subjects already receiving treatment in the study were permitted to complete treatment and clinical follow-up as per protocol. This report presents results of the evaluation of safety and tolerability (the primary objective), as well as preliminary anti-tumor activity (a secondary objective).

AEs were reported for all 22 (100%) of the subjects treated in this study. The most frequently reported AEs (> 25% of all treated subjects) were fatigue (45.5%), nausea (40.9%), malignant neoplasm progression (36.4%), back pain (27.3%), diarrhea (27.3%), pneumonia (27.3%), pyrexia (27.3%), and vomiting (27.3%). There were no apparent dose-related trends in the occurrence of any AEs. Of the 16 subjects for whom best overall response (BOR) was evaluable, 3 subjects had a partial response, 5 subjects had stable disease (SD), and 8 subjects had progressive disease (PD).

In conclusion, lirilumab was generally well tolerated when administered at doses of 0.1 to 1 mg/kg in combination with an approved dose of ipilimumab (3 mg/kg) in subjects with advanced or metastatic solid tumors.[12]

To date, the cumulative safety data support a manageable safety profile for lirilumab that is consistent with the profile of other immunotherapies.

1.1 Study Rationale

1.1.1 Rationale for the Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

Anti-PD-1 monoclonal antibody (nivolumab) is an activator of T-cell responsiveness (ie, adaptive immunity) and has demonstrated activity in clinical studies for subjects with refractory and metastatic solid tumors, including NSCLC, renal cell carcinoma (RCC), MEL, and possibly other tumor types. The safety profile of this agent is tolerable. KIR plays an important role in regulating

NK-cell activation, and diminution of KIR function is likely to potentiate the innate immune response. Lirilumab is a fully human anti-KIR monoclonal antibody that has shown minimal side effects in a Phase 1 study. The aim of this study is to coordinately potentiate adaptive and innate immunity to enhance the anti-tumor activity of anti-PD-1 antibody by the addition of an anti-KIR antibody in subjects with advanced solid tumors who currently have poor prognosis and limited treatment options. The Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) of this study will address the feasibility and safety and preliminary efficacy of the combined administration of lirilumab and nivolumab. **The Dose Escalation and Cohort Expansion (Part 1) has completed enrollment, and the SCCHN Cohort Expansion (Part 2) of this study will close to enrollment as the SCCHN Randomized Cohorts (Part 3) opens.**

1.1.2 Rationale for the SCCHN Randomized Cohorts (Part 3)

With Revised Protocol 12, enrollment in Part 3 is closed.

This cohort will formally assess the efficacy and safety of lirilumab and nivolumab combination therapy and nivolumab monotherapy in subjects with advanced or metastatic SCCHN in a randomized expansion.

Head and neck cancers are among the most common cancers worldwide, accounting for more than 550,000 cases and around 300,000 deaths each year[13] and these trends are increasing. In the US, ~48,330 new cases of oral cavity and pharynx cancer were reported; and ~9,570 people were predicted to die of this disease in 2016.[14] About ~90% of all head and neck cancers are squamous cell. Most SCCHNs arise from the epithelial lining of the oral cavity, oropharynx, larynx, and hypopharynx. The most important risk factors identified in SCCHNs include tobacco and alcohol use, and in a subgroup of SCCHNs (particularly oropharynx tumors), human papilloma virus (HPV) is a strong independent prognostic factor.[15] Metastatic and recurrent SCCHN that is no longer amenable to local surgical/radiation therapy causes substantial morbidity and high mortality, with a median progression-free survival (PFS) of < 6 months and median overall survival (OS) of less than 12 months.

Ongoing trials with immune checkpoint inhibitors in SCCHN have shown promising preliminary results. A 17.7% ORR has been observed in the ongoing KEYNOTE 012 (NCT01848834) clinical trial of 192 subjects with the recurrent/metastatic SCCHN treated with the anti-PD-1 agent pembrolizumab.[16] Recently, nivolumab was approved by the US FDA for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy. The approval was based on results from the Phase 3, CheckMate-141 trial in which nivolumab demonstrated statistically significant and clinically meaningful superior OS vs the comparator arm (the investigator's choice of methotrexate, docetaxel, or cetuximab), with a 30% reduction in the risk of death (HR = 0.70 [95% CI: 0.53 to 0.92; P = 0.0101]).[17] The median OS was 7.5 months (95% CI: 5.5 to 9.1) for nivolumab compared to 5.1 months (95% CI: 4.0 to 6.0) for the investigator's choice.[2,17] Despite this recent data, patients with recurrent or metastatic SCCHN are a population with unmet medical need and combination immunotherapy agents remains an area of active clinical evaluation.

At the time of Amendment 13, preliminary data from an initial cohort of subjects in Study CA223001 suggested a signal of potential efficacy in recurrent or metastatic SCCHN subjects with disease progression on or after platinum-based therapy. Specifically, preliminary data in 29 evaluable subjects treated with the combination of lirilumab plus nivolumab showed an ORR of 24% (7/29) in the all-comer population and an ORR of 41% (7/17) in the PD-L1+ population.[1] No responses (0/12) were observed in the PD-L1 negative population. To put into context nivolumab monotherapy in a similar population of patients with previously treated SCCHN (recently approved by the US FDA for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy) showed an ORR of 13.1% (32/240) in all SCCHN subjects and an ORR of 17.0% (15/88) in subjects with ≥ 1% PD-L1 expression.[2] Also of note, in 5 out of the 7 lirilumab plus nivolumab responders, the reduction in tumor burden was substantial, exceeding greater than 80%. Responses appeared durable, with the median DOR not reached. These results indicate lirilumab plus nivolumab may have clinically meaningful greater clinical activity than nivolumab alone, particularly in inflamed (PD-L1+) tumors and with little added toxicity.

Furthermore, lirilumab in combination with nivolumab has an acceptable safety profile in subjects with advanced refractory solid tumors. The safety profile associated with lirilumab in combination with nivolumab was generally consistent with that observed with nivolumab monotherapy. Overall treatment-related adverse events (TRAEs) was reported in 114 (72%) subjects, and Grade 3 to 4 TRAEs were reported in 24 (15%) subjects. Discontinuations due to TRAEs occurred in 12 (8%) subjects.[12]

Evaluating lirilumab in combination with nivolumab in subjects with tumor PD-L1+, platinum-refractory SCCHN will potentially provide further treatment options for patients with a high unmet medical need.

1.1.3 Rationale for the Signal Detection Cohort Expansion (Part 4)

With Revised Protocol 12, Part 4 is removed.

1.1.4 Rationale for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) and the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)

With Revised Protocol 12, Part 5 is closed to enrollment and Part 6 is removed.

The combination of nivolumab and ipilimumab has a well-established regimen and safety profile.

Nivolumab and ipilimumab clinical activity is well established in multiple tumor types including MEL and NSCLC and are described in Section 1.1.4.1. This combination continues to be evaluated in a range of tumor types including RCC, BC, SCCHN.

The safety profile of nivolumab and ipilimumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination. Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related AEs observed in clinical trials are those associated with activation of the immune system. The most common

types of immune-mediated AEs include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash. In the combination regimen, the frequency and intensity of these events may vary and will depend on the specific dose and schedule used. Study CA209012 evaluating multiple dose regimens of nivolumab in combination with ipilimumab showed numerically higher response rates in cohorts evaluating the approved dose of nivolumab 3 mg/kg and the safety of combination improved with the lower dose of ipilimumab, 1 mg/kg was given less frequently (Q6W or Q12W) (See Section 1.1.4.1). Therefore the combination dosing schedule selected for this study (nivolumab 3 mg/kg every 2 weeks [Q2W] plus ipilimumab 1 mg/kg every 6 weeks [Q6W]) utilizes the approved nivolumab dose and provides the highest dose and frequency of ipilimumab feasible in a combination regimen where the immune-mediated AEs were mostly low grade and manageable with prompt use of corticosteroids (see Section 1.1.4.1).

Safety Profile of Lirilumab in Combination with Nivolumab and with Ipilimumab

Safety and preliminary efficacy of lirilumab in combination with nivolumab and ipilimumab have been described in Section 1 "Clinical Experience with Lirilumab and Ipilimumab Combination Treatment" and "Clinical Experience with Lirilumab and Nivolumab Combination Treatment." To date, the cumulative safety data support a manageable safety profile for lirilumab in combination with nivolumab and ipilimumab that is consistent with the profile of other immunotherapies. Therefore, it is not expected that the addition of lirilumab will add additional toxicities to the known safety profile of nivolumab and ipilimumab.

As an additional safety measure, initially approximately 10 subjects will be enrolled and followed for at least 4 weeks of safety assessment from the start of study drug administration before additional subjects are enrolled in the study to ensure there is no major safety signal with the combination. Any findings will be discussed between the BMS Medical Monitor and investigators and an agreement will be reached as to whether a lower dose or an alternate dose schedule should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

Biological Rationale for the Combination of Lirilumab with Nivolumab and Ipilimumab

As described in Section 1 "Background of NK cells and KIR in Inflamed Tumors," immune infiltrate analysis in the inflamed tumors such as SCCHN and MEL, show infiltration with Tregs and KIR-overexpressing $CD56^{dim}$ NK cells, to a higher degree than other cancer types. These findings suggest that head and neck tumors possess an immune landscape that is poised to respond to immunotherapeutic approaches that block inhibitory signals to T cells and NK cells, such as immune checkpoint inhibitors (nivolumab and ipilimumab), including antibodies blocking KIR signaling (lirilumab).

Therefore, the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) will evaluate if the addition of ipilimumab, a Treg-targeted agent will enhance the efficacy seen with the combination of lirilumab and nivolumab in SCCHN.

1.1.4.1 Experience with Nivolumab and Ipilimumab Combination Treatment

Pre-clinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve anti-tumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased anti-tumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine MEL vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral Tregs, as compared to either agent alone.[18]

Clinical activity of nivolumab and ipilimumab combination was evaluated in subjects with stage IV non-squamous cell lung cancer (NSCLC) as first line treatment in CA209012 study.[19] This was a large phase 1, multi-arm safety study of nivolumab monotherapy and nivolumab in combination with various systemic anticancer therapies like ipilimumab, platinum based chemotherapies and EGFR tyrosine kinase inhibitor.

The regimens for these cohorts were:

- Arm N (n=31): nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W for 4 cycles, followed by nivolumab 3 mg/kg Q2W
- Arm O (n=40): nivolumab 1 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
- Arm P (n=38): nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W
- Arm Q (n=39): nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

The most frequently reported drug-related AEs in the newer nivolumab plus ipilimumab cohorts were fatigue (29.0%), diarrhea (25.0%), pruritus (23.7%), and fatigue (23.1%) in arms N, O, P, and Q, respectively. Drug-related SAEs reported in more than 2 subjects/cohort treated in the newer nivolumab plus ipilimumab cohorts were adrenal insufficiency, hypophysitis, pneumonitis, autoimmune hepatitis, diarrhea, colitis, and acute kidney injury. Drug-related Grade 3 to 4 AEs were reported in 9 (29.0%) subjects in Arm N, 16 (40.0%) subjects in Arm O, 14 (36.8%) subjects in Arm P, and 13 (33.3%) subjects in Arm Q. Drug-related AEs leading to discontinuation reported in more than 1 subject treated in the new nivolumab plus ipilimumab arms included alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, colitis, myalgia, pneumonitis, rash, autoimmune hepatitis, infusion-related reaction, facial nerve disorder, esophagitis, and transaminases increased. Most deaths in CA209012 were due to disease progression. The only deaths reported due to study drug toxicity were in the nivolumab + ipilimumab original treatment groups (respiratory failure following Grade 3 colitis, pulmonary hemorrhage, and toxic epidermal necrolysis in a subject with a history of ulcerative colitis).

[redacted]

Clinical activity was observed in all combination cohorts but numerically higher response rates were observed in cohorts evaluating the approved dose of nivolumab 3 mg/kg, with confirmed response rates ≥ 39% (cohorts P and Q).[19] With comparable efficacy and safety data from cohorts P and Q, the nivolumab plus ipilimumab every 6 week (Q6W) dosing schedule (cohort Q) was the selected regimen moving forward.[20] Aside from utilizing the approved nivolumab dose in NSCLC, it would also provide the highest dose and frequency of ipilimumab feasible in a combination regimen.

To date, there are no data on the combination of nivolumab and ipilimumab in SCCHN. CA209714 and CA209651 are studies evaluating this combination of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W in SCCHN and are ongoing.

Given the similarity in patient profiles of NSCLC and SCCHN, and that nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W have shown adequate safety and increased efficacy compared to single agent nivolumab in CA209012, our hypothesis is that we will see a similar effect in SCCHN. Given that the safety profile of lirilumab in combination with nivolumab (see Section 1: "Clinical Experience with Lirilumab and Nivolumab Combination Treatment") and ipilimumab is not different as compared to nivolumab or ipilimumab monotherapy, respectively, with the exception

of infusion reactions, which were only Grade 1 and 2, easily manageable, and did not lead to discontinuations, it is not anticipated that the addition of lirilumab at 3 mg/kg every 4 weeks (Q4W) to the combination of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W will increase the toxicity of the regimen.

Similarly, clinical activity of lirilumab when added to nivolumab plus ipilimumab has the potential to enhance the activity seen with nivolumab and ipilimumab in MEL. Nivolumab and ipilimumab in combination in subjects with previously untreated, unresectable or metastatic MEL evaluated in CA209067, a randomized Phase 3 study, demonstrated improved PFS; the median PFS was 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab-plus-ipilimumab group, 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group.

1.2 Research Hypothesis

1.2.1 The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

It is anticipated that the combination of anti-KIR antibody (lirilumab) and anti-PD-1 antibody (nivolumab) will demonstrate adequate safety and tolerability at pharmacologically relevant doses and suggest preliminary signs of clinical activity so as to permit further clinical testing.

1.2.2 The SCCHN Randomized Cohorts (Part 3 - Closed to enrollment)

It is anticipated that treatment with nivolumab alone or in combination with lirilumab will lead to clinically meaningful tumor reductions, as measured by ORR, in subjects with platinum-refractory recurrent or metastatic SCCHN who are PD-L1+.

1.2.3 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

1.2.4 The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - Closed to enrollment)

It is anticipated that the triplet regimen of anti-KIR antibody (lirilumab), anti-PD-1 antibody (nivolumab), and anti-CTLA-4 antibody (ipilimumab) to treat subjects with platinum-refractory recurrent or metastatic SCCHN will demonstrate adequate safety and tolerability at pharmacologically relevant doses for further clinical testing.

1.2.5 The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

1.3 Objectives

1.3.1 Primary Objective

1.3.1.1 Primary Objective for the Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

The Dose Escalation and Cohort Expansion (Part 1): To assess the safety and tolerability of lirilumab given in combination with nivolumab and to identify DLTs and the MTD of the combination in subjects with advanced (metastatic and/or unresectable) solid tumors.

The SCCHN Cohort Expansion (Part 2): To assess the safety and preliminary anti-tumor activity of the combination of lirilumab and nivolumab in subjects with advanced solid tumors.

1.3.1.2 Primary Objective for the SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

To estimate the ORR of lirilumab given in combination with nivolumab in subjects with recurrent or metastatic SCCHN that has relapsed or progressed within 6 months of the last dose of a platinum-containing therapy and whose tumors express PD-L1.

1.3.1.3 Primary Objective for the Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

1.3.1.4 Primary Objective for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)

To assess the safety and preliminary anti-tumor activity of the combination of lirilumab with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.

1.3.1.5 Primary Objective for the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

1.3.2 Secondary Objectives

1.3.2.1 Secondary Objectives for the Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

The secondary objectives are as follows:

- To characterize the PK of lirilumab and nivolumab when co-administered.
- To monitor immunogenicity of lirilumab and nivolumab when administered as combination therapy.
- To assess the pharmacodynamic effect in tumor tissue on TIL subsets from MEL and SCCHN subjects treated with lirilumab given in combination with nivolumab.

1.3.2.2 Secondary Objectives for the SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

The secondary objectives are as follows:

- To estimate disease control rate (DCR), DOR, and time to response of lirilumab given in combination with nivolumab.
- To assess depth of response of lirilumab given in combination with nivolumab and of nivolumab monotherapy.
- To assess the OS of lirilumab given in combination with nivolumab and nivolumab monotherapy.
- To assess the PFS of lirilumab given in combination with nivolumab and nivolumab monotherapy.
- To estimate the ORR by investigator assessment of lirilumab given in combination with nivolumab and nivolumab monotherapy.
- To assess the safety of lirilumab given in combination with nivolumab in subjects with SCCHN.

1.3.2.3 Secondary Objectives for the Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

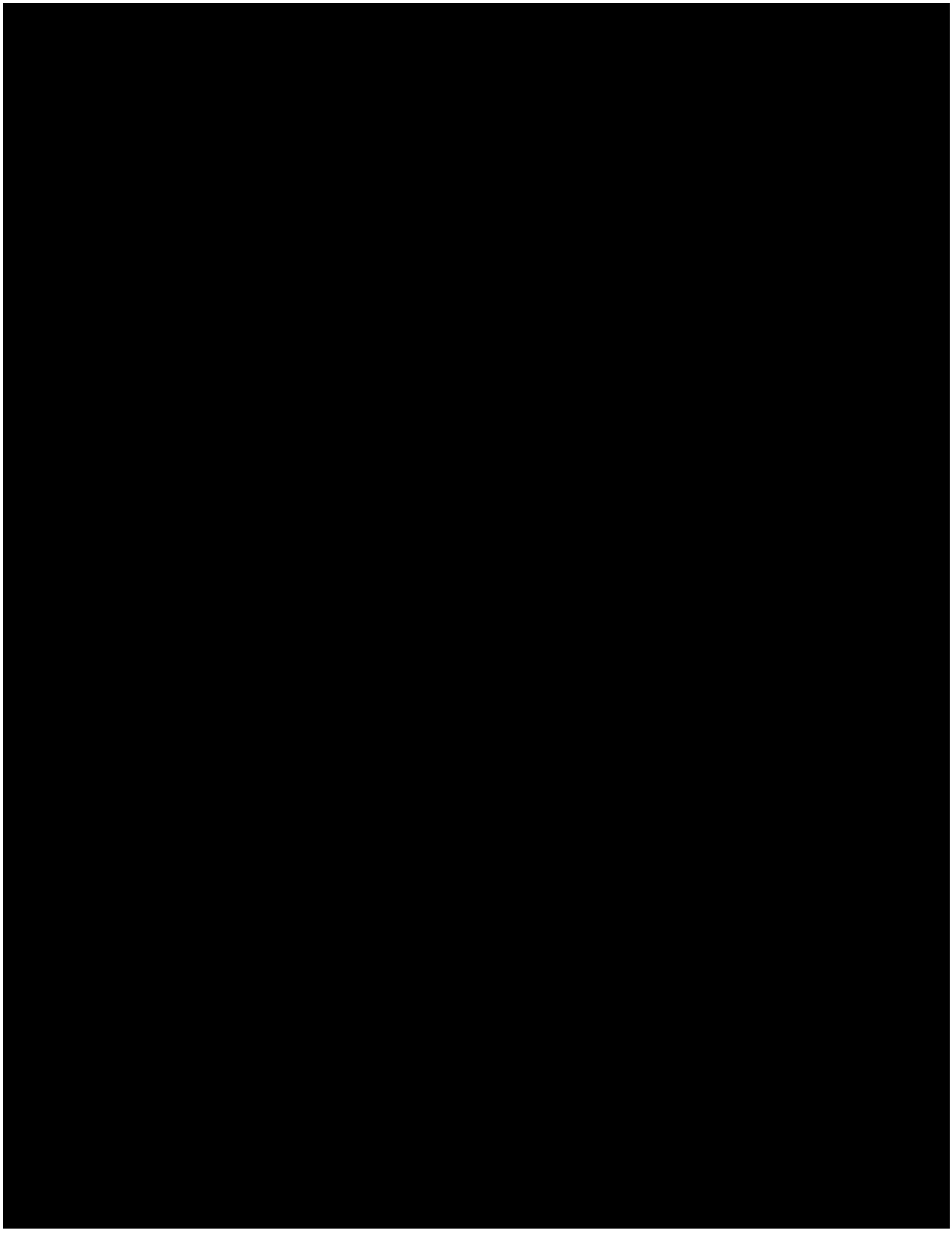
1.3.2.4 Secondary Objectives for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)

The secondary objective is as follows:

- To estimate DOR of lirilumab given in combination with nivolumab and ipilimumab.
- To assess depth of response of lirilumab given in combination with nivolumab and ipilimumab.
- To characterize the PK and immunogenicity of lirilumab in combination with nivolumab and ipilimumab.
- To investigate the immunomodulatory properties of lirilumab in combination with nivolumab and ipilimumab, and to evaluate potential baseline and on-treatment biomarkers in peripheral blood and tumor for association with efficacy in subjects with platinum-refractory recurrent or metastatic SCCHN.
- To explore biomarkers of lirilumab in combination with nivolumab and ipilimumab as therapy in all subjects with platinum-refractory recurrent or metastatic SCCHN.

1.3.2.5 Secondary Objectives for the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.



1.4 Product Development Background

Additional information for lirilumab (anti-KIR antibody), nivolumab (anti-PD-1 antibody), and ipilimumab (anti-CTLA-4 antibody) follows and is also available in the respective Investigator Brochures (IBs).[19,21,22]

1.4.1 Lirilumab: Pharmacology

Lirilumab is a fully human IgG4 monoclonal antibody that binds specifically and with high affinity to a subset of KIRs, namely KIR2DL-1, -2 and -3 and KIR2DS-1 and -2, thus preventing interaction between KIR and HLA-C. Surface plasmon resonance analysis demonstrated that the mean monovalent affinity of lirilumab for recombinant soluble KIR2DL-1 was 2.04×10^{-8} M (standard deviation 0.31×10^{-8}) and that for KIR2DL-3 was 3.01×10^{-10} M (standard deviation 0.41×10^{-10}).

1.4.2 Lirilumab: Toxicity

Neither lirilumab nor IPH-2101 binds to NK cells from non-human primate or other species traditionally used for safety testing. Safety testing was performed in mice because Ly49C/I, the murine inhibitory receptor, is functionally homologous to human KIR. There were no adverse

findings in mice treated with lirilumab at 10 mg/kg once weekly for 4 weeks or with the surrogate anti-Ly49 antibody 5E6 F(ab')$_2$ 10 mg/kg twice weekly for 13 weeks.

1.4.3 Lirilumab: Pre-clinical Metabolism and Pharmacokinetics

Please see the most recent IB for lirilumab for current data.[21]

1.4.4 Lirilumab: Clinical Pharmacology and Safety

As of the data cut-off for the current lirilumab IB (13-Jul-2017)[21], 550 subjects have been treated with lirilumab or placebo in 2 completed, 2 ongoing, and 1 terminated trials: 1 monotherapy Phase 1 trial, 1 monotherapy placebo-controlled Phase 2 trial, 1 combination therapy Phase 1/2 trial, and 2 combination therapy Phase 1 trials. Of those subjects, 37 subjects received lirilumab monotherapy (Study CA223003, Study IPH2102-101), 152 subjects received either lirilumab monotherapy or placebo in a 2:1 ratio (Study CA223004, Study IPH2102-201), 322 subjects received lirilumab in combination with nivolumab (Study CA223001), 22 subjects received lirilumab in combination with ipilimumab (Study CA223002), and 17 subjects received elotuzumab in combination with lirilumab (Study CA223028). In total, approximately 499 subjects received lirilumab. The majority of AEs in these 5 trials were mild or moderate (Grade 1 or 2), self-limiting, and manageable. The most common related AEs in the monotherapy trials were asthenia, bronchitis, diarrhea, headache, fatigue, pruritus, and thrombocytopenia. The most common related AEs in the combination trials were fatigue, infusion-related reaction, pruritus, rash, nausea, chills, diarrhea, rash maculo-papular, and pyrexia. The data to date support a positive safety profile of lirilumab.

1.4.4.1 Pharmacokinetics of Lirilumab

Final PK data from 1 Phase 1 and preliminary PK data from 2 Phase 1 studies that investigated escalating doses of lirilumab monotherapy (Study CA223003, Study IPH2102-101) or combination therapy with nivolumab (Study CA223001) or ipilimumab (Study CA223002) are presented below. Validated ligand binding assay methods were used to detect lirilumab, nivolumab, and ipilimumab in human serum.

A PK model suggests that the PK profile of lirilumab is likely to be comparable to IPH-2101. In previous IPH-2101 Phase 1 clinical studies in subjects with AML and multiple myeloma, a 2-compartment model with first order elimination was found to adequately describe the data with dose-dependent clearance (CL), such that CL decreased with increasing doses. The terminal half-life (T-HALF) at the highest dose (3 mg/kg) was determined to be within 15 to 21 days, which is consistent with reported values in the literature.

In Study CA223001, PK of lirilumab at a Dose Level of 0.1 to 3 mg/kg in combination with nivolumab 3 mg/kg was characterized after the first and fourth doses of lirilumab, based on the availability of the preliminary data. The accumulation ratio based on the area under the plasma concentration-time curve (AUC) following the fourth dose compared to the first dose ranged from 1.4 to 1.5, resulting in a mean effective T-HALF of BMS-986015 of 16 to 17 days. For the nivolumab 3-mg/kg Dose Level, across different Dose Levels of lirilumab, the geometric mean of maximum observed concentration (Cmax) and trough observed concentration (Cmin) after the first

dose were 59.8 µg/mL and 17.9 µg/mL, respectively, and after the seventh dose were 111.5 µg/mL and 61.7 µg/mL, respectively, which are consistent with PK parameters obtained after administration of nivolumab monotherapy.

In Study CA223002, PK of lirilumab at Dose Levels of 0.1 to 1 mg/kg in combination with ipilimumab (BMS-734016) 3 mg/kg was characterized after the first and fourth doses of lirilumab, based on the availability of the preliminary data. The geometric mean accumulation index was 1.4. For the ipilimumab 3-mg/kg Dose Level, across different Dose Levels of lirilumab, the geometric mean of Cmax and Cmin after the first dose was 66.5 µg/mL and 8.9 µg/mL, respectively, and the geometric mean of Cmax and Cmin after the fourth dose was 74.9 µg/mL and 13.0 µg/mL, respectively. These values are consistent with PK parameters obtained after administration of ipilimumab monotherapy.

1.4.5 Nivolumab: Pharmacology

Nivolumab is a fully human IgG4 monoclonal antibody that binds to PD-1 with nanomolar affinity (K_D = 3.06 nM) and a high degree of specificity, thus precluding binding to its ligands PD-L1 and PD-L2. Nivolumab does not bind to other related family members, such as BTLA, CTLA-4, ICOS, or CD28. Pre-clinical testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of IFN-γ in vitro.

1.4.6 Nivolumab: Toxicity

Toxicology studies in cynomolgus monkeys revealed that nivolumab was well tolerated at doses up to 50 mg/kg given twice weekly for 27 doses. Serum chemistry changes were limited to a reversible 28% decrease in triiodothyronine in females without concomitant abnormalities in other markers of thyroid function.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[23] The findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Additional non-clinical information on nivolumab toxicity can be found in the IB for nivolumab.[19]

1.4.7 Nivolumab: Pre-clinical Metabolism and Pharmacokinetics

Please see the most recent IB for nivolumab for current data.[19]

1.4.8 Nivolumab: Clinical Pharmacology and Safety

Extensive details on the safety profile of nivolumab are available in the IB and will not be repeated herein.[19]

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

severity, or causality of AEs with respect to nivolumab Dose Level. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone, and in some cases, both frequency and severity of AEs were greater than those observed with either agent alone.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 1. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (HRT; endocrinopathies) as instructed in these algorithms. Nivolumab should not be used in subjects with active autoimmune disease, given the mechanism of action of the antibody.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.[19]

1.4.8.1 Pharmacokinetics of Nivolumab

The PK of nivolumab were studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab Q2W or Q3W. Based on a population pharmacokinetics (PPK) analysis using data from patients with various tumor types, including MEL, NSCLC, and RCC and a time varying CL model, nivolumab CL was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (percent coefficient of variation [% CV]) of 8.2 mL/h (53.9%). The decrease in CLss is not considered to be clinically relevant. The geometric mean [% CV] apparent volume of distribution at steady state (Vss) is 6.8 L (27.3%), and geometric mean elimination T-HALF is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. The CL of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline lactate dehydrogenase, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment.

Although Eastern Cooperative Oncology Group (ECOG) status, baseline glomerular filtration rate, albumin, body weight, had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB.[19]

1.4.9 Ipilimumab: Pharmacology

Ipilimumab is a fully human IgG1κ monoclonal antibody that has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15 ng/mL,

whereas saturation was observed at approximately 0.1 μg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 μg/mL, respectively.

1.4.10 Ipilimumab: Toxicity

In IV repeat-dose toxicology studies in monkeys, ipilimumab was tolerated without adverse effects at doses up to 30 mg/kg/day administered every 3 days for 3 doses,[24,25,26] at 10 mg/kg (equivalent to human dose on body-weight basis) administered weekly for 1 month,[27] at 1 mg/kg administered weekly for 10 weeks,[28] and at doses up to 10 mg/kg/day administered approximately monthly for up to 6 months.[27,28,29,30] In the pivotal 6-month toxicity study (10 mg/kg administered on Days 0, 28, 56, 84, and 140), treatment-related findings were limited to decreases in absolute and relative thyroid (44% to 50%) and testicular (27% to 50%) weights. However, there were no corresponding microscopic changes in these organs, and thus, 10 mg/kg was considered to be the no observable adverse effect level.[30]

In addition, increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred following IV administration of ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition at doses of 2.6 or 7.2 times higher than the clinical exposure at a dose of 3 mg/kg or 0.9 to 2.1 times higher than the clinical exposure at a dose of 10 mg/kg every 21 days of ipilimumab. Based on the results of the monkey reproductive study, ipilimumab is not recommended for use during pregnancy unless the potential benefit justifies the potential risk to the fetus.

1.4.11 Ipilimumab: Pre-clinical Metabolism and Pharmacokinetics

Please see the most recent IB for ipilimumab for current data.[22]

1.4.12 Ipilimumab: Clinical Pharmacology and Safety

More than 19,500 subjects have been enrolled in ipilimumab studies in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in MEL, prostate cancer, and lung cancer, with advanced MEL being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

Phase 3 programs are ongoing in MEL, prostate cancer, and lung cancer. In MEL, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pre-treated advanced MEL and previously untreated advanced MEL, respectively. The safety profile of ipilimumab is generally consistent across these trials with a) the majority AEs being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies.

Additional details on the safety profile of ipilimumab, including results from clinical studies, are available in the ipilimumab IB.[22]

1.4.12.1 Pharmacokinetics of Ipilimumab

The PK of ipilimumab has been extensively studied in subjects with MEL at the 3- and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The mean CL (± standard deviation) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean Vss (± standard deviation) value was 5.75 ± 1.69 L.

The PPK of ipilimumab was studied in 785 subjects (3200 serum concentrations) with advanced MEL in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),[31] 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant, similar to that determined by non-compartmental analyses. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in body weight. However, there was no significant increase in exposure with increase in body weight when dosed on a milligram per kilogram basis, supporting dosing of ipilimumab based on a weight-normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy; prior therapy; body weight; performance status; or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance.

1.4.13 Rationale for Selection of Schedule, Dose, and Tumor Types

1.4.13.1 Rationale for Schedule, Dose, and Tumor Types for the Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed): Lirilumab and Nivolumab Weight-based Dosing

The nivolumab dose of 3 mg/kg is an active dose that is well tolerated. Doses of lirilumab given as a single agent have ranged from 0.1 to 10 mg/kg, resulted in pharmacodynamic modulation of the target, and been well tolerated. This is the first study evaluating the combination of these 2 antibodies. Therefore, the nivolumab dose will remain constant at 3 mg/kg and the lirilumab antibody will be tested in dose escalation at 0.1, 0.3, 1, and 3 mg/kg. Based on further data that may emerge, evaluating higher Dose Levels will be considered as appropriate. This is a Phase 1/2 study to determine the safety of the antibodies given in combination, so all subjects with solid tumors (with the exception of primary central nervous system [CNS] tumors) are eligible to participate during dose escalation. Nivolumab has shown clinical benefit in subjects with various solid tumors. Thus, following dose escalation, subjects with select tumor types will be eligible to participate in the cohort expansion part of the study in order to gather additional safety, tolerability, preliminary efficacy, and pharmacodynamic information regarding the combination of lirilumab and nivolumab.

1.4.13.2 Rationale for Schedule, Dose, and Tumor Types for the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) and the Signal Detection Cohort Expansion (Part 4 - removed): Flat Doses

A flat dose of nivolumab 240 mg Q2W (Study Days 1, 15, 29, and 43 in an 8-week cycle) will be used in combination with a flat dose of lirilumab 240 mg Q4W (Study Days 1 and 29) in the SCCHN Randomized Cohorts (Part 3) either in combination with lirilumab or as monotherapy in combination with placebo for lirilumab.

Nivolumab monotherapy has been extensively studied in the NSCLC patient population in Studies CA209003, CA209063, CA209017, and CA209057 with body-weight-normalized dosing (milligram per kilogram). Nivolumab PK and exposures of subjects in these studies have been characterized by PPK analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose-proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab CL and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a milligram per kilogram dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier subjects, relative to the exposures in lighter subjects.

Table 1.4.13.2-1 presents summary statistics of the estimated nivolumab steady-state trough, peak, and time-averaged concentration (steady-state trough concentration [Cminss], steady-state peak concentration [Cmaxss], and time-averaged concentration at dosing interval [Cavgss], respectively) in NSCLC subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat dose of nivolumab 240 mg. It should be noted that a dose of nivolumab 240 mg is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 clinical studies of nivolumab monotherapy in NSCLC subjects (CA209017, CA209057, and CA209063). As evident from the data presented in Table 1.4.13.2-1, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3-mg/kg dose, and the %CV in these measures of exposure is only slightly (< 10%) greater than that of the 3-mg/kg dosing.

Table 1.4.13.2-1: Summary Statistics of Nivolumab Steady-state Exposure

Nivolumab Dose	Cminss Geo. Mean [µg/mL] (%CV)	Cmaxss Geo. Mean [µg/mL] (%CV)	Cavgss Geo. Mean [µg/mL] (%CV)
240 mg	61.5 (44.6)	133.7 (35.0)	82.4 (38.2)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)

Geo = geometric.

Nivolumab has been shown to be safe and well tolerated up to a Dose Level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be

relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of nivolumab 240 mg will be similar to that of nivolumab 3 mg/kg and will be used in Part 3.

The PK and safety of nivolumab have been evaluated in the Asian population. The comparison of PK parameters in global and Japanese subjects suggests that the PK of nivolumab is similar in these populations. Nivolumab is shown to be safe and well tolerated in Japanese subjects. The similar PK and safety profile of nivolumab between global and Japanese subjects supports the use of similar dosing in the Asian population as is being used in global clinical studies.

Based on these data, a flat dose of nivolumab 240 mg Q2W is appropriate for further investigation.

Lirilumab is being studied as a potential immunotherapy alone and in combination with other agents in subjects with various hematologic malignancies and solid tumors with body weight normalized dosing (milligram per kilogram). A preliminary PPK analysis of data collected from 3 studies (CA223001, CA223002, and CA223003) suggests that lirilumab PK is linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Lirilumab CL and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a milligram per kilogram dose represents an over-adjustment for the effect of body weight on lirilumab PK. Conversely, given the relationship between lirilumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier subjects, relative to the exposures in lighter subjects.

Table 1.4.13.2-2 presents summary statistics of the estimated lirilumab peak and trough concentrations after the 1st dose and steady state (Cmin1, Cmax1, Cminss and Cmaxss) in subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat lirilumab dose of 240 mg. It should be noted that a dose of lirilumab 240 mg is identical to a dose of 3 mg/kg for subjects weighing 80 kg. As evident from the data presented in Table 1.4.13.2-2, the geometric mean values of Cmin1, Cmax1, Cminss and Cmaxss with flat dosing are slightly higher (< 10% difference) than that produced by a 3 mg/kg dose.

Table 1.4.13.2-2: Summary Statistics of Predicted Lirilumab Exposure

Lirilumab Dose	Cmin1 Geo. Mean [µg/mL] (cv %)	Cmax1 Geo. Mean [µg/mL] (cv %)	Cminss Geo. Mean [µg/mL] (cv %)	Cmaxss Geo. Mean [µg/mL] (cv %)
240 mg	8.897 (61.06)	66.113 (40.06)	14.262 (85.26)	83.209 (41.25)
3 mg/kg	8.261 (58.61)	61.513 (37.54)	13.263 (81.98)	77.678 (38.49)

Lirilumab has been shown to be well tolerated up to a dose level of 10 mg/kg. Similar observations have been made for nivolumab, which was converted from a weight-based dose to a flat dose. Taken together, the PK, safety, and efficacy profile of lirilumab 240 mg is expected to be similar to that of lirilumab 3 mg/kg and will be used in combination with nivolumab 240 mg Q2W in the SCCHN Randomized Cohorts (Part 3) to maintain continuity in order to pursue and confirm an ongoing signal (from the SCCHN Cohort Expansion [Part 2]). Doses of lirilumab given as a single

agent have ranged from 0.1 to 10 mg/kg, resulted in pharmacodynamic modulation of the target, and have been well tolerated.

For the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), utilizing the triple combination of lirilumab, nivolumab, and ipilimumab for the first time, the study drugs will be administered using the milligram per kilogram dosing regimen to assess safety of this combination before other dosing regimens (including flat dosing) will be considered.

1.4.13.3 Rationale for Schedule and Dose for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) or the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed): Lirilumab, Nivolumab, and Ipilimumab Weight-based Dosing

As of 30-Aug-2016, 159 subjects were treated with the lirilumab plus nivolumab combination in Study CA223001. Nivolumab was administered at 3 mg/kg Q2W and lirilumab was administered Q4W at doses ranging from 0.1 mg/kg to 3 mg/kg. Most of the 159 treated subjects were treated at the nivolumab 3 mg/kg + lirilumab 3 mg/kg Dose Level. TRAEs and Grade 3 to 4 TRAEs were reported in 72% (114/159) and 15% (24/159) of subjects, respectively. Discontinuations due to TRAEs occurred in 8% (12/159) of subjects. The rates of AEs of the combination of lirilumab and nivolumab are consistent to what has been reported with nivolumab monotherapy with the exception of infusion related reactions which were higher in the combination. These infusion reactions were Grade 1 and 2 events only, which occurred mainly with the first infusion and did not lead to discontinuation.

As of 15-Jul-2016, 22 subjects were treated with the lirilumab plus ipilimumab combination in Study CA223002. Ipilimumab was administered at 3 mg/kg and lirilumab was administered at doses ranging from 0.1 to 3 mg/kg. Subjects received lirilumab in combination with ipilimumab Q3W for a total of 4 doses (induction), and then Q12W for an additional 4 doses starting at Week 24 (maintenance). Three subjects were administered lirilumab 0.1 mg/kg + ipilimumab 3 mg/kg, 8 with lirilumab 0.3 mg/kg + ipilimumab 3 mg/kg, 6 with lirilumab 1 mg/kg + ipilimumab 3 mg/kg, and 5 with lirilumab 3 mg/kg + ipilimumab 3 mg/kg. At the second dose level (lirilumab 0.3 mg/kg + ipilimumab 3 mg/kg), 1 subject reported iridocyclitis during the DLT period. This was a Grade 2 event that did not improve to Grade 1 within 2 weeks despite treatment with topical and intraocular injection of steroids, resulting in a DLT. The second cohort (lirilumab 0.3 mg/kg + ipilimumab 3 mg/kg) was thus expanded to 6 evaluable subjects. In the third cohort (lirilumab 1 mg/kg + ipilimumab 3 mg/kg), 1 subject reported a DLT of Grade 3 rash. This cohort was thus expanded to 6 evaluable subjects, and no further DLT occurred in these subjects. In the fourth cohort (lirilumab 3 mg/kg + ipilimumab 3 mg/kg), 5 subjects were enrolled; 2 subjects completed DLT evaluation period while 3 subjects progressed during DLT period and withdrew from the study. The study was terminated on 08-Dec-2014, and last patient last visit was occurred on 21-Apr-2015. This termination was due to strategic reasons and not due to any safety concerns.

TRAEs were reported by 15 of 22 (68.2%) exposed subjects. Two subjects reported at least 1 Grade 3 event related to the combination of lirilumab and ipilimumab (erythematous rash and pruritus in 1 subject and hypopituitarism in the other subject). There were no related Grade 4 or

5 events reported. Discontinuations due to TRAEs occurred in 1 subject (iridocyclitis Grade 2). Two (9.1%) SAEs (iridocyclitis and hypopituitarism) were considered to be related to study therapy by the investigator. There were no treatment-related deaths.

Refer to Section 1.1.4.1 for data from CA209012 regarding nivolumab and ipilimumab combination treatment.

Preliminary assessment of the combination of 3 immunotherapy agents (lirilumab, nivolumab, and ipilimumab) will start with evaluating previously evaluated treatment schedules with a focus on understanding the safety and tolerability of these agents when combined. Initial dosing will test nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg Q6W, and lirilumab 3 mg/kg Q4W.

Since lirilumab has been well tolerated as single agent (up to 10 mg/kg) and in combination with nivolumab (Study CA223001) and ipilimumab (Study CA223002) at 3 mg/kg,[21] lirilumab at 3mg/kg will be used in this combination. Additional refinement of the dose/schedule of administering this combination may be pursued via a future protocol amendment.

1.4.14 Rationale for Use of Immune-Related Response Criteria

NOTE: This section will only be applicable for the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed) of this study.

Clinical evidence suggests that some subjects treated with immune-modulating agents may have PD before demonstrating clinical response.[32] The mechanism behind this finding is unknown but may include an early inflammatory and immune cell trafficking phase that can be misinterpreted as tumor growth or as the kinetics of fast tumor growth vs initial slow anti-tumor activity. What is clear is that the use of standard response criteria has the potential of removing subjects from study too early. In the ipilimumab study, approximately 10% of subjects who were deriving clinical benefit had evidence of disease progression as determined by modified World Health Organization criteria.[22] Therefore, exploratory response criteria modified from Response Evaluation Criteria in Solid Tumors (RECIST) have been developed to take into account an immune-mediated pattern of objective response (irRECIST).[9]

Appendix 2 lists irRECIST criteria. The 2 main modifications are that disease progression will require confirmation at least 4 weeks following the restaging scan and that the appearance of new lesions may not be considered disease progression. In this protocol, irRECIST will be used for study conduct. Statistical analyses will be primarily based on RECIST version 1.1 (v1.1) criteria (see Appendix 3).

With Amendment 13 (Revised Protocol 10), additional study parts will use RECIST v1.1 instead of irRECIST.

1.4.15 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

No longer applicable with Revised Protocol 12.

Accumulating clinical evidence indicates that some subjects 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 subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[32] 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 anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects in this study will be allowed to continue study therapy after initial investigator-assessed RECIST v1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 3.5.1). Such subjects must discontinue study therapy upon further evidence of progression.

1.4.16 Rationale for Use of Blood and Tumor Tissue in Biomarker Studies

The sample collection and biomarker assessment strategy is designed to address key questions regarding the actions of lirilumab in combination with nivolumab and ipilimumab and the simultaneous modulation of innate and adaptive immune systems. Specifically, the measurements obtained from the various biomarker assessments will help answer the following questions:

[redacted]

[redacted]

[redacted]

The tumor-based biomarker analysis will be mandatory for 10 subjects in the MEL cohort expansion and the SCCHN cohort of the Dose Escalation and Cohort Expansion (Part 1; completed).

For all subjects in [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), biopsies will be mandatory at baseline if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed clinically acceptable as judged by the investigator. In addition [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), all subjects will have a fresh biopsy collected on treatment if biopsy risk is acceptable. All subjects will be offered the opportunity to undergo biopsies at any time during the study. In addition, any tumor that remains following clinically indicated procedures should be saved as fresh frozen tumor or formalin-fixed, paraffin-embedded (FFPE) tumor or both and submitted for biomarker testing. Tumor biopsies are required in these cohorts in order to characterize status [redacted] and expression of tumor specific proteins such as PD-L1 [redacted] A previous amendment has changed the timing of the on-treatment biopsy to approximately 4 weeks ± 3 days on therapy to increase the likelihood of obtaining tumor tissue in subjects. In [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) the on-treatment biopsy will be collected at Day 15 ± 3 to ensure that tumor tissue is available from all subjects.

[redacted]

[redacted]

1.4.17 Rationale for Shorter Infusion Durations in the SCCHN Randomized Cohorts (Part 3 - closed to enrollment), the Signal Detection Cohort Expansion (Part 4 - removed), the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment), and the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)

1.4.17.1 Rationale for Shorter Infusion Times for Nivolumab Monotherapy

The impact of infusion time on nivolumab safety has been assessed in an ongoing community-based trial (CA209153) in subjects with previously treated advanced or metastatic NSCLC.[33] As of an interim data lock on 26-Oct-2015, 322 subjects received nivolumab 3 mg/kg Q2W via a 30-minute infusion and 355 subjects were administered the same regimen with a 60-minute infusion time.

Overall, the safety profiles of the 30- and 60-minute infusion groups were similar with regard to the incidence of any-grade treatment-related AEs (53% and 51%, respectively). The incidence of Grade 3 to 4 select AEs occurring in ≥ 2% of subjects was comparable in the pulmonary (3% and 2%), hepatic (2% and 3%), and gastrointestinal (2% and 2%) categories between the 30- and 60-minute infusion groups. Any-grade infusion reactions occurred in 3% and 2% of subjects given 30- or 60-minute infusions, respectively. The incidence of Grade 3 to 4 infusion reactions was < 1% for both infusion groups. Table 1.4.17.1-1 shows the individual AEs reported within the hypersensitivity/infusion reaction category.

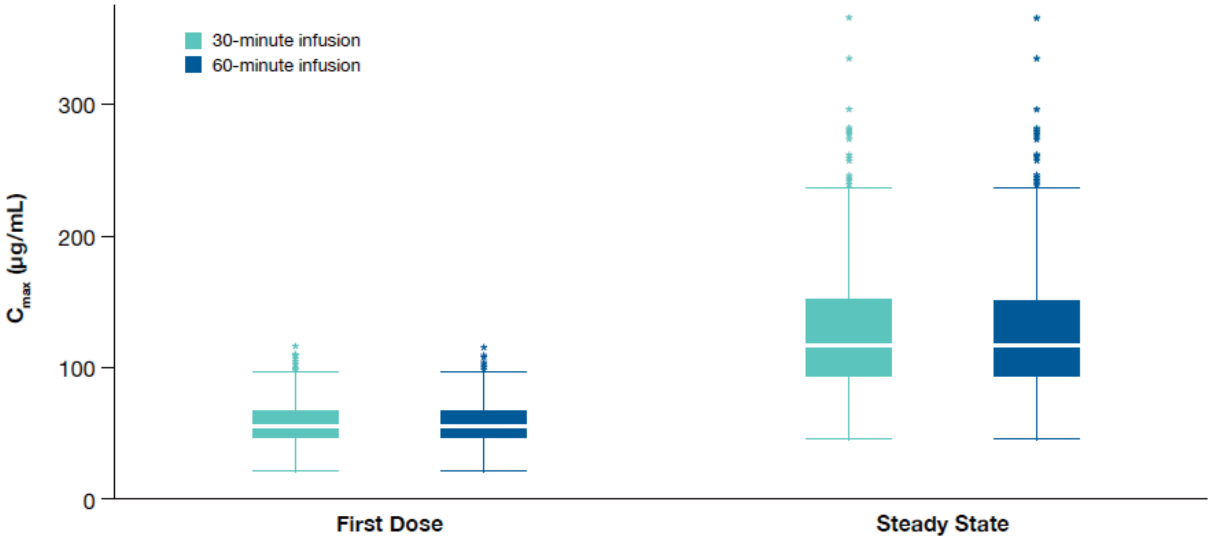
Table 1.4.17.1-1: Hypersensitivity/Infusion Reaction AEs by Infusion Time

	Nivolumab 3 mg/kg Q2W			
	30-minute Infusion n = 322		60-minute Infusion n = 355	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Infusion reaction, n (%)	9 (3)	2 (< 1)	6 (2)	3 (< 1)
Hypersensitivity	5 (2)	0	1 (< 1)	0
Infusion-related reaction	2 (< 1)	0	5 (< 1)	3 (< 1)
Anaphylaxis	1 (< 1)	1 (< 1)	0	0
Bronchospasm	1 (< 1)	1 (< 1)	0	0

Hypersensitivity/infusion reactions were generally manageable using dosing interruptions (8 subjects in the 30-minute infusion and 3 subjects in the 60-minute infusion), with only a limited impact on the dose received. Systemic corticosteroids were administered in a limited number of cases (3 subjects in the 30-minute infusion and 1 subject in the 60-minute infusion), and treatment was discontinued as a result of hypersensitivity/infusion reactions in even fewer cases (1 subject in the 30-minute infusion and 2 subjects in the 60-minute infusion).

In addition, the PPK modeling demonstrated similar exposures in both infusion groups (Figure 1.4.17.1-1), suggesting that the 30-minute infusion does not pose an increased risk to subjects.

Figure 1.4.17.1-1: Model-predicted Cmax After the First Dose and at Steady State by Infusion Time



Box plots show mean values and 25%/75% quartiles, with whiskers indicating 1.5 times the interquartile range; stars indicate outliers

In conclusion, nivolumab can be safely infused over 30 minutes, and the safety profile is comparable to the 60-minute infusion, with a low incidence of infusion-related reactions. As a result, the 30-minute infusion time has been implemented across the entire nivolumab program.

1.4.17.2 Rationale for Shorter Infusion Times for Nivolumab in Combination with Ipilimumab

Long infusion times, especially when multiple agents are administered sequentially to an individual, place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30-minute duration for nivolumab and ipilimumab in combination with 60-minute infusion of lirilumab in subjects will diminish the burden provided there is no change in safety profile.

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab

and 90-minute infusion duration for ipilimumab (1- to 3-mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration:

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1 to 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg, or 240 mg, or 360 mg is not expected to present any safety concerns compared to the prior experience with the nivolumab 10-mg/kg dose infused over a 60-minute duration.
- Similarly, ipilimumab 10 mg/kg has been safely administered over 90 minutes. In Study CA184022, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug-related hypersensitivity events (Grade 1 to 2) were reported in 1 subject (1.4%) in the 0.3 mg/kg group and in 2 subjects (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 to 4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90-minute infusion in large Phase 3 studies in prostate cancer (Study CA184043) and as adjuvant therapy for stage 3 MEL (Study CA184029), with infusion reactions occurring in subjects. Administering ipilimumab 1 mg/kg represents one-tenth of the 10-mg/kg dose.

Of note, Study CA209153, a Phase 3b/4 safety study of nivolumab in subjects with advanced or metastatic NSCLC who have progressed during or after at least 1 prior systemic regimen, has used a 30-minute infusion in a cohort of 332 subjects with no safety issues.[19]

Lirilumab infusion for all parts of the study will remain at 60 minutes. In this study, the rate of infusion reactions seen with nivolumab and lirilumab combination is 18%. These reactions were Grades 1 and 2, occurred mostly with the first infusion, were manageable, and did not lead to discontinuation.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the nivolumab and ipilimumab combination and the lirilumab and nivolumab combination. Furthermore, a 30-minute break after the infusion of each drug of the combination will ensure the appropriate safety monitoring before the start of the subsequent infusion. Overall, a change in safety profile is not anticipated with a 30-minute infusion of nivolumab, ipilimumab, with 60-minute infusion of lirilumab.

1.4.18 Rationale for Patient-Reported Outcomes Evaluation in the SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

No longer applicable with Revised Protocol 12.

1.4.19 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. In Study CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of

retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[34]

Moreover, accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. In study CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[35] These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16% - 18% for squamous and non-squamous NSCLC respectively).[36]

Taken together, the data suggest shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. Also, 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.

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in study CA223001 treatment with lirilumab and nivolumab as well as lirilumab, nivolumab and ipilimumab will be extended for up to 2 years in this study.

1.5 Overall Risk/Benefit Assessment

Subjects with recurrent, unresectable or metastatic tumors represent an important unmet need. Lirilumab is an NK cell-directed anti-KIR antibody and has the potential to improve clinical outcomes in tumors where NK cell biology plays an important role. There is clinical data available to suggest the potential to improve clinical outcomes in tumors included in this study.

- Clinical activity of nivolumab monotherapy in subjects with recurrent or metastatic SCCHN who progressed from a platinum-containing therapy evaluated in CA209141 randomized Phase 3 study, demonstrated prolonged survival benefit with nivolumab as compared to investigator's

choice (IC) of chemotherapy. In these populations, the safety profile of nivolumab was shown to be favorable as compared to standard of care chemotherapy.

- At the time of Amendment 13, preliminary data in 29 evaluable recurrent and metastatic SCCHN subjects whose disease progressed on or after platinum-based therapy treated with the combination of lirilumab plus nivolumab showed an ORR of 24% (7/29) in the all-comer population and an ORR of 41% (7/17) in the PD-L1+ population.[1] No responses (0/12) were observed in the PD-L1 negative population. Also of note, in 5 out of 7 lirilumab plus nivolumab responders, the reduction in tumor burden was substantial, exceeding greater than 80%. Responses appeared durable, with the median DOR not reached. Subsequent efficacy analysis of additional SCCHN subjects treated with the combination of lirilumab and nivolumab did not demonstrate a differential efficacy signal as compared to nivolumab monotherapy treatment in a similar population of SCCHN subjects. Therefore, with Revised Protocol 12, enrollment in Parts 3 and 5 is closing and Parts 4 and 6 are removed from the protocol. Individual subjects who continue to have clinical benefit with the combination of lirilumab and nivolumab without an increase in adverse events will be permitted to remain on study treatment until protocol-specified discontinuation criteria are met.
- Transcriptome data from 280 tumors profiled by TCGA showed that SCCHN, NSCLC, and bladder tumors have high infiltration of NK cells and KIR gene expression suggesting that KIR blockade with lirilumab may enhance antitumor activity of nivolumab in patients with SCCHN. In addition analysis of tumor tissues from patients with NSCLC showed that the expression of NK cells in squamous cell carcinoma was significantly higher than in adenocarcinoma and large cell carcinoma and the survival time of lung cancer patients was positively related to NK-cell infiltration degree in lung cancer[37] supporting the evaluation of lirilumab in combination with nivolumab in tumors with squamous histology
- Clinical activity of ipilimumab when added to lirilumab plus nivolumab has the potential to enhance the activity seen with lirilumab and nivolumab in SCCHN. Analysis of the immune infiltration in a large cohort of head and neck tumors, integrating genetic data with RNA-seq–based deconvolution of immune cell populations and effector/regulatory molecules was done[3] and found that SCCHN tumors, are infiltrated with Tregs and KIR-overexpressing $CD56^{dim}$ NK cells, to a higher degree than other cancer types. These findings suggest that head and neck tumors possess an immune landscape that is poised to respond to immunotherapeutic approaches that block inhibitory signals to T cells and NK cells, such as immune checkpoint inhibitors (nivolumab and ipilimumab), including antibodies blocking KIR signaling (lirilumab). In addition, clinical activity of nivolumab plus ipilimumab combination in subjects with stage IIB-IV NSCLC as first-line treatment in CA209012 study, a large Phase 1, multi-arm safety study of nivolumab monotherapy and nivolumab in combination with various systemic anticancer therapies including ipilimumab. Clinical activity was observed in all combination cohorts with numerically higher response rates observed in cohorts evaluating nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, with confirmed response rates ≥ 30% and median PFS ~8 months. Given the similarity in patient profiles of NSCLC and SCCHN, nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W will be the treatment regimen used in the reference arm and the backbone regimen for the experimental arm to which lirilumab 3 mg/kg Q4W will be added.

Furthermore, lirilumab in combination with nivolumab or with ipilimumab has an acceptable safety profile in subjects with advanced refractory solid tumors. The safety profile associated with lirilumab in combination with nivolumab was generally consistent with that observed with nivolumab monotherapy. TRAEs were reported in 217 of 322 (67.4%) patients and Grade 3 to 4 TRAEs were reported in 36 (11.2%) patients. Discontinuations due to TRAEs occurred in 14 (4.3%) patients.[12] The safety profile associated with lirilumab in combination with ipilimumab was generally consistent with that observed with ipilimumab monotherapy. AEs were reported for all 22 (100%) of the subjects treated in this study. The most frequently reported AEs (> 25% of all treated subjects) were fatigue (45.5%), nausea (40.9%), malignant neoplasm progression (36.4%), back pain (27.3%), diarrhea (27.3%), pneumonia (27.3%), pyrexia (27.3%), and vomiting (27.3%). Lastly, the safety profile of nivolumab and ipilimumab is well characterized from a large safety database at different doses and schedules as monotherapy or in combination. Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related AEs observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated AEs include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used. In the combination dosing schedule selected for this study (nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W), immune-mediated AEs were mostly low grade and manageable with prompt use of corticosteroids.

Lirilumab in combination with nivolumab and ipilimumab will be evaluated for the first time.

To assure an ongoing favorable risk/benefit assessment for subjects enrolled onto CA223001, the following safety measures will be employed throughout the conduct of the study:

- Rigorous safety monitoring by BMS to ensure subjects' safety including regular and systematic review of safety data, close follow-up of reported safety events, intensive site and study investigator training/education on the implementation of the immune-related toxicity management algorithms as well as regular safety conference calls with study investigators.
- **Safety lead-in:** Initially approximately 10 subjects will be enrolled each in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) and followed for at least 4 weeks of safety assessment from the start of study drug administration before additional subjects are enrolled in the study to ensure there is no major safety signal with the combination. Any findings will be discussed between the BMS Medical Monitor and investigators and an agreement will be reached as to whether a lower dose or an alternate dose schedule should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study. As of 06-Apr-2018, preliminary analysis of 10 subjects treated during the safety lead-in have not identified any new safety signals of the lirilumab, nivolumab and ipilimumab triplet combination relative to monotherapy or doublet combinations of these study treatments. Individual subjects who continue to have clinical benefit with the combination of lirilumab and nivolumab without an increase in adverse events will be permitted to remain on study treatment until protocol-specified discontinuation criteria are met.
- There is some risk associated with tumor biopsies, including bleeding, infection, and pain. While there is no direct benefit to subjects who undergo these procedures, there is the distinct

possibility that the data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors.

The potential direct benefit to subjects who participate in this study is that therapy with these agents may result in SD, PR, or even complete response (CR).

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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 or debarment).

2.2 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, subject 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 IB(s) or product labeling, information to be provided to subjects, and any updates.

The investigator or BMS 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.

2.3 Informed Consent

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 to 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 subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) that 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:

1) Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form(s) 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.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject'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 informed consent form and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

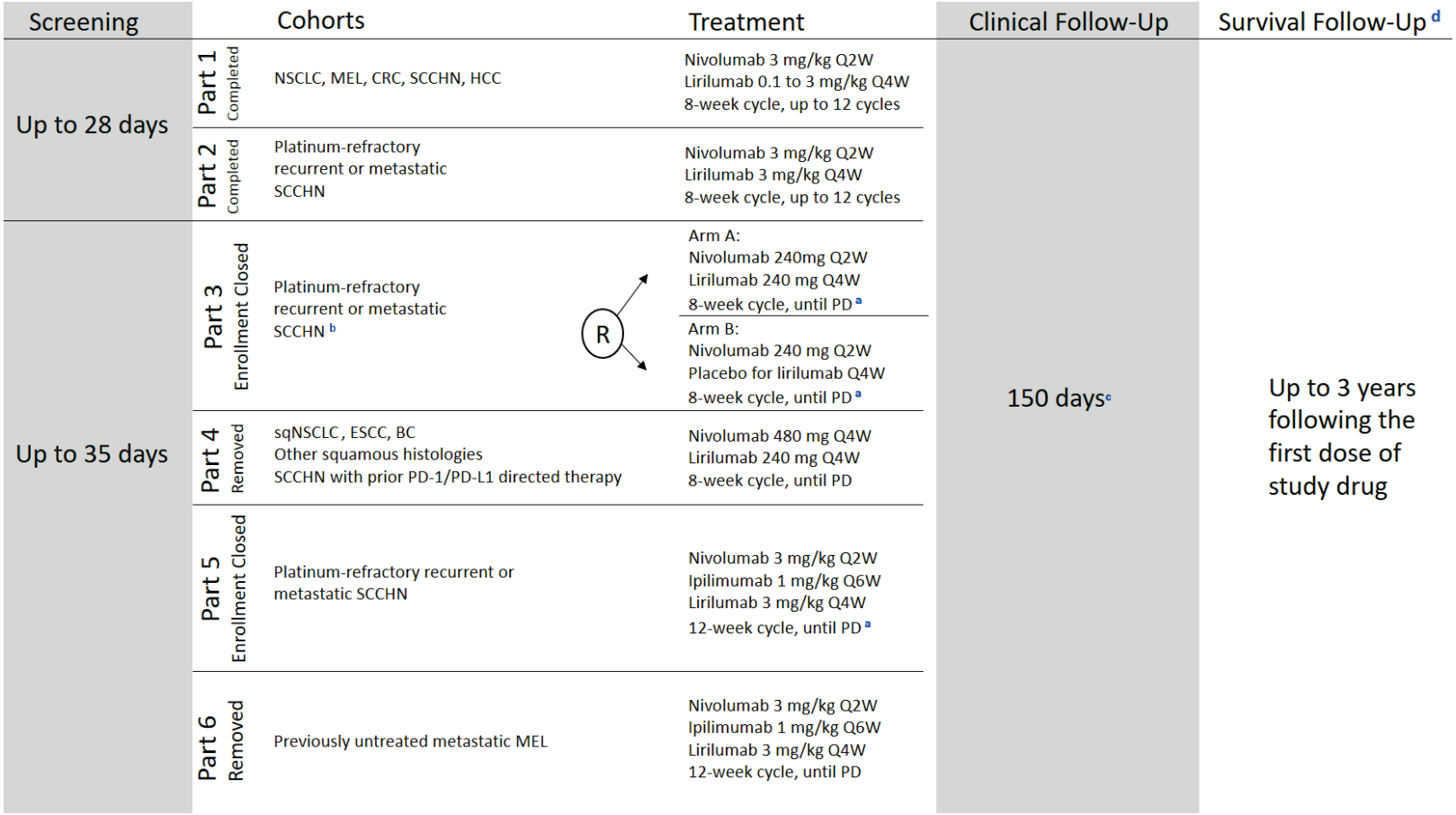
This is a Phase 1/2 study that will be conducted in 6 parts. A brief overview of the study parts follows below.

Please note that the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) have both completed enrollment and are not applicable starting with Amendment 13 and all subsequent amendments. For preliminary safety results, see Section 1 "Clinical Experience with Lirilumab and Nivolumab Combination Treatment."

- Part 1 (Completed): The Dose Escalation and Cohort Expansion of the study will consist of a dose escalation assessment of the safety and tolerability of lirilumab administered in combination with nivolumab in subjects with advanced solid tumors and 5 cohort expansions at either the MTD, maximum administered dose (MAD), or at an alternative dose as determined by the investigators and the Sponsor.
- Part 2 (Completed): The SCCHN Cohort Expansion will be an additional cohort expansion at Dose Level 4 in subjects with platinum-refractory recurrent or metastatic SCCHN.
- Part 3 (Closed to enrollment): The SCCHN Randomized Cohorts will involve a single-blinded, placebo-controlled, randomized cohort expansion of lirilumab in combination with nivolumab vs nivolumab monotherapy in subjects with platinum-refractory recurrent or metastatic SCCHN who are PD-L1+.
- Part 4 (Removed): The Signal Detection Cohort Expansion will be an additional cohort expansion of nivolumab and lirilumab at a flat dose in subjects with sqNSCLC, ESCC, BC, and other squamous histologies (including squamous cell cancers of the skin, cervix, vulva, vagina, penis, anorectal and of unknown primary site) and in subjects with SCCHN who have received prior PD-1/PD-L1 directed therapy.
- Part 5 (Closed to enrollment): The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination will be an open-label safety and signal detection cohort with a triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with platinum-refractory recurrent or metastatic SCCHN.
- Part 6 (Removed): The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination will be a safety and signal detection cohort with a first-line triplet regimen of lirilumab in combination with nivolumab and ipilimumab in subjects with previously untreated metastatic MEL.

Subjects will not be allowed to crossover between any parts or allowed to crossover to other BMS studies, including CA209714 and CA209651 for SCCHN.

Figure 3.1-1: Overall Study Design for All Study Arms (Study CA223001)



[a] Treatment period is until PD, treatment discontinuation, or a maximum of up to 2 years of treatment as specified in the individual study parts, whichever occurs earlier.

[b] Subjects must have PD-L1+ tumors. PD-L1+, defined as PD-L1 expressed in > 1% of tumor cells.

[c] 150 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 150 days after last dose

[d] No longer required with Revised Protocol 12.

CRC=colorectal cancer; HCC=hepatocellular carcinoma; R=randomization.

3.1.1 The Dose Escalation and Cohort Expansion (Part 1; Completed)

Subjects in the dose escalation and cohort expansion periods of the Dose Escalation and Cohort Expansion (Part 1) will complete up to 4 study periods: screening, treatment, clinical follow-up, and survival follow-up. **Screening** (up to 28 days). **Treatment** (up to maximum of 2 years). **Clinical follow-up** (150 days). **Survival follow-up** (up to 3 years following the first dose of study drug). Survival follow-up is no longer applicable with Revised Protocol 12 and no further visits should be conducted. With revised protocol 12, the total time on study for any individual subject will not exceed approximately 2.5 years.

The treatment period will last up to twelve 8-week treatment cycles. For subjects receiving lirilumab and nivolumab combination therapy in the Dose Escalation and Cohort Expansion (Part 1), each treatment cycle is composed of 4 doses of nivolumab and 2 doses of lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each treatment cycle, and lirilumab will be administered on Days 1 and 29 of each treatment cycle.

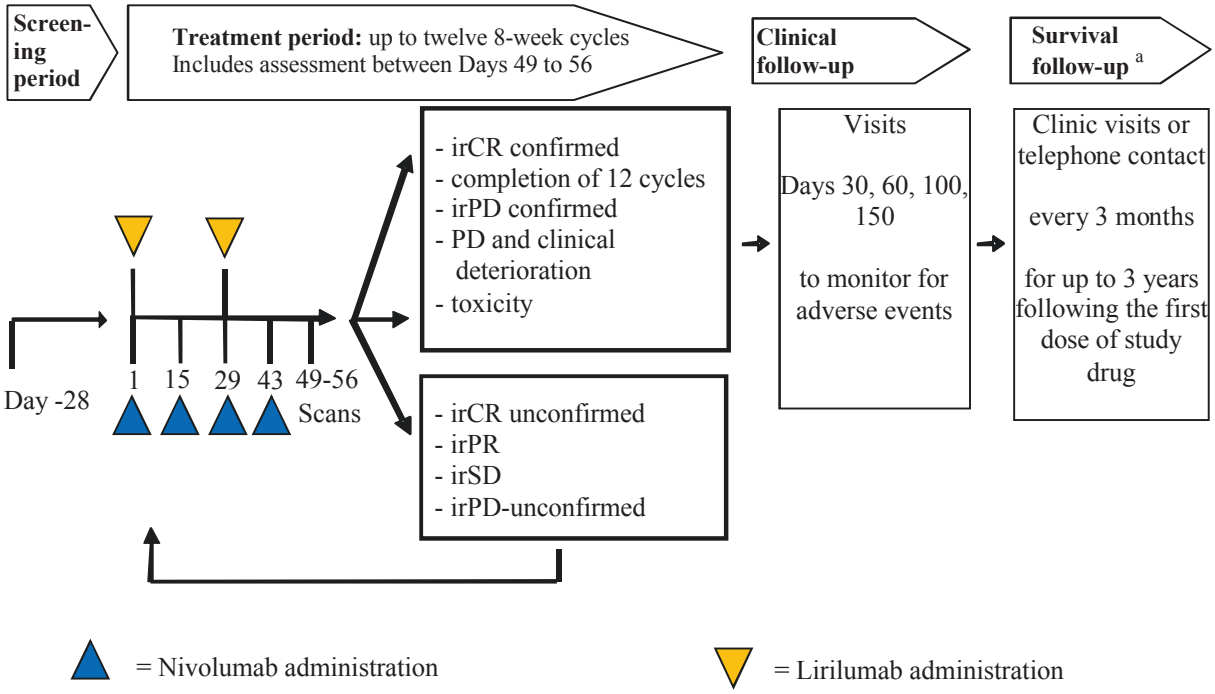
Following each treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next cycle). Treatment decisions related to subject management will be based exclusively on irRECIST for the Dose Escalation and Cohort Expansion (Part 1) (see Section 1.4.14 for the rationale and Appendix 2 for definitions).

For the Dose Escalation and Cohort Expansion (Part 1), subjects with an overall response of irPD-unconfirmed, irSD, irPR, or irCR-unconfirmed at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of any of the following: 1) achievement of irCR-confirmed; 2) completion of 12 cycles; 3) confirmation of irPD; 4) clinical deterioration suggesting that no further benefit from treatment is likely; 5) intolerability to therapy; or 6) meeting criteria for discontinuation of study therapy as outlined in Sections 3.5 and 4.9.5.

The subjects listed above will enter the clinical follow-up period, with visits scheduled on Days 30, 60, 100, and 150 to monitor for AEs.

A study schematic is presented below in Figure 3.1.1-1.

Figure 3.1.1-1: Study Period Schematic for the Dose Escalation and Cohort Expansion (Part 1; Completed)



[a] Survival follow-up no longer applicable with Revised Protocol 12

3.1.1.1 Dose Escalation (Completed)

A 3 + 3 + 3 design will be used to assess the safety of lirilumab given in combination with nivolumab. The dosages during dose escalation are provided in Table 3.1.1.1-1. The DLT observation period will last for 8 weeks or until the completion of Cycle 1, whichever is longer. Three subjects will be treated initially at each Dose Level. If 0 DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher Dose Level. If 1 of 3 subjects experiences a DLT, that cohort will be expanded to 6 subjects. If 1 of 6 subjects experiences a DLT, a new cohort of 3 subjects will be treated at the next higher Dose Level. If 2 of 6 DLT subjects experience a DLT, that cohort will be expanded to 9 subjects. If 2 of 3, 3 of 6, or 3 of 9 subjects experience DLTs within a cohort, then that Dose Level will be determined to have exceeded the MTD. If no MTD is reached through Cohort 4, then additional cohorts at lirilumab 6 mg/kg and lirilumab 10 mg/kg, given in combination with nivolumab 3 mg/kg, may be considered based on the aggregate safety experience during dose escalation and in consultation and agreement between investigators and Sponsor via a protocol amendment.

After determining the MTD, MAD, or completion of dose escalation without identifying the MTD and to further explore pharmacodynamic/biomarker objectives, 3 to 12 additional subjects may be enrolled in each Dose Level for a total of up to 15 subjects at any Dose Level (original 3 to 12 subjects from dose escalation plus additional subjects required to have a total cohort size of 15).

No intra-subject dose escalation or reduction is allowed. Subjects who withdraw from the study during the DLT period for reasons other than a DLT may be replaced within the same Dose Level. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled nivolumab doses through the 8-week observation period only if the 1 missed dose was secondary to non-medical reasons. In addition, subjects with dosing delays of ≥ 3 weeks in Cycle 1 for non-DLT events will be considered not evaluable for making decisions on dose escalation and should be replaced.

Dose escalation will be based on the number of DLTs experienced during Cycle 1.

The initial 6 subjects at each Dose Level will have peripheral blood evaluations for pharmacodynamic markers.

Table 3.1.1.1-1: Dosages During Dose Escalation

Dose Level Number	Total Subjects [a]	Lirilumab (IV; mg/kg)	Nivolumab (IV; mg/kg)
1	n = approximately 3 to 15	0.1	3
2	n = approximately 3 to 15	0.3	3
3	n = approximately 3 to 15	1	3
4	n = approximately 3 to 15	3	3
Total	n = approximately 12 to 60		

[a] 3 to 12 subjects will be enrolled during dose escalation. Additional subjects may be added to each Dose Level after completion of the dose escalation period of the study for a total of up to 15 subjects per Dose Level.

All available clinical and laboratory data and the nature, time of onset, and time to resolution of DLTs observed during dose escalation will be reviewed to determine whether an alternative dose schedule should be examined after consultation between the investigators and the Sponsor, if needed. If agreed upon, the alternative schedule will be identified by a protocol amendment.

3.1.1.2 Cohort Expansion (Completed)

The purpose of the cohort expansions is to gather additional safety, tolerability, preliminary efficacy, and pharmacodynamic information regarding the combination of lirilumab and nivolumab. Once the safety profile of all doses tested has been characterized and the MTD of combined administration of lirilumab and nivolumab has been defined, the cohort expansion will be initiated at the MTD, the MAD, or an alternate dose, if recommended by the investigators and the Sponsor. Treatment doses in the cohort expansion groups will not exceed the MAD. Five cohort expansions will be restricted to the tumor types listed in Table 3.1.1.2-1. The NSCLC and MEL cohorts, which have demonstrated activity with nivolumab monotherapy, will be used to assess increased activity of the combination therapy. The colorectal cancer (CRC), SCCHN, and hepatocellular carcinoma (HCC) cohorts will explore activity of the combination therapy in tumors with unknown or historically low responses to nivolumab monotherapy. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the cohort

expansions. If the rate of DLTs exceeds 33%, then the findings will be discussed and further enrollment may be interrupted. If a cohort expansion is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower Dose Level.

In each of the NSCLC and MEL cohorts, approximately 35 subjects will be enrolled to allow for a more precise estimate of the ORR in these tumors following combination treatment. The sample size for the other 3 cohorts will be guided by Gehan[38] design. In order to determine if a target response rate (eg, 25 to 30%) is likely, an initial number of subjects (eg, 9) will be treated at first (Stage I) in a cohort, as outlined in Table 3.1.1.2-1. In the tumor cohort in which no responses are observed, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate and no more subjects will be enrolled in that cohort. Otherwise, in the cohorts in which at least 1 response among the Stage I subjects is observed, up to 9 additional subjects will be treated for a total of 18 subjects per tumor type, as guided by Table 3.1.1.2-2. In Stage I, approximately 9 subjects will be enrolled per tumor type. The number of subjects enrolled in Stage II per tumor cohort will be guided by the number of responders observed in Stage I and the required precision of the ORR estimate. This is summarized in Table 3.1.1.2-2 below, using a precision of 12% around the ORR point estimate.

Table 3.1.1.2-1: Tumor Types Eligible for Cohort Expansion

Tumor Type	Stage I Subjects	Stage II Subjects	Total Subjects
NSCLC	N/A	N/A	Approx. 35
MEL	N/A	N/A	Approx. 35
CRC	9	4 to 9	Approx. 9 to 18
SCCHN	9	4 to 9	Approx. 9 to 18
HCC	9	4 to 9	Approx. 9 to 19
Totals			Approx. 97 to 124

Approx. = approximately; N/A = not applicable.

The actual sample size per cohort in Stage II to achieve desired precision (standard error) of 12% for the ORR estimate, as guided by the Gehan design, depends on the number of responses observed in Stage I (see Table 3.1.1.2-2), assuming a target ORR of 25% to 30%.

Table 3.1.1.2-2: Cohort Expansion Sample Sizes by n of Responses in Stage I for CRC, SCCHN, and HCC Tumors

Stage I Number of Responses in the First 9 Subjects	Stage II n [a]	Total n/Cohort
0	0	9
1	4	13
2	8	17
3	9	18

Table 3.1.1.2-2: Cohort Expansion Sample Sizes by n of Responses in Stage I for CRC, SCCHN, and HCC Tumors

Stage I Number of Responses in the First 9 Subjects	Stage II n [a]	Total n/Cohort
4	8	17
5	5	14
6	0	9

[a] Based on 12% precision for the ORR estimates and a target ORR of 25% to 30%.

3.1.2 The SCCHN Cohort Expansion (Part 2; Completed)

To further explore emerging efficacy and safety data in subjects with SCCHN; an additional cohort of approximately 35 subjects will be treated at Dose Level 4 (see Table 4.1-1). The null hypothesis that the true ORR is 25% will be tested against a one-sided alternative: ORR = 40%. The null hypothesis will be rejected if 12 or more responses are observed in 35 subjects. This design gives a 1-sided type I error rate of 0.15 and a power of 0.81.

Subjects will complete up to 4 study periods: screening, treatment, clinical follow-up, and survival follow-up. **Screening** (up to 28 days). **Treatment** (up to maximum of 2 years). **Clinical follow-up** (150 days). **Survival follow-up** (up to 3 years following the first dose of study drug). Survival follow-up is no longer applicable with Revised Protocol 12 and no further visits should be conducted. With revised protocol 12, the total time on study for any individual subject will not exceed approximately 2.5 years.

The treatment period will last up to twelve 8-week treatment cycles for the SCCHN Cohort Expansion (Part 2). For subjects receiving lirilumab and nivolumab combination therapy in the SCCHN Cohort Expansion (Part 2), each treatment cycle is composed of 4 doses of nivolumab and 2 doses of lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each treatment cycle, and lirilumab will be administered on Days 1 and 29 of each treatment cycle.

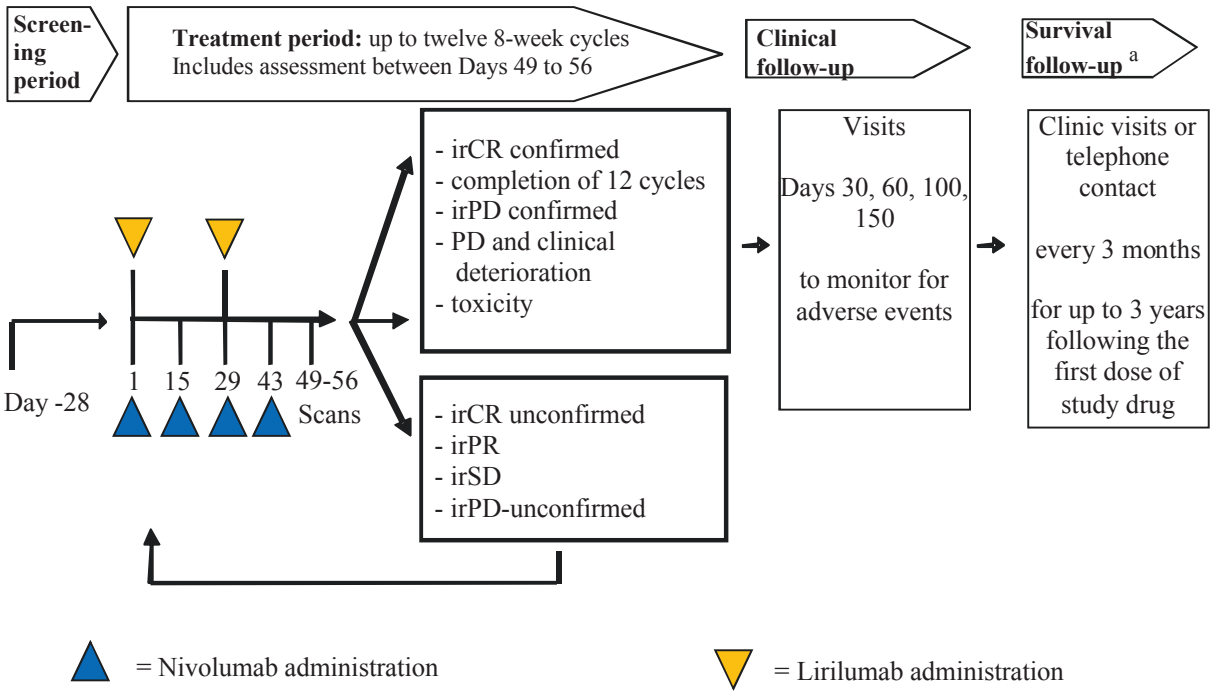
Following each treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next cycle). Treatment decisions related to subject management will be based exclusively on irRECIST for the SCCHN Cohort Expansion (Part 2) (see Section 1.4.14 for the rationale and Appendix 2 for definitions). For the SCCHN Cohort Expansion (Part 2), subjects with an overall response of irPD-unconfirmed, irSD, irPR, or irCR-unconfirmed at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of any of the following: 1) achievement of irCR-confirmed; 2) completion of 12 cycles; 3) confirmation of irPD; 4) clinical deterioration suggesting that no further benefit from treatment is likely; 5) intolerability to therapy; or 6) meeting criteria for discontinuation of study therapy as outlined in Sections 3.5 and 4.9.5.

The subjects listed above will enter the clinical follow-up period, with visits scheduled on Days 30, 60, 100, and 150 to monitor for AEs.

A study schematic is presented below in Figure 3.1.2-1.

The SCCHN Cohort Expansion (Part 2) of this study closed to enrollment when the SCCHN Randomized Cohorts (Part 3) opened.

Figure 3.1.2-1: Study Period Schematic for Part 2 (Completed)



[a] Survival follow-up no longer applicable with Revised Protocol 12

3.1.3 The SCCHN Randomized Cohorts (Part 3 closed to enrollment)

To further explore emerging efficacy and safety data in subjects with SCCHN, lirilumab in combination with nivolumab and nivolumab monotherapy will be evaluated in a single-blind, placebo-controlled, randomized, expansion study. All subjects will submit fresh tumor biopsies that will be tested for PD-L1 status, and subjects will be enrolled if they have PD-L1+ tumors. (Refer to Section 5.7.3.1 for the definition of PD-L1+.)

Subjects will be treated with 1 of the following:

- Arm A: flat dose of lirilumab 240 mg Q4W (Days 1 and 29) and flat dose of nivolumab 240 mg Q2W (Days 1, 15, 29, 43) until PD
- Arm B: placebo for lirilumab Q4W (Days 1 and 29) and flat dose of nivolumab 240 mg Q2W monotherapy (Days 1, 15, 29, 43) until PD

Approximately 225 subjects will be randomized to the 2 treatment arms in a 2:1 ratio (150 subjects to Arm A and 75 subjects to Arm B) and stratified by the following factors: PD-L1 ≥ 50% expression and prior treatment with cetuximab.

Subjects will complete up to 4 study periods: screening, treatment, clinical follow-up, and survival follow-up. **Screening** (up to 35 days). **Treatment** (until PD, treatment discontinuation, or a maximum of up to 12 cycles of treatment, whichever occurs earliest). **Clinical follow-up** (150 days). **Survival follow-up** (up to 3 years following the first dose of study drug). With revised protocol 12, the total time on study for any individual subject will not exceed approximately 2.5 years. Survival follow-up is no longer applicable with Revised Protocol 12.

The treatment begins with the contact to the Interactive Voice Response System (IVRS) to randomize the subject. Randomization should take place within approximately 35 days of enrollment. The treatment period will last up until PD for the SCCHN Randomized Cohorts (Part 3). For subjects receiving lirilumab and nivolumab combination therapy in Arm A of the SCCHN Randomized Cohorts (Part 3), each 8-week treatment cycle is composed of 4 doses of nivolumab and 2 doses of lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each treatment cycle, and lirilumab will be administered on Days 1 and 29 of each treatment cycle. For subjects in Arm B receiving nivolumab monotherapy, each treatment cycle is composed of 4 doses of nivolumab and 2 doses of placebo for lirilumab. Nivolumab will be administered on Days 1, 15, 29, and 43 of each treatment cycle, and placebo for lirilumab will be administered on Days 1 and 29 of each treatment cycle.

Following each 8-week treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next cycle). Treatment decisions related to subject management will be based on RECIST v1.1 (see Appendix 3). Subjects will generally be allowed to continue study therapy until the first occurrence of any of the following: 1) PD (confirmed or unconfirmed); 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) intolerability to therapy; 4) meeting criteria for discontinuation of study therapy as outlined in Sections 3.5 and 4.9.5 or 5) maximum treatment duration of 12 treatment cycles.

The subjects listed above will enter the clinical follow-up period, with visits scheduled on Days 30, 60, 100, and 150 to monitor for AEs.

A study schematic of the study period is presented below in Figure 3.1.3-1.

Tumor progression or response endpoints will be assessed using a centralized imaging review (independent radiologic review committee) and the RECIST v1.1 criteria. With Revised Protocol 12, submission of scans to centralized imaging review is no longer required. For the purposes of subject management, clinical decision making will be based on investigator-assessed radiographic assessment using RECIST v1.1. Therefore timepoint tumor response evaluations will be recorded on the case report form (CRF) based on investigators' assessments using RECIST v1.1 criteria.

Dose reductions will be not be allowed for lirilumab or nivolumab. Crossover will not be permitted.

The primary endpoint is ORR based on IRC assessment.

The study design schematic is presented in Figure 3.1.3-2. See Section 3.1 for a description of the study phases for this cohort.

Figure 3.1.3-1: Study Design Schematic for the SCCHN Randomized Cohorts (Part 3)

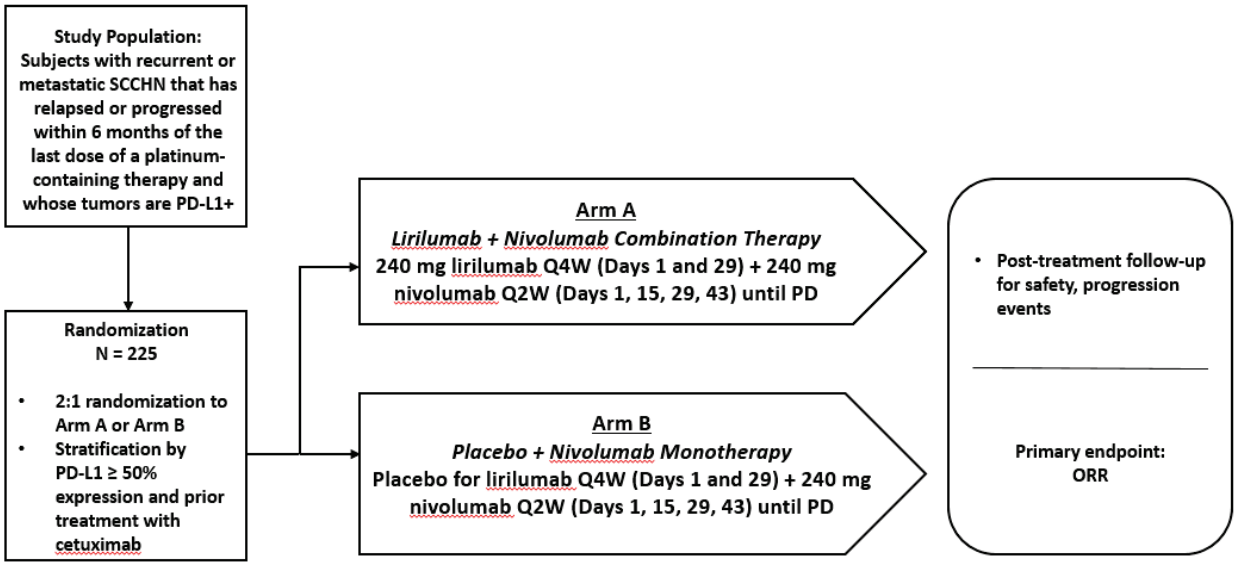
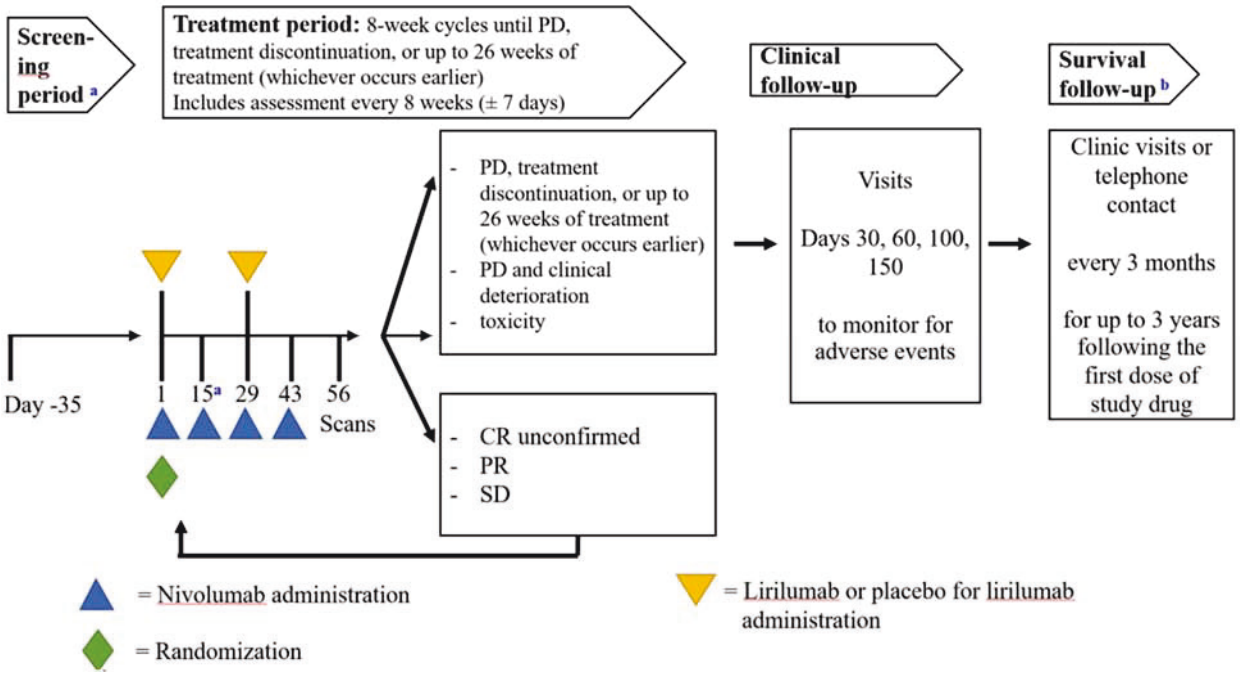


Figure 3.1.3-2: Study Period Schematic for the SCCHN Randomized Cohorts (Part 3)



[a] Biopsy will be taken at screening and at Day 15 (± 3days).

[b] Survival follow-up no longer applicable with Revised Protocol 12

3.1.4 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

3.1.5 The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)

The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) is an open-label, Phase 2 cohort expansion study in subjects ≥ 18 years old with platinum-refractory recurrent or metastatic SCCHN that is not amenable to curative therapy evaluating lirilumab in combination with nivolumab and ipilimumab as a treatment. There will be continuous monitoring of safety via a safety lead-in, described in detail later in this section. Subjects must have tumor progression or recurrence after prior platinum-containing systemic therapy for recurrent or metastatic disease. In addition, subjects who have progressed within 6 months of platinum-based therapy used as part of concurrent chemoradiation (definitive or adjuvant therapy) are also eligible.

All subjects in this cohort with be tested for PD-L1 status. All testing for PD-L1 status will be performed on a fresh biopsy obtained during screening, and results must be available prior to randomization. In the event that the biopsy sample collected during screening is not evaluable for PD-L1, the site will be notified and an archival specimen may be submitted for PD-L1 testing. Additional subjects may be enrolled, if necessary, to ensure an adequate representation of the patient population (ie, non-, lower-, and higher-PD-L1 expressers). [redacted] (see Sections 5.7.3.1 [redacted]). Subjects will undergo PD-L1 [redacted] screening evaluations to determine eligibility within 35 days prior to enrollment.

Subjects will be treated with lirilumab, nivolumab, and ipilimumab combination (see Table 5.1.4-2 for dosing schedule) as follows:

- Nivolumab 3 mg/kg IV Q2W (± 3 days)
- Ipilimumab 1 mg/kg IV Q6W (± 3 days) following the administration of nivolumab
- Lirilumab 3 mg/kg IV Q4W (± 3 days) will be the final drug administered on any specific treatment day

Approximately 40 subjects will be enrolled.

The total duration of the study from enrollment to primary endpoint ORR analysis is expected to be approximately 21 months, assuming 12 to 15 months accrual duration.

Subjects will complete up to 4 study periods: screening, treatment, clinical follow-up, and survival follow-up. **Screening** (up to 35 days). **Treatment** (until PD, treatment discontinuation, or a maximum of 8 cycles of treatment, whichever occurs earlier). **Clinical follow-up** (150 days). **Survival follow-up** (up to 3 years following the first dose of study drug). With revised protocol 12, the total time on study for any individual subject will not exceed approximately 2.5 years. Survival follow-up is no longer applicable with Revised Protocol 12.

The treatment begins with the contact to the IVRS to assign the subject's treatment. The first dose of study drug should take place within approximately 35 days of enrollment. The treatment period will last up until PD for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5). Nivolumab will be administered Q2W, ipilimumab will be administered Q6W, and lirilumab will be administered Q4W in all subjects.

Safety lead-in: There will be continuous monitoring of safety. Initially approximately 10 subjects will be enrolled and followed for at least 4 weeks of safety assessment from the start of study drug administration before additional subjects are enrolled in the study to ensure there is no major safety signal with the combination. Any findings will be discussed between the BMS Medical Monitor and investigators and an agreement will be reached as to whether a lower dose or an alternate dose schedule should be examined or whether any additional treatment guidelines should be implemented prior to enrollment of additional subjects on study.

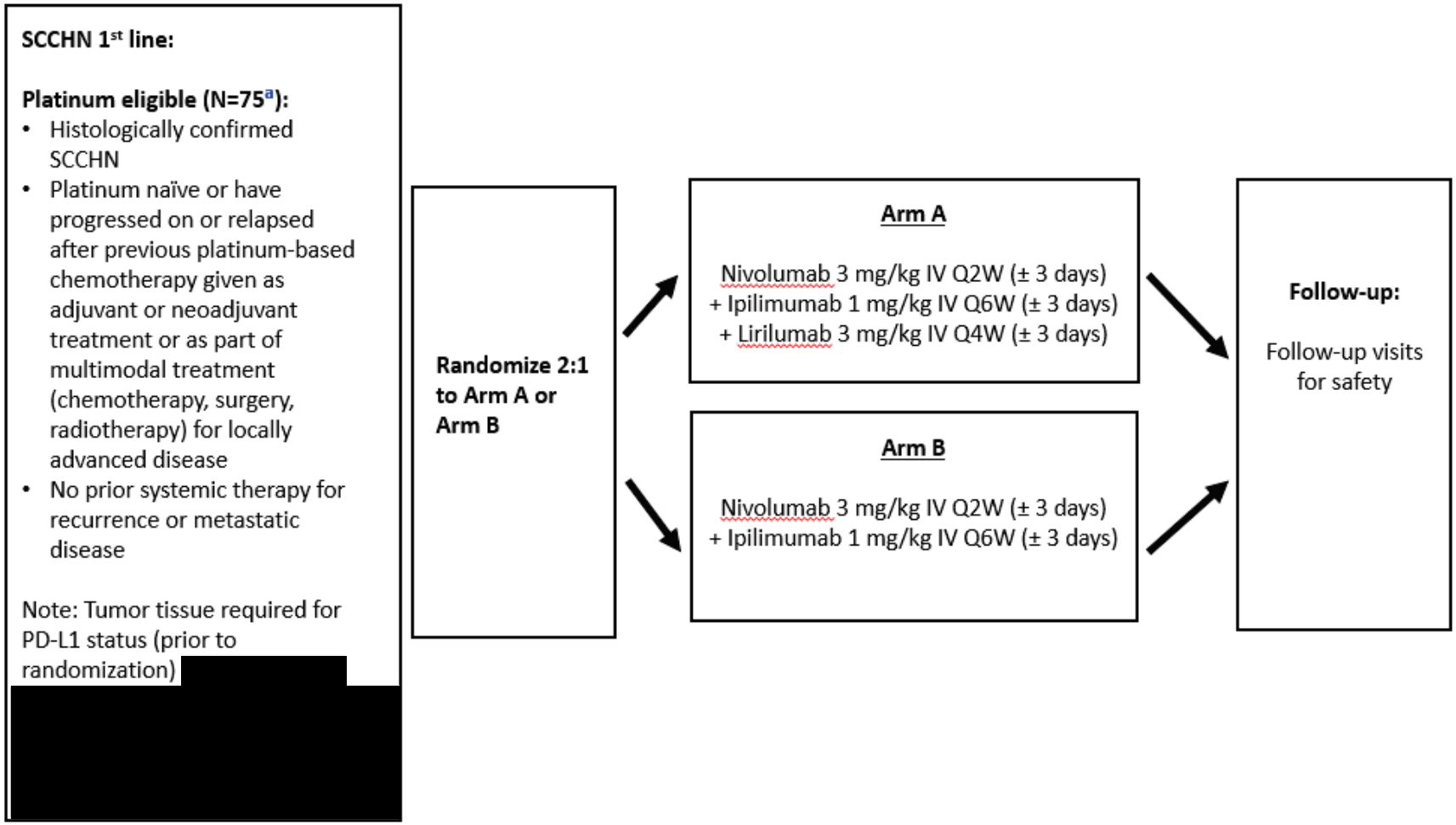
Following each treatment cycle (12 weeks of study therapy consisting of 6 doses of nivolumab given Q2W, 2 doses of ipilimumab given Q6W, and 3 doses of lirilumab given Q4W), the decision to treat a subject with additional study therapy will be based on tumor assessment done Q8W (evaluation performed Q8W and completed before study therapy is continued). Treatment decisions related to subject management will be based on investigator-assessed radiographic assessment using RECIST v1.1 (see Appendix 3). Subjects with an overall response of SD, PR, or CR-unconfirmed at the time of each assessment may continue study drug. Subjects will generally be allowed to continue study drug until the first occurrence of any of the following: 1) achievement of CR-confirmed; 2) PD (confirmed or unconfirmed); 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; 5) meeting criteria for discontinuation of study therapy as outlined in Sections 3.5 and 4.9.5 or 6) maximum treatment duration of 8 treatment cycles.(See section 3.5.1).

The subjects listed above will enter the clinical follow-up period, with visits scheduled on Days 30, 60, 100, and 150 to monitor for AEs.

A study period schematic is presented below in Figure 3.1.5-1 and Figure 3.1.5-2.

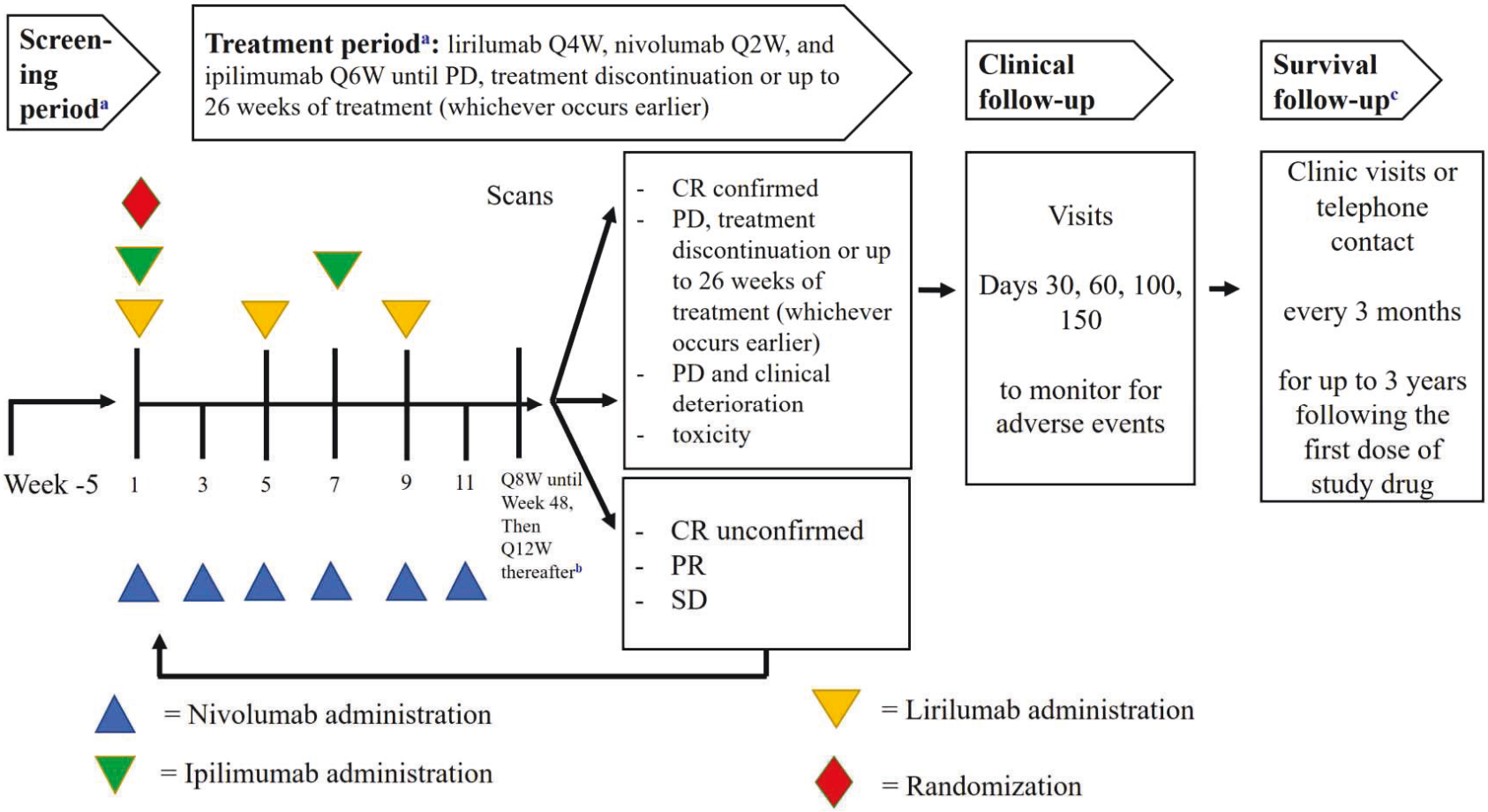
For the purposes of subject management, clinical decision-making will be based on RECIST v1.1. Therefore, timepoint tumor response evaluations will be recorded on the CRF based on investigators' assessments using RECIST v1.1 criteria.

Figure 3.1.5-1: Study Schematic for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5)



[a] Biopsy will be taken at screening. Initially approximately 10 subjects will be enrolled and followed for at least 4 weeks of safety assessment from the start of study drug administration before additional subjects are enrolled in the study to ensure there is no major safety signal with the combination.

Figure 3.1.5-2: Study Period Schematic for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5)



[a] Biopsy will be taken at screening and Day 15 (± 3 days). Initially approximately 10 subjects will be enrolled and followed for at least 4 weeks of safety assessment from the start of study drug administration before additional subjects are enrolled in the study to ensure there is no major safety signal with the combination.

[b] Until PD, treatment discontinuation, or a maximum of 8 cycles of treatment, whichever occurs earliest.

[c] Survival follow-up no longer applicable with Revised Protocol 12

3.1.6 The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

3.2 Post-study Access to Therapy

At the end of the treatment phase of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study. No exceptions to these criteria will be granted by the Sponsor.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The subject must sign the informed consent form prior to the performance of any study related procedures that are not considered part of standard of care.

2) Target Population

a) Subjects must have histologic or cytologic confirmation of a solid malignancy that is advanced (metastatic and/or unresectable):

i. Dose Escalation (Part 1) Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

i. All solid tumor histologies will be permitted during dose escalation, except for subjects with primary CNS tumors or with CNS metastases as the only site of active disease.

ii. Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists (except for subjects with MEL).

ii. Cohort Expansion (Part 1) Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

i. The following 5 tumor types will be permitted during cohort expansion.

1. NSCLC

a) Must have recurrent or PD during or after platinum doublet-based chemotherapy for advanced or metastatic disease *or* must have recurrent or PD within 6 months after completing platinum-based chemotherapy for local disease.

b) Subjects must have known epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status.

c) Subjects with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor.

d) Subjects with an ALK translocation must have received an ALK inhibitor.

2. MEL

a) Must have received prior therapy with ipilimumab.

b) BRAF mutation status must be known, and if a BRAF mutation (V600E or V600K) is present, the subject must have received a RAF or a MEK inhibitor.

3. CRC

a) Subjects must have phenotypes:

i. Microsatellite instability (MSI) stable (no alterations) or MSI low (only 1 alteration) with MSI expression detected by an accredited laboratory per local process. See Section 5.3.1 or

ii. Deoxyribonucleic acid (DNA) mismatch repair gene proficient on tumor immunohistochemistry (IHC).

b) Known Kirsten Ras (KRAS) mutation status.

c) Prior therapy requirement:

i. Must have received at least 1 standard systemic therapy, such as fluoropyrimidine, oxaliplatin or irinotecan, bevacizumab, cetuximab or panitumumab (if KRAS wild type), or regorafenib.

or

ii. Subject refused standard therapy for the treatment of metastatic (Stage 4) or locally advanced disease. The subject's refusal must be documented.

4. SCCHN (oral cavity, pharynx, larynx)

a) Must document HPV status and subtype, particularly HPV16 and HPV18.

b) Must have evidence of progression or recurrence within 6 months of last dose of platinum therapy.

c) Radiation therapy must have been completed at least 4 weeks prior to study drug administration.

5. HCC that is not amenable to surgical resection
    a) Subjects must have PD, or been intolerant to, at least 1 line of therapy or refuse treatment with sorafenib.
    b) Child-Pugh score of B (7 points or less and must not have encephalopathy) (see Appendix 5).
    c) Subjects must have testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA polymerase chain reaction (PCR), hepatitis C antibody, hepatitis C ribonucleic acid (RNA) PCR.
    d) Subjects with hepatitis B infection must have hepatitis B DNA viral load < 100 IU/mL and must be on anti-viral therapy per institutional guidelines.
    e) Subjects with hepatitis B infection must not have co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).
    f) Subjects must not have clinically significant ascites or clinically significant variceal bleeding.
6. The SCCHN Cohort Expansion (Part 2; completed) in squamous cell carcinoma of the head and neck (oral cavity, pharynx, larynx) Not applicable starting with Protocol Amendment 13 and all subsequent amendments.
    a) Histologically confirmed, incurable, locally advanced, recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage 3/4 and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
    b) Confirmation of tumor HPV status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.
    c) Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (eg, superficial skin lesion as per RECIST v1.1) or a lesion that has been

visualized, photographically recorded with measurements, and shown to have progressed.

d) Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

e) Subjects must consent to allow the acquisition of existing FFPE material for performance of correlative studies including (but not limited to) the analysis of PD-L1 expression by IHC (additional subjects may be enrolled if necessary to ensure an adequate number of higher PD-L1 expressers):

i. FFPE tissue may be in the form of either a block or unstained slides, but a fresh biopsy may be performed when a subject's prior archived tumor tissue has been exhausted;

ii. Tumor tissue must be confirmed as shipped to the central laboratory prior to subjects receiving study drug.

ii. Subjects must have ≤ 5 prior treatment regimens. The following are not considered separate lines of treatment: addition of a compound to an ongoing regimen, restarting the same regimen after a drug holiday, or switching from IV to oral therapy.

iii. The SCCHN Randomized Cohorts (Part 3 - enrollment closed)

1. Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage 3/4 and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

2. Documentation of p16-positive or p16-negative disease to determine HPV status of tumor for SCCHN of the oropharynx.[39] Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis and confirmed as shipped.

3. Tumor progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (eg, superficial skin lesion as per RECIST v1.1) or

a lesion that has been visualized and photographically recorded with measurements and shown to have progressed.

4. Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

5. Subjects must be PD-L1+ on fresh biopsies by IHC testing performed by the central laboratory during the screening period. Refer to Section 5.7.3.1 for the definition of PD-L1+.

iv. The Signal Detection Cohort Expansion (Part 4 - removed with Revised Protocol 12)

1. Squamous non-small cell lung cancer:

a) Subjects with histologically or cytologically documented squamous cell NSCLC who present with Stage IIIB/Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or PD following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease).

b) Subjects must have experienced disease recurrence or progression during or after 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

i. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.

ii. Subjects who received platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

iii. Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.

c) Subjects must be PD-L1+ on fresh biopsies by IHC testing performed by the central laboratory during the

screening period. Refer to Section 5.7.3.1 for the definition of PD-L1+.

2. Squamous cell esophageal cancer:

   a) Subjects with histologically confirmed ESCC who must meet all of the following:

      i. Subjects must have progression or refractory disease. Subjects must have had at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease.

      or

      ii. Subject actively refuses chemotherapy or biological therapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. Subjects actively refusing chemotherapy must have had progression or refractory disease prior to starting study drug. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the Sponsor's Medical Monitor to confirm eligibility.

3. Bladder cancer:

   a) Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter, or renal pelvis. Minor histologic variants (< 50% overall) are acceptable.

      i. Subjects must have metastatic or surgically unresectable (cT4b, or any N+ [N1-3], or any M-1) disease.

   b) Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.

4. Other Squamous Histologies:

   a) Histologic or cytological confirmation of squamous cell carcinoma (excluding SCCHN, sqNSCLC, and ESCC) that is advanced (metastatic, recurrent and/or unresectable) such as, but not limited to, SCC of the skin,

cervix, vulva, vagina, penis, anorectal and of unknown primary site.

b) Participants must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.

c) HPV status (except for SCC of the skin) must be documented if known.

5. Subjects with SCCHN who have received prior PD-1/PD-L1 directed therapy:

a) Histologically confirmed, incurable, locally advanced, recurrent or metastatic SCCHN (oral cavity, pharynx, and larynx), Stage 3/4, and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

b) Documentation of p16-positive or p16-negative disease to determine HPV status of tumor for SCCHN of the oropharynx.[39] Note: If results are not available, then a sample (tissue on microscopic slides, tissue block, or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis and confirmed as shipped.

c) Subjects must have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy.

d) The last dose of prior anti-PD-1/anti-PD-L1 must be ≥ 28 days from initiation of study therapy.

e) Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed ≥ 2 weeks before study drug administration.

f) Subjects must be PD-L1+ on fresh biopsies by IHC testing performed by the central laboratory during the screening period. Refer to Section 5.7.3.1 for the definition of PD-L1+.

v. The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - enrollment closed)

1. Histologically confirmed SCCHN, from any of the following primary sites only: oral cavity, oropharynx, hypopharynx, and larynx [redacted].

2. Subjects must have metastatic or recurrent SCCHN that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects who refuse potentially curative salvage surgery for recurrent disease are ineligible. Subjects must have tumor progression or recurrence after prior platinum-containing systemic therapy for recurrent or metastatic disease. In addition, subjects who have progressed within 6 months of platinum-based therapy used as part of concurrent chemoradiation (definitive or adjuvant therapy) are also eligible.

[redacted]

4. Submission of tumor tissue specimen to the central laboratory for documentation of PD-L1 status by IHC at screening. Subject must have documentation of PD-L1 status by IHC performed by the central lab at randomization. Sample must be from a tumor biopsy collected during screening. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.
5. Prior palliative radiotherapy must have been completed at least 4 weeks prior to first dose of study drug if radiotherapy was to the head and neck region and 2 weeks prior to first dose of study drug if radiotherapy was to other regions.

vi. The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed with Revised Protocol 12)

1. Histologically confirmed unresectable Stage 3 or 4 MEL as per American Joint Committee on Cancer staging system.
2. Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period.
3. Treatment-naïve subjects (ie, no prior systemic anticancer therapy for unresectable or metastatic MEL).
    a) Note: Prior adjuvant or neoadjuvant MEL therapy is permitted if it was completed at least 6 weeks prior to randomization and all related AEs have either returned to baseline or stabilized.

4. Submission of tumor tissue specimen to the central laboratory for documentation of PD-L1 status by IHC at screening. Subject must have documentation of PD-L1 status by IHC performed by the central lab at randomization. Sample must be from a tumor biopsy collected during screening biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.

b) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for response assessment. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately. As of Protocol Amendment 13, subjects undergoing biopsy do not need to have a biopsy lesion that is distinct from an index lesion.

c) Subjects must consent to allow the acquisition of existing FFPE material tissue block or tumor tissue sections for performance of correlative studies. In the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed), for NSCLC, tissue must have been collected within 6 months of study entry. For MEL, tissue must have been collected after prior systemic therapy, if any (these criteria related to the Dose Escalation and Cohort Expansion [Part 1; completed] and the SCCHN Cohort Expansion [Part 2; completed] are not applicable starting with Protocol Amendment 13 and all subsequent amendments).

   i. In the SCCHN Randomized Cohorts (Part 3) and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5): Subjects must consent to allow the acquisition of existing FFPE material tissue block or tumor tissue sections for performance of correlative studies. **All subjects will be required to provide fresh biopsies at baseline** if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable. In addition, all subjects in the SCCHN Randomized Cohorts (Part 3) and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) will be **required to provide a fresh on-treatment biopsy** if risk is acceptable. Fresh biopsy samples obtained during screening must be submitted to the central laboratory for PD-L1 testing prior to subjects receiving study drug. In the event that the biopsy sample collected during screening is not evaluable for PD-L1, the site will be notified and an archival specimen may be submitted for PD-L1 testing.

d) A minimum of 10 subjects each in the MEL cohort and the SCCHN cohort (the Dose Escalation and Cohort Expansion [Part 1; completed]) will be required to undergo mandatory pre-treatment and on-treatment biopsies in the cohort expansion phase at acceptable clinical risk as judged by the investigator. All other subjects will have the option of undergoing pre-treatment, on-treatment, and post-treatment biopsies. The biopsy lesion must be distinct from an index lesion. In the SCCHN Cohort Expansion (Part 2; completed); a minimum of 15 subjects will be required to undergo mandatory pre-treatment and on-treatment biopsies at acceptable clinical risk as judged by the investigator. The biopsy lesion cannot be the sole lesion of measureable disease. Additional subjects may be enrolled in order to satisfy this requirement. These criteria related to the Dose Escalation and Cohort Expansion (Part 1; completed) and the

SCCHN Cohort Expansion (Part 2; completed) are not applicable starting with Protocol Amendment 13 and all subsequent amendments.

e) The first dose of study drug must be at least 28 days from the last dose of prior therapy.

f) ECOG status of 0 or 1.

g) Life expectancy of ≥ 12 weeks.

h) Adequate organ function for all subjects except those with HCC as defined by the following:

   i. White blood cell (WBC) ≥ 2000/μL

   ii. Neutrophils ≥ 1500/μL

   iii. Platelets ≥ 100×10^3/μL

   iv. Hemoglobin ≥ 9.0 g/dL

   v. Creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

   vi. ALT and AST ≤ 3 × ULN

   vii. Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who must have a total bilirubin level of < 3.0 × ULN)

   viii. Normal thyroid function, or have controlled thyroid disorder

i) Adequate organ function for all HCC subjects as defined by the following. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

   i. WBC ≥ 2000/μL (stable off any growth factor within 4 weeks of first study drug administration)

   ii. Neutrophils ≥ 1000/μL (stable off any growth factor within 4 weeks of first study drug administration)

   iii. Platelets ≥ 40×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

   iv. Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

   v. Creatinine ≤ 1.5 × ULN

   vi. ALT and AST ≤ 5 × ULN

   vii. Total bilirubin ≤ 3 mg/dL

   viii. International normalized ratio ≤ 2.3 or prothrombin time ≤ 6 sec above control

   ix. Albumin ≥ 2.8 g/dL

   x. Normal thyroid function, or have controlled thyroid disorder

j) Ability to comply with treatment, PK and pharmacodynamics sample collection and required study follow-up.

k) Subject re-enrollment: this study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

l) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

m) Subjects must have resting baseline oxygen saturation measured by pulse oximetry of ≥ 92% at rest on room air.

3) Age, Sex, and Reproductive Status

a) Men and women, ages ≥ 18 years.

b) Women of childbearing potential (WOCBP) must have a negative 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 drug.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study drug (ie, 30 days [duration of ovulatory cycle] plus the time required for the study drug to undergo approximately 5 half-lives.)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study drug (ie, 90 days [duration of sperm turnover] plus the time required for the study drug to undergo approximately 5 half-lives.)

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception (see Appendix 6).

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with untreated CNS metastases. Subjects are eligible if CNS metastases have been adequately treated and have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks. In addition, subjects must be either off corticosteroids or on a stable or decreasing dose of prednisone 10 mg daily (or equivalent) for at least 2 weeks. Please note: For SCCHN subjects only, cases including base of skull lesions without definitive evidence of dural or brain parenchymal involvement, should be discussed with the Medical Monitor.

b) Participation in any prior clinical study with ipilimumab or with nivolumab, including subjects in comparator arms (including CA209651 and CA209714), in which OS is listed as the primary or co-primary endpoint and which has not completed analysis based on the primary endpoint.

c) SCCHN subjects only: Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, and the skin and salivary gland or non-squamous histologies are not allowed.

d) Subjects with carcinomatous meningitis.

2) Medical History and Concurrent Diseases

a) Subjects with previous malignancies (except non-MEL skin cancers, and the following in situ cancers: bladder, gastric, colon, esophageal endometrial, cervical/dysplasia, MEL, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.

b) Subjects with an active, known, or suspected autoimmune disease. Subjects 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.

c) A known or underlying medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study drug hazardous to the subjects (such as ongoing interstitial pneumonitis), or could adversely affect the ability of the subject to comply with or tolerate study. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

d) Uncontrolled or significant cardiovascular disease including, but not limited to any of the following:

i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

ii) Uncontrolled angina within the past 3 months

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation or torsades de pointes)

iv) QTc prolongation > 480 msec

v) History of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association functional classification 3 to 4, pericarditis, significant pericardial effusion)

vi) Requirement of daily supplemental oxygen therapy

vii) History of myocarditis

e) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. No HIV testing is required during screening. NOTE: Testing for HIV must be performed at study sites where mandated locally.

i) Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

ii) Subjects with a history of resolved hepatitis A virus infection are eligible. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

f) Evidence of active infection ≤ 7 days prior to initiation of study drug therapy (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry). Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

g) Any serious or uncontrolled medical disorders.

h) Any major surgery within 4 weeks of study drug administration.

i) Subjects who are unable to undergo venipuncture and/or to tolerate venous access. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

j) Any other sound medical, psychiatric and/or social reason as determined by the investigator. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

k) All toxicities attributed to systemic prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 [v4.03]) or baseline before administration of study drug. Subjects with toxicities attributed to systemic prior anti-cancer therapy, that are not expected to resolve, and that result in long lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.

l) Subjects with a condition requiring systemic treatment with either corticosteroids (prednisone > 10 mg daily or equivalent) or other immunosuppressive medications within 14 days of start of study drug (or randomization, for the SCCHN Randomized Cohorts [Part 3] and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5]). Inhaled or topical steroids, and adrenal replacement steroid doses prednisone > 10 mg daily or equivalent, are permitted in the absence of active autoimmune disease.

3) Prohibited Prior Treatments and/or Therapies

a) Prior treatment with an anti-KIR antibody or an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways except as noted below.

b) Prior treatment regimens with any immune cell modulating antibody such as anti-CD137 and anti-OX40. However, prior anti-CTLA-4 therapy is allowed if the last dose is 101 days or more from the first dose of study drug. Not applicable starting with Amendment 13 and all subsequent amendments.

c) Exposure to any other investigational drug within 4 weeks prior to the first dose of study drug.

d) Treatment with any anti-cancer therapy, chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study drug (subjects with prior radiation, cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and Sponsor, if toxicities from the prior treatment have been resolved to Grade 1 [NCI CTCAE v4.03]).

e) Prior focal palliative radiotherapy within 2 weeks prior to the first dose of study administration.

f) Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to study drug. The use of the inactivated seasonal influenza vaccine (Fluzone®) is allowed. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

g) Use of growth factors, including, but not limited to, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, or erythropoietin within 4 weeks prior to the first dose of study drug. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

h) Use of packed red blood cells or platelet transfusion within 2 weeks prior to the first dose of study drug. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

i) Inhaled or topical steroids and adrenal replacement doses prednisone > 10 mg/day or equivalent are permitted in the absence of active autoimmune disease.

j) Use of receptor activator of nuclear factor kappa-B ligand inhibitors within 10 weeks prior to the first dose of study drug. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

k) Use of bisphosphonates within 4 weeks prior to the first dose of study drug. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

l) Use of any medicinal herbal preparations within 2 weeks prior to the first dose of study drug. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

4) Physical and Laboratory Test Findings

a) Positive tests for HIV antibody (may obtain additional testing or substitute testing per institutional guidelines to rule out infection) or known acquired immunodeficiency syndrome.

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

i) Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

ii) Subjects with a history resolved hepatitis A virus infection are eligible. Not applicable starting with Protocol Amendment 13 and all subsequent amendments.

c) Any Grade 4 laboratory abnormalities.

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components (eg, history of severe hypersensitivity reactions to drugs formulated with polysorbate 80).

6) Sex and Reproductive Status

a) Women who are pregnant or are breastfeeding.

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

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

3.3.3 Women of Childbearing Potential

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is **not** postmenopausal.

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

Females treated with 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 durations of the washout periods below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

- 1 week minimum for vaginal hormonal products (ie, rings, creams, and 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents (except as stated in Section 3.4.3).
- Immunosuppressive doses of systemic corticosteroids (except as stated in Sections 3.4.2 and 3.4.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents).

3.4.2 Other Restrictions and Precautions

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

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses prednisone > 10 mg daily are permitted. A brief (< 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.

Subjects may continue to receive HRT.

Regular concomitant use of bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANK-L) inhibitors for prevention or reduction of skeletal-related events in subjects with bone metastases is allowed if initiated prior to first dose of study drug. Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization

Prior palliative radiotherapy must have been completed at least 4 weeks prior to randomization for cases of radiotherapy to the head and neck, and completed within 2 weeks prior to randomization for radiotherapy to other sites. On-study palliative radiotherapy is only allowed for treatment of painful bone lesions. Palliative surgical resection of tumor sites is not permitted. Subjects requiring palliative radiotherapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects must discontinue study drug.

The potential for overlapping toxicities with radiotherapy and nivolumab/lirilumab; nivolumab/ipilimumab/lirilumab and nivolumab/ipilimumab currently is not known; however, anecdotal data suggest these combinations may be tolerable. As concurrent radiotherapy and the IO combination therapy have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then study drug should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade $\leq$ 1 prior to resuming nivolumab or nivolumab plus ipilimumab.

Palliative and supportive care for disease related symptoms may be offered to all subjects on the study; for subjects in the Dose Escalation and Cohort Expansion (Part 1; completed), this must be after the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for subjects who have investigator-assessed clinical benefit (eg, irSD or irPR) following consultation with the BMS Medical Monitor. Subjects should not receive study drug during radiation or surgery.

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, laboratory abnormality, clinical deterioration, or concurrent illness that in the opinion of the investigator indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

- Documented and confirmed irPD as defined by irRECIST for the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed) (see Appendix 2).
- Documented PD for the SCCHN Randomized Cohorts (Part 3), and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) as defined by RECIST v1.1 (see Appendix 3).
- Documented and confirmed irCR as defined by irRECIST for the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed) (see Appendix 2)
- Documented and confirmed CR for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) as defined by RECIST v1.1 (see Appendix 3).
- Discretion of the investigator
- Inability to comply with the protocol requirements
- Protocol defined reasons for discontinuation (see Section 4.9.5)
- Maximum treatment duration of up to a maximum of 2 years; 12 cycles in Parts 1, 2, and 3 or 8 cycles in Part 5.

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject withdraws consent for all study procedures 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 drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.5.1 Treatment Beyond Disease Progression

With Revised Protocol 12, no additional subjects are permitted to enter Treatment Beyond Disease progression. At the time of initial progressive disease, subjects will be required to discontinue study treatment and enter clinical follow-up.

As defined in Section 5.4; treatment related decisions will be governed by irRECIST based response assessments. The proposed irRECIST criteria allows for continued study therapy beyond initial RECIST v1.1 defined PD and will only be permitted provided the following criteria are met:

- Clinical benefit as assessed by the investigator
- Disease progression is not rapid

- Continues to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subjects have provided written informed consent prior to receiving additional treatment with their assigned treatment.

In the combination setting, subjects who meet criteria may continue on lirilumab and nivolumab in combination but may not continue on 1 treatment or the other alone.

For the SCCHN Randomized Cohorts (Part 3), and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), decisions related to treatment beyond progression will be made with RECIST v1.1.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measureable 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 least15 mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable 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).

3.6 Treatment of Infusion Reactions

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (v4.03) guidelines.

Of note, since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

Treatment recommendations applicable for all study drugs are provided below and may be modified based on local treatment standards and guidelines as appropriate:

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

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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 no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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; presser or ventilatory support indicated).

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

If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated.

The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or SAE page.

When slowing or restarting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (± 5 minutes) or as directed by the investigator until the infusion is completed

and/or the subject is stabilized. If a subject has an infusion reaction with nivolumab, the lirilumab, ipilimumab, or placebo for lirilumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the lirilumab, ipilimumab, or placebo for lirilumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

3.7 Post-treatment Study Follow-up

Overall survival data will no longer be collected with Revised Protocol 12.

In this study, OS is a secondary endpoint for the SCCHN Randomized Cohorts (Part 3) [redacted]. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 4.9.5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol-defined window (see Section 5.1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.7.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects 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 drug only or also from study procedures and/or post-treatment study follow-up; the information should be entered on the appropriate CRF page. In the event that vital status (whether the subject 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.

3.7.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the study site will use permissible local methods to obtain the date and cause of death.

If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a BMS-retained third-party representative to assist study site staff with obtaining subject's contact information or

other public vital status data necessary to complete the follow-up portion of the study. If, after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

The study drugs include lirilumab (BMS-986015), nivolumab (BMS-936558), and ipilimumab (BMS-734016). Table 4.1-1 below indicates the Dose Level to be used for each panel in the Dose Escalation and Cohort Expansion (Part 1; Completed). The placebo for lirilumab injection is normal saline injection, which is administered in a similar fashion as described for the lirilumab injection. The normal saline to use as placebo will not be provided by the Sponsor.

Table 4.1-1: Treatment Administration (Dose Escalation and Cohort Expansion [Part 1; Completed])

Dose Level	Lirilumab	Nivolumab
1	0.1 mg/kg	3 mg/kg
2	0.3 mg/kg	3 mg/kg
3	1 mg/kg	3 mg/kg
4	3 mg/kg	3 mg/kg

Product description and storage information is described in Table 4.1-2.

Cohort expansions will be treated at the highest tested dose or a different Dose Level as selected by the Sponsor.

The Dose Escalation and Cohort Expansion (Part 1; completed), and the SCCHN Cohort Expansion (Part 2; completed): For treatment visits where both lirilumab and nivolumab are administered, nivolumab will be administered first followed by lirilumab. Nivolumab will be administered as a 60-minute infusion; 30 minutes after completion of the nivolumab infusion, lirilumab will be administered as a 60-minute infusion.

The SCCHN Randomized Cohorts (Part 3) (Arm A): For treatment visits where both lirilumab and nivolumab are administered, nivolumab will be administered first followed by lirilumab. Nivolumab will be administered as a 30-minute infusion; 30 minutes after completion of the nivolumab infusion, lirilumab will be administered as a 60-minute infusion.

The SCCHN Randomized Cohorts (Part 3) (Arm B): For treatment visits where both placebo for lirilumab and nivolumab are administered, nivolumab will be administered first followed by placebo for lirilumab. Nivolumab will be administered as a 30-minute infusion; 30 minutes after completion of the nivolumab infusion, placebo for lirilumab will be administered as a 60-minute infusion.

The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5): On days when all 3 study drugs are given, nivolumab will be given first followed by ipilimumab followed by lirilumab. Nivolumab will be administered as a 30-minute infusion; 30 minutes after completion of the nivolumab infusion, ipilimumab will be administered as a 30-minute infusion; and 30 minutes after completion of the ipilimumab infusion, lirilumab will be administered as a 60-minute infusion. On days when nivolumab and lirilumab are given, nivolumab will be given first followed by lirilumab. Nivolumab will be administered as a 30-minute infusion; 30 minutes after completion of the nivolumab infusion, lirilumab will be administered as a 60-minute infusion.

Detailed administration instructions will be provided separately via study site training materials and Dosing Procedure Manual.

Table 4.1-2: Product Description and Dosage Form

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (Per Label)
BMS-986015-01 Solution for Injection, 50 mg/vial (10 mg/mL) [a]	10 mg/mL	5-mL vial/open	Box/open	Clear to opalescent, colorless liquid. Essentially free of particles.	Store at 2°C to 8°C (36°F to 46°F) protect from light, protect from freezing
BMS-986015-01 Solution for Injection, 100 mg/vial (10 mg/mL) [a]	10 mg/mL	10-mL vial/open	Box/open	Clear to opalescent, colorless liquid. Essentially free of visible particles.	Store at 2°C to 8°C (36°F to 46°F), protect from light, protect from freezing
BMS-936558-01 Solution for Injection, 40 mg/vial (10 mg/mL) [b]	10 mg/mL	10-mL vial/open	Box/open (as kit containing 2×100 mg vials BMS-936558-01 with 1× 40 mg vial)	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	Store at 2°C to 8°C (36°F to 46°F), Do not freeze. Protect from light.
BMS-936558-01 Solution for Injection, 10 mg/mL, 10 mL (100 mg/vial) [b]	10 mg/mL	10-mL vial/open	Box/open OR Box/open (as kit containing 2×100 mg vials with 1× 40 mg vial BMS-936558-01)	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present	Store 2°C to 8°C (36°F to 46°F); protect from light; protect from freezing.
Ipilimumab Solution for Injection, 5 mg/mL, 40mL (200 mg/vial) [c]	5 mg/mL	50-mL vial/open	Box/open	Clear to slightly opalescent, colorless to pale yellow liquid. Light (few) particulates may be present	Store 2°C to 8°C. Store in original package. Do not freeze. Protect from light.

[a] BMS-986015-01 is also referred to as lirilumab.

[b] BMS-936558-01 is also referred to as nivolumab.

[c] BMS-734016 is also referred to as ipilimumab.

Solutions used as placebo (Normal Saline, ie, 0.9% Sodium Chloride Injection) should be sourced by investigative sites if available and permitted by local regulations. Storage should be in accordance with the product label.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

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) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, investigational product(s) is/are: lirilumab, nivolumab, ipilimumab, and placebo.

4.1.2 Noninvestigational Product

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

In this protocol, noninvestigational product(s) is/are medications used to treat adverse events.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug 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 drug arise, do not dispense the study drug and contact BMS immediately.

4.1.4 Preparation of Study Drug(s)

The study drugs will be administered by IV infusion. Details with regard to IV admixing, infusion rates, and stability will be provided separately in study site training materials and the Dosing Procedure Manual.

4.2 Method of Assigning Subject Identification

CA223001 is an open-label study with the exception of the SCCHN Randomized Cohorts (Part 3), which is site- and subject-blind. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to dosing for the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) and 35 days for all other study parts. Enrolled subjects will be assigned a subject number, [redacted] increasing sequentially with each additional enrolled subject. The subject number will be assigned by the Sponsor via IVRS once the subject signs the informed consent form. Each subject will then be identified by a distinct patient identification number (PID) which is composed of the study site number and the subject number. For example, the first subject screened (ie, enrolled) at study site number 1, will have a

PID [redacted]. The investigator or designee will register the subject following the enrollment procedures established by BMS. The following information is required for registration:

- Date of birth
- Gender
- Diagnosis
- Tumor Type
- Date of Informed Consent
- Planned date of 1st dose

Enrolled subjects meeting all eligibility criteria will be assigned to a dose cohort. Specific instructions regarding enrollment and dose cohort assignment will be provided to the study sites in their training materials.

The SCCHN Randomized Cohorts (Part 3)

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS for the SCCHN Randomized Cohorts (Part 3). Once enrolled in IVRS, enrolled subjects who have met all eligibility criteria and have been assigned to the SCCHN Randomized Cohorts (Part 3) will be ready to be randomized through the IVRS in a 2:1 ratio of Arm A to Arm B:

- Arm A: flat dose of lirilumab 240 mg Q4W (Days 1 and 29) and flat dose of nivolumab 240 mg Q2W (Days 1, 15, 29, and 43) until PD
- Arm B: placebo for lirilumab Q4W (Days 1 and 29) and flat dose of nivolumab 240 mg monotherapy Q2W (Days 1, 15, 29, and 43) until PD

The following information is required for subject randomization:

- Subject number
- Date of birth
- Prior cetuximab treatment (yes/no)
- PD-L1 status

The stratification factor includes:

- PD-L1 $\geq$ 50% expression (yes/no)
- Prior cetuximab treatment (yes/no)

The first dose of study drug is to be administered within 3 days following randomization.

Specific instructions for using IVRS will be provided to the study sites in a separate document.

4.3 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific Dose Level as listed in Table 3.1.1.1-1 in sequential order during dose escalation. Subjects in cohort expansion will be treated at the MTD, the MAD, or at an alternate dose, if recommended by the investigators and the Sponsor.

Subjects in the SCCHN Randomized Cohorts (Part 3) will be treated with a flat dose of nivolumab 240 mg Q2W in combination with a flat dose of lirilumab 240 mg Q4W or placebo for lirilumab Q4W.

Subjects in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) will be treated with a triplet combination of lirilumab 3 mg/kg Q4W, nivolumab 3 mg/kg Q2W, and ipilimumab 1 mg/kg Q6W. If conditions in Section 3.1.5 are met, a lower dose or an alternate dose schedule should be examined.

4.4 Blinding/Unblinding

Applicable for the single-blinded SCCHN Randomized Cohorts (Part 3).

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is the Interactive Response Technology (IRT).

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. Following the unblinding, the investigator shall notify the Medical Monitor and/or study director.

For information on how to unblind for emergency, please consult the IRT manual.

The subjects, investigator, and site staff will be blinded to the study drug administered (lirilumab in combination with nivolumab or nivolumab monotherapy). For all subjects in the SCCHN Randomized Cohorts (Part 3), and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), each investigative site must assign an unblinded

pharmacist/designee and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation.

4.5 Treatment Compliance

Study drug will be administered in the clinical facility. The investigator or their designated study personnel will maintain a log (Drug Accountability Log) of all study drugs received, dispensed and destroyed. The investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during study site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor. For the SCCHN Randomized Cohorts (Part 3), treatment compliance will be monitored by drug accountability as well as the subject's medical record and CRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by BMS or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, 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.

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable

4.8 Dose Limiting Toxicities

This section only applies to the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2), which have both completed enrollment and therefore this section and its subsections are not applicable starting with Amendment 13 and all subsequent amendments or revised protocols.

4.8.1 Definition

DLT will be determined based on the incidence, intensity, and duration of AEs as defined below that are related to study drug and that occur within 56 days (8 weeks, through the completion of Cycle 1) of initiation of study drug in the Dose Escalation and Cohort Expansion (Part 1; completed). The severity of AEs will be graded according to the NCI CTCAE v4.03. Hepatic, non-hematologic, and hematologic DLT will be defined separately as outlined below.

4.8.2 Definition of Hepatic DLT

Any of the following events will be considered a hepatic DLT except for subjects with HCC:

- ALT or AST > 8 × ULN, regardless of duration
- ALT or AST > 5 × and ≤ 8 × ULN, that fails to return to Grade 1 or less within 5 days despite medical intervention
- Grade 3 total bilirubin
- ALT or AST > 3 × ULN and concurrent total bilirubin > 2 × ULN

4.8.2.1 Definition of Hepatic DLT for Subjects with HCC

In August 2011, an advisory board panel was convened to discuss treatment of subjects with hepatitis B infection with or without HCC. The potential for hepatic flare with anti-viral therapy such as entecavir, lamuvidine, or tenofovir was discussed. It was the consensus of the panel members that the risk for this toxicity was low in subjects with low viral DNA loads who were on anti-viral therapy for several months. In subjects with hepatitis C infection, transient Grade 4 transaminase levels can be observed. Protocol Section 4.8.2 describes the hepatic toxicity DLT parameters used for subjects without HCC for this protocol. Due to the potential for hepatic inflammation that could be greater due to viral infection the panel recommended that parameters be adjusted to permit a higher level of hepatic toxicity with AST or ALT > 10 × ULN for > 2 weeks, AST or ALT > 15 × ULN irrespective of duration, total bilirubin > 8 × ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 × ULN for those with normal total bilirubin at study entry, concurrent AST or ALT > 3 × ULN and total bilirubin > 5 × ULN for subjects entering treatment with a normal bilirubin and up to 8 × ULN for subjects with elevated bilirubin, or clinical deterioration manifested by drug-related hepatic decompensation not identified above.

Therefore, for subjects with HCC, hepatic DLT criteria will differ due to intrinsic involvement of the liver. In addition, for subjects with hepatitis B or hepatitis C, it is possible that virological breakthrough may occur, leading to temporary hepatic damage that is greater than the parameters detailed above. In these cases, subjects who regain virologic control may be allowed to resume study therapy after agreement between the PI and the Medical Monitor.

Any of the following events will be considered a hepatic DLT for subjects with HCC:

- ALT or AST > 15 × ULN, regardless of duration
- ALT or AST > 10 × ULN for greater than 2 weeks

- total bilirubin > 8 × ULN regardless of duration for subjects with elevated bilirubin at study entry or > 5 × ULN for subjects with normal bilirubin at study entry
- ALT or AST > 3 × ULN and concurrent total bilirubin > 2 × ULN

4.8.3 Definition of Non-hematologic DLT

Any of the following events will be considered a non-hematologic DLT:

- Grade 2 eye pain or reduction in visual acuity that requires systemic treatment
- Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy
- Grade 3 non-hepatic or non-hematologic toxicity, with the following exceptions:

The following Grade 3 non-hematologic events **will not** be considered DLTs:

- Grade 3 electrolyte abnormality that lasts less than 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
- Grade 3 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
- Grade 3 nausea or vomiting that lasts less than 48 hours, and resolves to Grade 1 or less, either spontaneously or with conventional medical intervention
- Grade 3 fever that lasts less than 72 hours, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)
- 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 less than 6 hours

4.8.4 Definition of Hematologic DLT

Any of the following events will be considered a Hematologic DLT:

- Grade 4 neutropenia that lasts longer than 5 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 3 febrile neutropenia that lasts longer than 48 hours
- Grade 3 hemolysis

4.9 Guidelines for Dose Modification

Intra-subject dose escalation or reduction of lirilumab, nivolumab, and ipilimumab is not permitted in this study in order to allow better evaluation of extended safety and efficacy at individual Dose Levels and schedules.

4.9.1 Intra-subject Dose Escalation

No intra-subject dose escalation is allowed.

4.9.2 Dose Reductions

No dose reductions of lirilumab, nivolumab, and ipilimumab are permitted in this study.

4.9.3 Dose Delays Due To Toxicity

Subjects who experience a DLT must have therapy held. Subjects who are required to permanently discontinue study drug administration are listed in Section 4.9.5. All other subjects will be permitted to resume study drug administration at the same doses for all study drugs following resolution of the AE to Grade 1 or less, or to baseline.

Study drug administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, and total bilirubin will require dose discontinuation (see Section 4.8)
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, warrants delaying the dose of study drug

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when retreatment criteria are met.

4.9.4 Criteria for Subsequent Dosing

Subsequent dosing may continue if subjects continue to meet laboratory criteria as listed in Section 3.3.1. The investigator will determine if subsequent dosing is appropriate for subjects who have laboratory or clinical abnormalities that do not meet DLT (Section 4.8) or discontinuation criteria (Section 4.9.5). All related Grade 2 toxicities should be discussed with the BMS Medical Monitor prior to subsequent dosing.

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.8) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.

- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.9.5 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue all study drugs for the following AEs:

1) Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment
2) For subjects receiving lirilumab in combination with nivolumab or nivolumab monotherapy (the Dose Escalation and Cohort Expansion [Part 1; completed] and the SCCHN Cohort Expansion [Part 2; completed], the SCCHN Randomized Cohorts [Part 3],): Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
   a) Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
   b) Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement, do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
   c) Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
      i) Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding
      ii) Grade ≥ 3 drug-related AST, ALT, or total bilirubin*
      iii) Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

3) For subjects receiving lirilumab in combination with nivolumab and ipilimumab (the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5]): Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
   a) Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
   b) Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement, do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

c) Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

iv) Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding

v) Any drug-related liver function test abnormality that meets the following criteria:

(1) Grade ≥ 3 drug-related AST, ALT, or total bilirubin*

(2) Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

4) Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events, which do not require discontinuation:

a) Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

b) Grade 4 neutropenia ≤ 7 days

c) Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase

d) Grade 4 lymphopenia < 5 days in duration

e) Grade 4 drug-related endocrinopathy AEs, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids or thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

5) Any DLT as outlined in Section 4.8 will require permanent discontinuation with the following exceptions:

a) Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention

b) Grade 3 ALT or AST that returns to Grade 1 or baseline within 7 days with medical intervention

c) Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days or baseline with medical intervention

6) Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

a) Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.

b) Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

c) Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor 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 Q6W or more frequently if clinically indicated during such dosing delays.

7) Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation between the investigator and the study Sponsor.

In cases where the AE meets the criteria for permanent discontinuation from study therapy, but the investigator and the Sponsor believe that re-initiation of study therapy may be potentially beneficial and justified, details will be submitted in advance to the FDA or other relevant health authorities for review, prior to re-initiation of study therapy.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of lirilumab and/or ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for lirilumab and/or ipilimumab but not for nivolumab, treatment with nivolumab may continue if lirilumab and/or ipilimumab is discontinued.

If a subject in any of the study drug combination cohorts meets criteria for discontinuation and investigator is unable to determine whether the event is related to a single study drug, the subject should discontinue all study drugs and be taken off the treatment phase of the study.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

5.1.1 Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

Table 5.1.1-1: Screening Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Screening Visit (D -28 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A subject is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X			
Medical History	X			May include more detailed medical history of risk factors for potential events such as pulmonary related events.
Archived tumor tissue samples	X			One paraffin block or 5 to 15 FFPE unstained slides identified prior to enrollment/randomization. For the SCCHN Cohort Expansion (Part 2), confirmation of tumor tissue receipt at central laboratory is required before subjects receive study drug.
Safety Assessments				
Physical Examination	X			If the screening PE is performed within 24 hours of dosing on Cycle 1 Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Performance Status	X			ECOG Performance Status (see Appendix 7).
Physical Measurements	X			Includes height, weight.
Vital Signs	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation			X[a]	Collected at rest. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate

Table 5.1.1-1: Screening Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Screening Visit (D -28 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
				pulmonary/respiratory status. Changes in oxygen levels will not be used in isolation to document or diagnose pulmonary toxicity.
Electrocardiogram	X			12-lead ECG.
Chest Radiograph	X			
Laboratory Tests		X		Day -14 to -1 prior to Cycle 1 Day 1. To include: CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, glucose, albumin, amylase, lipase, CRP, TSH with reflex (free T3 and free T4), hepatitis B/C, and HIV testing (Subjects with HCC only, PT, PTT, INR, and fibrinogen) If performed within 72 hours of dosing on Cycle 1 Day 1, then Cycle 1 Day 1 laboratories are not required.
HPV Status	X			The Dose Escalation and Dose Cohort (Part 1): SCCHN subjects only. Sites must submit and document prior HPV status and subtype, particularly HPV16 and HPV18 (p16 immunohistochemistry positive or negative status is recommended). The SCCHN Cohort Expansion (Part 2) Sites must submit prior HPV status if known. For subjects with unknown status, tumor tissue will be required, per inclusion criteria. Subjects must consent to HPV testing.
MSI Status	X			CRC subjects only. Sites must submit and document prior MSI testing and results. If MSI status is known prior to study entry, repeat testing will not be required during the screening period, but tissue must be available for repeat MSI testing if requested.
Child-Pugh Score	X			HCC subjects only. See Appendix 5
Serum Pregnancy Test			X [a]	

Table 5.1.1-1: Screening Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Screening Visit (D -28 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
Concomitant Medication		X		Collected for the period 2 weeks prior to Cycle 1 Day 1. (Note: Immunosuppressive medications are recorded on a separate log page.)
Assessment of Signs and Symptoms		X		Collected for the period 2 weeks prior to Cycle 1 Day 1.
Adverse Event Reporting				
Monitor for Serious Adverse Events	X			All SAEs must be collected starting at the time the subject signs informed consent and through 150 days after discontinuation of dosing. SAEs should be approved in TAO within 4 days of entry
Efficacy Assessments				
Diagnostic Imaging	X			CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X			Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases or who have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan	X			As clinical indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Serologic Tumor Markers	X			To include measuring for tumor types with known serologic markers (ie, CEA for subjects with CRC, PSA for subjects with prostate ca, CA-125 for subjects with ovarian/breast cancer, alpha fetoprotein for subjects with HCC, hepatitis B DNA PCR for subjects with hepatitis B, and hepatitis C RNA PCR for subjects with hepatitis C, etc). To be collected prior to the first dose of study drug.

Table 5.1.1-1: Screening Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Screening Visit (D -28 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
Clinical Drug Supplies				
Subject Registration			X	

[a] May be obtained on Cycle 1 Day 1 with results evaluated prior to study drug administration.

BUN = blood urea nitrogen; Ca = calcium; CEA = carcinoembryonic antigen; CBC = complete blood count; Cl = chloride; CRP = C-reactive protein; D = Day; ECG = electrocardiogram; INR = international normalized ratio; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; PE = physical examination; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.1-2: On-treatment Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Cycles 1 to 12					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
Safety Assessments						
Physical Examination	X					A symptom directed physical examination performed by the investigator or designee is required at each subsequent visit.
Performance Status	X	X	X	X		ECOG score (see Appendix 7)
Physical Measurements	X	X	X	X		Weight only.
Vital Signs	X	X	X	X		Vital signs will be obtained before the nivolumab infusion, after the nivolumab infusion, and after the lirilumab infusion. If any vital sign is abnormal at the final check, the subject must be observed further for a period of time, as clinically indicated. The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious adverse event page. When slowing or restarting an infusion due to an infusion reaction, vital signs should be monitored every 15 minutes (± 5 minutes) or as directed by the investigator until the infusion is completed and/or the subject is stabilized. If a subject has an infusion reaction with nivolumab, the lirilumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the lirilumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
Electrocardiogram	X					12-lead ECG (if performed on same day as study drug administration it is to be performed prior to dosing). Not required on Cycle 1 Day 1

Table 5.1.1-2: On-treatment Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Cycles 1 to 12					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
Chest Radiograph						As clinically indicated.
Oxygen Saturation Levels	X	X	X	X		Collected at rest prior to dosing.
Laboratory Tests	X	X	X	X		On-study laboratory tests (including pregnancy testing) to be done on site/local. Within 72 hours of re-dosing to include CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, and lipase. Results should be examined by the investigator or appropriate designee prior to dose administration. (Subjects with HCC only, PT, PTT, INR, and fibrinogen) CBC with differential should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7.3.3-1, Table 5.7.3.3-3, and Table 5.7.3.3-4.
Child-Pugh Score	X					HCC only.
Endocrine Panel	X					To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test	X	X	X	X		Serum or urine.
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy.
Monitor for Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation

Table 5.1.1-2: On-treatment Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Cycles 1 to 12					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
						of dosing. SAEs should be approved in TAO within 4 days of entry
Sample Collection						
PK Assessments						See Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4. To be collected on Days 1, 2, 8, 15, 29, 85, 86, 92, and 113.
Immunogenicity Assessments						See Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4. To be collected on Days 1, 2, 8, 15, 29, 85, 86, 92, and 113
Biomarker Assessments						See Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4. To be collected on Days 1, 2, 8, 15, 29, 85, 86, 92, and 113. Subjects in Cohort Expansion (Part 1) with MEL and SCCHN must utilize Table 5.7.3.3-3.
Efficacy Assessments						
Diagnostic Imaging					X	By methods used at baseline. Scans will be performed Q8W relative to the Cycle 1 Day 1 visit regardless of treatment delays.
Brain Imaging					X	As clinically indicated.
Bone Scan					X	As clinically indicated.
Serologic Tumor Markers					X	To include measuring for tumor types with known serologic markers (ie, CEA for subjects with CRC, PSA for subjects with prostate ca, CA-125 for subjects with ovarian/breast cancer, alpha fetoprotein for subjects with HCC, hepatitis B DNA PCR for subjects with hepatitis B, and hepatitis C RNA PCR for subjects with hepatitis C, etc).

Table 5.1.1-2: On-treatment Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Cycles 1 to 12					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
Clinical Drug Supplies						
Nivolumab Administration	X	X	X	X		
Lirilumab Administration	X		X			To be administered 30 minutes after completion of the nivolumab infusion.

BUN = blood urea nitrogen; Ca = calcium; CEA = carcinoembryonic antigen; CBC = complete blood count; Cl = chloride; D = Day; ECG = electrocardiogram; INR = international normalized ratio; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; Q8W = every 8 weeks; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.1-3: Follow-up Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up	Notes
	1 30 days (± 5 days)	2 60 days (± 5 days)	3 100 days (± 5 days)	4 150 days [a] (± 5 days)	Q12W (± 2 weeks)	
Safety Assessments						
Physical Examination	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Performance Status	X	X	X			ECOG score (see Appendix 7)
Laboratory Tests			X			CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, and lipase.
Child-Pugh Score			X			HCC subjects only
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy.
Monitor for Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation of

Table 5.1.1-3: Follow-up Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up	Notes
	1 30 days (± 5 days)	2 60 days (± 5 days)	3 100 days (± 5 days)	4 150 days [a] (± 5 days)	Q12W (± 2 weeks)	
						dosing. SAEs should be approved in TAO within 4 days of entry.
Sample Collection						
PK Assessments	X	X	X			See Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4.
Immunogenicity (ADA) Assessments	X	X	X			See Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4
Efficacy Assessments						
Diagnostic Imaging			X		X	By method used at baseline. At the end of the clinical follow-up period, non-progressive subjects will continue to have scans Q12W for up to 1 year and then at a minimum of every 6 months thereafter until PD. Imaging to include brain or bone imaging as clinically indicated.

Table 5.1.1-3: Follow-up Procedural Outline the Dose Escalation and Dose Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up	Notes
	1 30 days (± 5 days)	2 60 days (± 5 days)	3 100 days (± 5 days)	4 150 days [a] (± 5 days)	Q12W (± 2 weeks)	
Survival Status						
Assessment Subject Survival Status[b]					X	Subject status will be assessed by either a clinic visit or telephone contact Q12W (± 2 weeks) for up to 3 years following the first dose of study drug. The nature and start dates of any new therapies during this period will be recorded.

[a] 150-day follow-up may be performed via clinic visit or telephone contact.

[b] No longer required with Revised Protocol 12.

BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; TAO = Trial Access Online.

5.1.2 The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

Table 5.1.2-1: Screening Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	Screening Visit (D -35 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A subject is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X			
Medical History	X			May include more detailed medical history of risk factors for potential events such as pulmonary related events.
Archived tumor tissue samples	X			One paraffin block or 10 to 15 FFPE unstained slides must be shipped to the testing laboratory at the same time as the biopsy samples.
Mandatory Fresh Tumor Biopsy	X			All subjects will be required to provide fresh biopsies at baseline and on-treatment if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable. A minimum of 2 cores must be collected. Core 1 will be formalin fixed and paraffin embedded. This core must be submitted to analysis laboratory for PD-L1 testing as soon as possible. Core 2 will be placed into RNAlater immediately upon collection. Specific processing instructions will be provided in the laboratory manual.
Safety Assessments				
Physical Examination		X		If the screening PE is performed within 24 hours of dosing on Cycle 1 Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Performance Status		X		ECOG Performance Status (see Appendix 7).
Physical Measurements		X		Includes height, weight, BSA.
Vital Signs		X		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation			X [a]	Collected at rest.

Table 5.1.2-1: Screening Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	Screening Visit (D -35 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
Electrocardiogram	X			12-lead ECG.
Chest Radiograph	X			
Laboratory Tests		X		To include: CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, glucose, albumin, amylase, lipase, CRP, TSH with reflex (free T3 and free T4), hepatitis B/C, HIV testing, and troponin. If performed within 72 hours of dosing on Cycle 1 Day 1, then Cycle 1 Day 1 laboratories are not required.
HPV Status	X			Oropharyngeal cancer sites are defined in Appendix 4. Sites must submit prior HPV status if known. For subjects with unknown status, tumor tissue will be required, per inclusion criteria. Subjects must consent to HPV testing. Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis and confirmed as shipped.
Serum Pregnancy Test			X [a]	WOCBP only.
Concomitant Medication		X		(Note: Immunosuppressive medications are recorded on a separate log page.)
Assessment of Signs and Symptoms		X		
Adverse Event Reporting				
Monitor for Serious Adverse Events	X			All SAEs must be collected starting at the time the subject signs informed consent and through 150 days after discontinuation of dosing. SAEs should be approved in TAO within 4 days of entry.
Efficacy Assessments				
Diagnostic Imaging	X			CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and

Table 5.1.2-1: Screening Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	Screening Visit (D -35 to -1)	D -14 to -1	D -3 to -1 Visit	Notes
				should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X			Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases or who have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan	X			As clinical indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Clinical Drug Supplies				
Subject Randomization	X			Within 3 days from vial allocation, the subject must receive the first dose of study drug.

[a] May be obtained on Cycle 1 Day 1 with results evaluated prior to study drug administration.

BSA = body surface area; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; CRP = C-reactive protein; D = Day; ECG = electrocardiogram; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; PE = physical examination; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.2-2: On-treatment Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	8-week Cycle, until PD					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
Safety Assessments						
Physical Examination	X					A symptom directed physical examination performed by the investigator or designee is required at each subsequent visit.
Performance Status	X	X	X	X		ECOG score (see Appendix 7)
Physical Measurements	X	X	X	X		Weight only.
Vital Signs	X	X	X	X		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. Vital signs will be obtained before the nivolumab infusion, after the nivolumab infusion, and after the lirilumab or placebo for lirilumab infusion.
Electrocardiogram	X					12-lead ECG (if performed on same day as study drug administration it is to be performed prior to dosing). Not required on Cycle 1 Day 1
Chest Radiograph						As clinically indicated.
Oxygen Saturation Levels	X	X	X	X		Collected at rest and after mild to moderate exertion prior to dosing.
Laboratory Tests	X	X	X	X		On-study laboratory tests (including pregnancy testing) to be done on site/local. Within 72 hours of re-dosing to include CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, lipase, and troponin. Results should be examined by the investigator or appropriate designee prior to dose administration.

Table 5.1.2-2: On-treatment Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	8-week Cycle, until PD					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
						[redacted]
Endocrine Panel	X					To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test	X	X	X	X		Serum or urine. WOCBP only.
Concomitant Medication	X	X	X	X	X	(Note: Immunosuppressive medications are recorded on a separate log page.)
On-treatment Tumor Biopsy		X				Fresh on-treatment tumor biopsy must be collected from the same lesion as screening biopsy if possible. A minimum of 2 cores are required. Core 1 will be FFPE. Core 2 will be placed in RNAlater. Additional cores, if available, will alternate between FFPE and RNAlater. Specific processing instructions will be provided in the laboratory manual
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy..
Monitor for Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation of dosing. SAEs should be approved in TAO within 4 days of entry
[redacted]						

Table 5.1.2-2: On-treatment Procedural Outline the SCCHN Randomized Cohorts (Part 3 - closed to enrollment) (CA223001)

Procedure	8-week Cycle, until PD					Notes
	D1 (± 2 days)	D15 (± 2 days)	D29 (± 2 days)	D43 (± 2 days)	D49 to 56	
[redacted]						
Efficacy Assessments						
Diagnostic Imaging					X	By methods used at baseline. Scans will be performed Q8W relative to the Cycle 1 Day 1 visit regardless of treatment delays.
Brain Imaging					X	As clinically indicated.
Bone Scan					X	As clinically indicated.
Clinical Drug Supplies						
Nivolumab Administration	X	X	X	X		
Lirilumab Administration	X		X			For subjects on Arm A: To be administered 30 minutes after completion of the nivolumab infusion.
Placebo for Lirilumab Administration	X		X			For subjects on Arm B: To be administered 30 minutes after completion of the nivolumab infusion.

BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; D = Day; ECG = electrocardiogram; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; Q8W = every 8 weeks; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.2-3: Follow-up Procedural Outline the SCCHN Randomized Cohorts (Part 3-closed to enrollment) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up[a]	Notes
	1 30 days [b] (± 5 days)	2 60 days [c] (± 5 days)	3 100 days [d] (± 5 days)	4 150 days [e] (± 5 days)	Q12W (± 2 weeks)	
Safety Assessments						
Physical Examination	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Performance Status	X	X	X			ECOG score (see Appendix 7)
Laboratory Tests			X			CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, lipase, and troponin.
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy.
Monitor for Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation of

Table 5.1.2-3: Follow-up Procedural Outline the SCCHN Randomized Cohorts (Part 3-closed to enrollment) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up[a]	Notes
	1 30 days [b] (± 5 days)	2 60 days [c] (± 5 days)	3 100 days [d] (± 5 days)	4 150 days [e] (± 5 days)	Q12W (± 2 weeks)	
						dosing. SAEs should be approved in TAO within 4 days of entry.
Sample Collection						
[redacted]						
Efficacy Assessments						
Diagnostic Imaging			X		X	By method used at baseline. At the end of the clinical follow-up period, non-progressive subjects will continue to have scans Q12W for up to 1 year and then at a minimum of every 6 months thereafter until PD. Imaging to include brain or bone imaging as clinically indicated.
Survival Status						
Assessment Subject Survival Status[e]					X	Subject status will be assessed by either a clinic visit or telephone contact Q12W (± 2 weeks) for up to 3 years following the first dose of study drug. The nature and start dates of any new therapies during this period will be recorded.

[a] Survival follow-up no longer applicable with Revised Protocol 12.

[b] 30 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 30 days after last dose.

[c] 60 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 60 days after last dose.

[d] 100 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 100 days after last dose.

[e] 150 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 150 days after last dose. 150-day follow-up may be performed via clinic visit or telephone contact.

BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; TAO = Trial Access Online.

5.1.3 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12

5.1.4 *The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) and the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed with Revised Protocol 12)*

Table 5.1.4-1: Screening Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Screening Visit (Day -35 to -1)	Day -14 to -1	Day -3 to -1 Visit	Notes
Eligibility Assessments				
Informed Consent	X			A subject is considered enrolled only when a protocol-specific informed consent is signed.
Inclusion/Exclusion Criteria	X			
Medical History	X			May include more detailed medical history of risk factors for potential events such as pulmonary-related events.
Archived Tumor Tissue Samples	X			One paraffin block or 10 to 15 FFPE unstained slides must be shipped to the testing laboratory at the same time as the biopsy samples.
Mandatory Fresh Tumor Biopsy	X			All subjects will be required to provide fresh biopsies at baseline if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable (subjects in the Signal Detection in SCCHN with Lirilumab, nivolumab, and Ipilimumab Combination [Part 5] will also be required to have fresh on-treatment biopsies and if the risks associated with obtaining biopsies are deemed acceptable). A minimum of 2 cores must be collected. Core 1 will be FFPE. This core must be submitted to analysis laboratory for PD-L1 testing as soon as possible. Core 2 will be placed into RNAlater immediately upon collection. Specific processing instructions will be provided in the laboratory manual.
Safety Assessments				
Physical Examination		X		If the screening PE is performed within 24 hours of dosing on Week 1 Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Performance Status		X		ECOG Performance Status (see Appendix 7)

Table 5.1.4-1: Screening Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Screening Visit (Day -35 to -1)	Day -14 to -1	Day -3 to -1 Visit	Notes
Physical Measurements		X		Includes height, weight, BSA.
Vital Signs		X		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen Saturation			X [a]	Collected at rest.
Electrocardiogram	X			12-lead ECG
Echocardiogram	X			
Chest Radiograph	X			
Laboratory Tests		X		Days -14 to -1 prior to Week 1 Day 1. To include: CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, glucose, albumin, amylase, lipase, CRP, TSH with reflex (free T3 and free T4), hepatitis B/C, HIV testing, and troponin. If performed within 72 hours of dosing on Week 1 Day 1, then Week 1 Day 1 laboratories are not required.
[redacted]				
Mutation Status	X			Documentation of BRAF mutation status only for MEL
Serum Pregnancy Test			X [a]	WOCBP only.
Concomitant Medication		X		(Note: Immunosuppressive medications are recorded on a separate log page.)

Table 5.1.4-1: Screening Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Screening Visit (Day -35 to -1)	Day -14 to -1	Day -3 to -1 Visit	Notes
Assessment of Signs and Symptoms		X		
Adverse Event Reporting				
Monitor for Serious Adverse Events	X			All SAEs must be collected starting at the time the subject signs informed consent and through 150 days after discontinuation of dosing. SAEs should be approved in TAO within 4 days of entry.
Efficacy Assessments				
Diagnostic Imaging	X			Must be performed within 28 days prior to first dose of study drug. CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum and should include other anatomic regions as indicated by individual subject disease histories.
Brain Imaging	X			Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases or who have not had brain imaging within 30 days of anticipated first study drug administration.
Bone Scan	X			As clinical indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.
Clinical Drug Supplies				
Subject Randomization	X			Within 3 days from vial allocation, the subject must receive the first dose of study drug

[a] May be obtained on Week 1 Day 1 with results evaluated prior to study drug administration.

BSA = body surface area; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; CRP = C-reactive protein; D = Day; ECG = electrocardiogram; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; PE = physical examination; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.4-2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Until PD				Part 5 Only	Notes
	Week 1, 13, 25, and 37 Day 1 (± 2 days)	Weeks 3, 11, 15, 23, 27, 35, 39, and 47 Day 1 (± 2 days)	Weeks 5, 9, 17, 21, 29, 33, 41, and 45 Day 1 (± 2 days)	Weeks 7, 19, 31, and 43 Day 1 (± 2 days)	Weeks 9, 17, 25, 33, 41, and 49 Day 1 (±7 days)	
Safety Assessments						
Physical Examination	X					A symptom-directed physical examination performed by the investigator or designee is required at each subsequent visit.
Performance Status	X	X	X	X		ECOG score (see Appendix 7)
Physical Measurements	X	X	X	X		Weight only
Vital Signs	X	X	X	X		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. Vital signs will be obtained before the nivolumab infusion, before the ipilimumab infusion, before the lirilumab infusion, and after the lirilumab infusion.
Electrocardiogram	X					12-lead ECG (if performed on same day as study drug administration, it is to be performed prior to dosing). Not required on Week 1 Day 1
Echocardiogram						As clinically indicated.
Chest Radiograph						As clinically indicated.

Table 5.1.4-2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Until PD				Part 5 Only	Notes
	Week 1, 13, 25, and 37 Day 1 (± 2 days)	Weeks 3, 11, 15, 23, 27, 35, 39, and 47 Day 1 (± 2 days)	Weeks 5, 9, 17, 21, 29, 33, 41, and 45 Day 1 (± 2 days)	Weeks 7, 19, 31, and 43 Day 1 (± 2 days)	Weeks 9, 17, 25, 33, 41, and 49 Day 1 (±7 days)	
Oxygen Saturation Levels	X	X	X	X		Collected at rest.
Laboratory Tests	X	X	X	X		On-study laboratory tests (including pregnancy testing) to be done on site/local. Within 72 hours of re-dosing to include CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, lipase, and troponin. Results should be examined by the investigator or appropriate designee prior to dose administration. CBC with differential should also be collected at each timepoint where samples for immunophenotyping are collected as listed in Table 5.7.3.3-7.
Endocrine Panel	X					To include TSH with reflex testing (free T3 and free T4). Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test	X	X	X	X		Serum or urine. WOCBP only.
Concomitant Medication	X	X	X	X	X	(Note: Immunosuppressive medications are recorded on a separate log page.)

Table 5.1.4-2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Until PD				Part 5 Only	Notes
	Week 1, 13, 25, and 37 Day 1 (± 2 days)	Weeks 3, 11, 15, 23, 27, 35, 39, and 47 Day 1 (± 2 days)	Weeks 5, 9, 17, 21, 29, 33, 41, and 45 Day 1 (± 2 days)	Weeks 7, 19, 31, and 43 Day 1 (± 2 days)	Weeks 9, 17, 25, 33, 41, and 49 Day 1 (±7 days)	
On-treatment Tumor Biopsy		X (See note)				The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) only: Day 15 on-treatment tumor biopsy must be collected from the same lesion as screening biopsy if possible. A minimum of 2 cores are required. Core 1 will be FFPE. Core 2 will be placed in RNAlater. Additional cores, if available, will alternate between FFPE and RNAlater. Specific processing instructions will be provided in the laboratory manual.
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X	X	Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy.
Monitor for Serious Adverse Events	X	X	X	X	X	All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation of dosing. SAEs should be approved in TAO within 4 days of entry.

Table 5.1.4-2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Until PD				Part 5 Only	Notes
	Week 1, 13, 25, and 37 Day 1 (± 2 days)	Weeks 3, 11, 15, 23, 27, 35, 39, and 47 Day 1 (± 2 days)	Weeks 5, 9, 17, 21, 29, 33, 41, and 45 Day 1 (± 2 days)	Weeks 7, 19, 31, and 43 Day 1 (± 2 days)	Weeks 9, 17, 25, 33, 41, and 49 Day 1 (±7 days)	
Sample Collection						
PK Assessments						See Table 5.7.3.3-7.
Immunogenicity Assessments						See Table 5.7.3.3-7.
Biomarker Assessments						See Table 5.7.3.3-7.
Efficacy Assessments						
Diagnostic Imaging					X	By methods used at baseline. The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5): Scans will be performed Q8W relative to the Week 1 Day 1 visit regardless of treatment delays for 1 year (48 weeks), and then Q12W afterwards.
Brain Imaging					X	As clinically indicated.
Bone Scan					X	As clinically indicated.

Table 5.1.4-2: On-treatment Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Until PD				Part 5 Only	Notes
	Week 1, 13, 25, and 37 Day 1 (± 2 days)	Weeks 3, 11, 15, 23, 27, 35, 39, and 47 Day 1 (± 2 days)	Weeks 5, 9, 17, 21, 29, 33, 41, and 45 Day 1 (± 2 days)	Weeks 7, 19, 31, and 43 Day 1 (± 2 days)	Weeks 9, 17, 25, 33, 41, and 49 Day 1 (±7 days)	
Clinical Drug Supplies						
Nivolumab Administration	X	X	X	X		To be administered first on days when multiple study drugs are given.
Ipilimumab Administration	X			X		To be administered 30 minutes after completion of the nivolumab infusion.
Lirilumab Administration	X		X			On days when all 3 study drugs are given, lirilumab is to be administered 30 minutes after completion of the ipilimumab infusion. On days when nivolumab and lirilumab are given, lirilumab is to be administered 30 minutes after completion of the nivolumab infusion.

BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; D = Day; ECG = electrocardiogram; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; T3 = triiodothyronine; T4 = thyroxine; TAO = Trial Access Online; TSH = thyroid-stimulating hormone.

Table 5.1.4-3: Follow-up Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up[a]	Notes
	1 30 days [b] (± 5 days)	2 60 days [c] (± 5 days)	3 100 days [d] (± 5 days)	4 150 days [e] (± 5 days)	Q12W (± 2 weeks)	
Safety Assessments						
Physical Examination	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Performance Status	X	X	X			ECOG score (see Appendix 7)
Laboratory Tests			X			CBC with differential, LFTs (to include a minimum of AST, ALT, alkaline phosphatase, total bilirubin, and LDH), BUN, creatinine, glucose, Ca, Mg, Na, K, carbon dioxide, Cl, phosphorous, amylase, lipase, and troponin.
Adverse Event Reporting						
Monitor for Non-serious Adverse Events	X	X	X	X		Non-serious AEs will be collected starting with the first dose of study drug and through 150 days after discontinuation of dosing or until the start of subsequent anti-cancer therapy.
Monitor for Serious Adverse Events	X	X	X	X		All SAEs must be collected starting at the time a subject signs informed consent and through 150 days after discontinuation of

Table 5.1.4-3: Follow-up Procedural Outline the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) (CA223001)

Procedure	Clinical Follow-up				Survival Follow-up[a]	Notes
	1 30 days [b] (± 5 days)	2 60 days [c] (± 5 days)	3 100 days [d] (± 5 days)	4 150 days [e] (± 5 days)	Q12W (± 2 weeks)	
						dosing. SAEs should be approved in TAO within 4 days of entry.
Sample Collection						
PK Assessments	X	X	X			See Table 5.7.3.3-7.
Immunogenicity (ADA) Assessments	X	X	X			See Table 5.7.3.3-7.
Efficacy Assessments						
Diagnostic Imaging			X		X	By method used at baseline. At the end of the clinical follow-up period, non-progressive subjects will continue to have scans Q12W for up to 1 year and then at a minimum of every 6 months thereafter until PD. Imaging to include brain or bone imaging as clinically indicated.
Survival Status						
Assessment Subject Survival Status[e]					X	Subject status will be assessed by either a clinic visit or telephone contact Q12W (± 2 weeks) for up to 3 years following the first dose of study drug. The nature and start dates of any new therapies during this period will be recorded.

[a] Survival follow-up no longer applicable with Revised Protocol 12.

[b] 30 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 30 days after last dose.

[c] 60 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 60 days after last dose.

[d] 100 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 100 days after last dose.

[e] 150 days from the last dose of study drug (± 5 days) or coinciding with the date of discontinuation of study drug (± 5 days) if date of discontinuation of study drug is greater than 150 days after last dose. 150-day follow-up may be performed via clinic visit or telephone contact.

BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; K = potassium; LDH = lactate dehydrogenase; LFT = liver function test; Mg = magnesium; Na = sodium; TAO = Trial Access Online.

5.2 Study Materials

The following materials will be provided prior to the start of the study:

- NCI CTCAE v4.03;
- Lirilumab, nivolumab, and ipilimumab IBs;
- Pharmacy binder;
- Laboratory manuals for collection and handling of blood (including PKs, biomarker, and immunogenicity) and tissue specimens;
- Enrollment/randomization worksheets;
- SAE forms;
- Pregnancy surveillance forms.
- Subject questionnaires: EORTC-QLQ-C30, EORTC-QLQ-H&N35, EQ-5D-3L (for the Signal Detection Randomized Cohorts [Part 3] only).
- Dosing Procedure Manual.

5.3 Safety Assessments

AEs will be assessed continuously during the study and for 150 days after the last treatment or until the start of subsequent anti-cancer therapy. AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. AEs will be evaluated according to the NCI CTCAE v4.03. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

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

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to subject registration. The baseline physical examination should include weight, height, heart rate, blood pressure, temperature and ECOG status and should be performed within 28 days of treatment assignment for the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) and within 35 days of treatment assignment or randomization for all other study parts. Concomitant medications will be collected from within 2 weeks prior to treatment assignment or randomization through the study treatment period (see Section 5.1).

Subjects will be considered evaluable for safety if they have received any dose of either study drug. Toxicity assessments will be continuous during the treatment period and the clinical follow-up periods.

Body weight and performance status should be assessed at each on-study visit. Vital signs will be obtained at timepoints according to Section 5.1. For further details related to infusion reactions, see Section 3.6.

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 clinical follow-up period via on-site/local laboratories until all study-drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Clinical laboratory measures will be assessed (see Section 5.1). Sites should collect these samples between -28 to -1 days from registration to insure that results required for eligibility purposes are verified prior to registration (or between -35 to -1 days for subjects in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5]). Pregnancy testing must be performed within 72 hours prior to the initial administration of investigational product at baseline and then prior to administration of either study drug during study therapy and at the 3 clinical follow-up visits. Complete blood count plus differential and serum chemistry panel should be drawn within 72 hours prior to each subsequent scheduled cycle. On-study laboratory tests will be performed on site/locally. Laboratory tests may be obtained more frequently if indicated. Additional laboratory tests should be performed as per standard of care.

If a subject shows pulmonary-related signs (eg, hypoxia or fever) or symptoms (eg, dyspnea, cough, or fever) consistent with possible pulmonary AEs, the subject should be immediately evaluated to rule out pulmonary toxicity according to the suspected pulmonary toxicity management algorithm in the nivolumab IB.[19]

5.3.1 *Microsatellite Instability Testing*

MSI-high in tumors refers to changes in 2 or more of the 5 NCI-recommended panels of microsatellite markers in tumor tissue. The original (1997) Bethesda guidelines proposed a panel of 5 microsatellite markers for the uniform analysis of MSI in hereditary non-polyposis CRC. This panel, which is referred to as the Bethesda panel, included 2 mononucleotide (BAT-25 and BAT-26) and 3 dinucleotide (D5S346, D2S123, and D17S250) repeats.[40] Individual testing sites may utilize a slightly different panel of markers incorporating alternative mononucleotide or dinucleotide markers. Regardless of the panel of markers, samples with instability in zero or 1 marker are designated as non-MSI-high. Those with 1 unstable marker are designated as MSI-low. Samples with no detectable alterations are MSI-stable. Samples with detectable alterations in 2 or more markers are considered MSI-high.

5.4 Efficacy Assessments

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and every 8 weeks until disease progression, at the completion of clinical follow-up, or until subjects withdraw from the study. Disease assessments at other timepoints may be performed if the investigator is concerned about tumor progression. Tumor responses will be derived for appropriate populations of subjects as defined by RECIST v1.1[41] (see Appendix 3) from tumor measurements. For the Dose Escalation and Cohort Expansion (Part 1; completed) and the SCCHN Cohort Expansion (Part 2; completed), investigator-assessed responses and treatment decisions related to subject management will be based on irRECIST[9] (see Appendix 2); all other study parts

will use only RECIST v1.1. Radiographic assessments may be submitted to the third-party radiology vendor for any part of the study as they are performed on an ongoing basis. Submission of radiographic scans to the third-party vendor is no longer required with Revised Protocol 12.

Changes in tumor measurements and tumor responses will be assessed by the investigator using irRECIST criteria. Investigators will also report the number and size of new lesions that appear while on-study. The timepoint tumor assessments will be reported on the CRF based on investigators' assessment using irRECIST criteria. The SCCHN Randomized Cohorts (Part 3), and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), however, will use only RECIST v1.1 for all assessments. Please refer to Appendix 3 for specifics of RECIST v1.1 and Appendix 2 for specifics of irRECIST criteria to be utilized in this study.

The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

The primary endpoint is ORR based on assessment in all subjects randomized to lirilumab plus nivolumab.

The secondary efficacy endpoints of the SCCHN Randomized Cohorts (Part 3) are DCR, DOR, time to response, depth of response, OS, PFS, , and ORR according to investigator-assessed response. All randomized subjects will be monitored by radiographic assessment Q8W (± 7 days) beginning from the first dose date until Week 48 and Q12W (± 7 days) thereafter until PD or treatment discontinuation (whichever occurs earlier), to determine changes in tumor size.

The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

[redacted]

The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

5.5 Pharmacokinetic Assessments

Serum samples for lirilumab, nivolumab, and/or ipilimumab PK assessments will be collected for all subjects in both dose escalation and cohort expansion. [redacted]

[redacted] PK of lirilumab and ipilimumab will be derived from serum concentration vs time. The PK parameters to be assessed include:

Cmax	Maximum observed concentration
Tmax	Time of maximum observed concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
Ctrough	Trough observed serum concentration
AUC(TAU)	Area under the plasma concentration-time curve in 1 dosing interval
CL	Clearance
Vz	Apparent volume of distribution during terminal phase
T-HALF	Half-life

Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

In addition, nivolumab end of infusion and trough (Cmin) concentrations will be calculated at specified visits.

5.5.1 Pharmacokinetics: Collection and Processing

[redacted] Further details of blood collection and processing will be provided to the study site in the procedure manual.

5.5.2 Pharmacokinetic Sample Analyses

Serum samples will be analyzed for lirilumab, nivolumab, and ipilimumab by a validated immunoassay. [redacted]

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the study site in the procedure manual.

5.6 Biomarker Assessments

No further biomarker samples are required to be collected with Revised Protocol 12. [redacted]

5.7 [redacted] Biomarker Assessments

Blood/tissue will be collected at the times indicated in Section 5.7.3.3. Further details of blood collection and processing will be provided to the study site in the procedure manual. The pharmacodynamics of lirilumab, nivolumab, and ipilimumab in combination, as well as nivolumab monotherapy treatment, will be assessed by quantifying biomarkers from peripheral blood and serial tumor biopsies.

[redacted]

[redacted]

5.7.3 Assessments for Subjects Undergoing Tumor Biopsies

Blood will be drawn at the times indicated in Section 5.7.1 and will be used to perform all of the studies listed for those subjects in dose escalation (see Section 5.7.1). Blood will be obtained for all subjects in order to obtain tumor/normal pairs. Mandatory pre-treatment and on-treatment tumor biopsies will be obtained in a minimum of 10 subjects in the MEL and SCCHN cohorts of Cohort Expansion (Part 1; completed). In the SCCHN Cohort Expansion (Part 2; completed), a minimum of 15 subjects will be required to undergo mandatory pre-treatment and on-treatment biopsies at acceptable clinical risk as judged by the investigator.

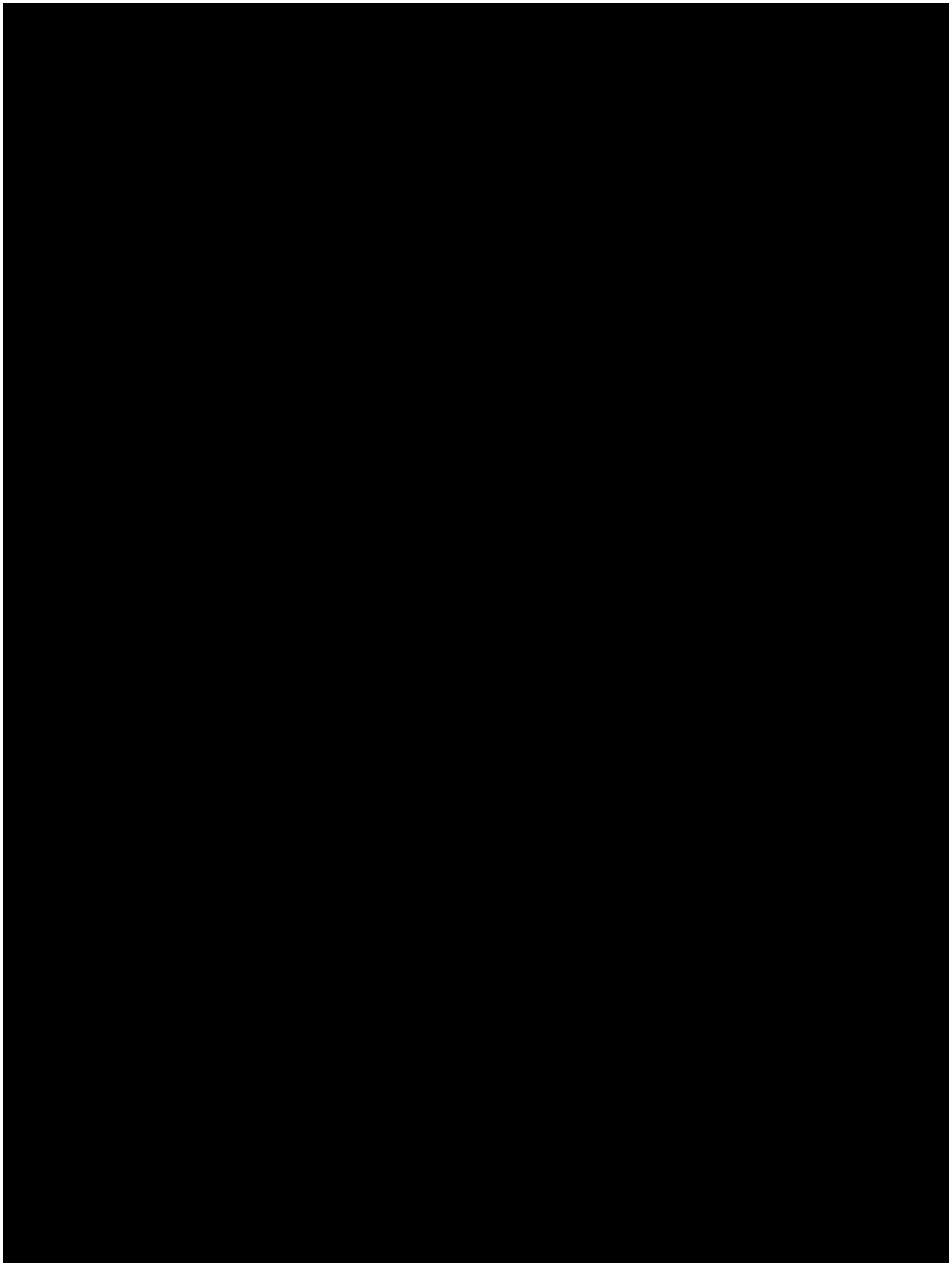
In [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5); **all subjects will be required to provide fresh biopsies at baseline** if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable. In addition, all subjects in [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment) will be **required to have a fresh on-treatment biopsy** if biopsy risk is acceptable.

On-treatment biopsies will be collected at Day 29 ± 3 days for the SCCHN Cohort Expansion (Part 2; completed); and at Day 15 ± 3 days for [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5). Post-treatment biopsies (following completion of all study therapy) will be optional. [redacted]

5.7.3.1 PD-L1 Testing on Screening Tumor Biopsies

All subjects in the SCCHN Randomized Cohorts (Part 3); and the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) must have PD-L1 testing performed on tumor biopsies obtained during screening. Subjects in the SCCHN Randomized Cohorts (Part 3) must be PD-L1+ on fresh biopsies by IHC testing performed by the central laboratory during the screening period to be enrolled in the study. All subjects in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) must be tested for PD-L1 on the screening biopsy but will be enrolled regardless of PD-L1 status. PD-L1-stained tissue samples will be assessed by a pathologist at a central laboratory identified by the Sponsor and will be scored as PD-L1+ if membrane staining is observed in ≥ 1% of tumor cells among a minimum of 100 evaluable tumor cells. If the screening biopsy sample is not evaluable for PD-L1 testing, a second test of the screening biopsy will be performed. If the second test is not evaluable, the study site may submit archival tumor samples (minimum of 10 unstained FFPE slides or a FFPE tumor block). PD-L1 testing must be performed during screening period to determine eligibility.

[redacted]



[redacted]

5.7.3.3 Pharmacokinetics, Immunogenicity (Anti-drug antibodies) and Biomarker Assessment Schedules

Detailed schedules of the PK, immunogenicity (ADA), and biomarker assessments are presented below for all study parts. Effective with Revised Protocol 12, PK and ADA samples will continue to be collected but will not be analyzed except as clinically indicated in specific cases such as Grade 3/4 toxicity, infusion reactions, etc.

Table 5.7.3.3-1: PK, Immunogenicity (ADA) and Biomarker Assessment Schedule: Dose Escalation (the Dose Escalation and Cohort Expansion [Part 1; completed])

Collection Timing					Serum				[redacted]	Tumor
Study Week	Study Day	Relative Study Day	Time (Event)	Time	PK anti-KIR	PK anti-PD-1	ADA anti-KIR	ADA anti-PD-1		Archived Tumor Sample
Screening										X
Week 1	C1D1	D1	0 h [b]	00:00	X	X	X	X		
	C1D1	Djj1	EOI [c]		X	X				
	C2D2	D2	24 h [d]	24:00	X					
	C1D8	D8	168 h [d]	168:00	X					
Week 3	C1D15	D15	336 h [b]	336:00	X	X	X	X		
Week 5	C1D29	D29	0 h [b]	00:00	X	X	X	X		
Week 13	C2D29	D85	0 h [b]	00:00	X	X	X	X		
	C2D29	D85	EOI [c]		X	X				
	C2D30	D86	24 h [d]	24:00	X					
	C2D36	D92	168 h [d]	168:00	X					
Week 17	C3D1	D113	0 h [b]	00:00	X	X	X	X		
Week 33	C5D1	D225	0 h [b]	00:00	X	X	X			
Week 49	C7D1	D337	0 h [b]	00:00	X	X	X			
Week 65	C9D1	D449	0 h [b]	00:00	X	X	X			

Table 5.7.3.3-1: PK, Immunogenicity (ADA) and Biomarker Assessment Schedule: Dose Escalation (the Dose Escalation and Cohort Expansion [Part 1; completed])

Collection Timing					Serum				[redacted]	Tumor
Study Week	Study Day	Relative Study Day	Time (Event)	Time	PK anti-KIR	PK anti-PD-1	ADA anti-KIR	ADA anti-PD-1		Archived Tumor Sample
Week 81	C11D1	D561	0 h [b]	00:00	X	X	X			
EOT					X	X	X	X		
Follow-ups 1-3					X	X	X			

[redacted]

[b] Samples to be collected prior to the infusion of nivolumab.

[c] Samples must be collected immediately following the end of lirilumab infusion. It is imperative that the actual time that the sample is obtained is recorded. All listed studies should be obtained prior to this point.

[d] Samples may be collected at any time during the day, but it is imperative that the actual time that the sample is obtained is recorded.

C = Cycle; CBC = complete blood count; D = Day; EOI = End of Infusion; EOT = End of Treatment.

Table 5.7.3.3-2: PK, Immunogenicity (ADA) and Biomarker Assessment Schedule: Cohort Expansion (except for subjects with MEL or SCCHN) (the Dose Escalation and Cohort Expansion [Part 1; completed])

Collection Timing					Serum				[redacted]	Tumor
Study Week	Study Day	Relative Study Day	Time (Event)	Time (relative)	PK anti-KIR	PK anti-PD-1	ADA anti-KIR	ADA anti-PD-1		Archived Tumor Sample
Screening										X
Week 1	C1D1	D1	0 h [a]	00:00	X	X	X	X		
	C1D1	D1	EOI [b]		X	X				
	C1D2	D2	24 h[c]	24:00	X					
	C1D8	D8	168 h[c]	168:00	X					
Week 3	C1D15	D15	336 h[a]	336:00	X	X	X	X		
Week 5	C1D29	D29	0 h[a]	00:00	X	X	X	X		
Week 13	C2D29	D85	0 h[a]	00:00	X	X	X	X		
	C2D29	D85	EOI[b]		X	X				
	C2D30	D86	24 h[c]	24:00	X					
	C2D36	D92	168 h[c]	168:00	X					
Week 17	C3D1	D113	0 h[a]	00:00	X	X	X	X		
Week 33	C5D1	D225	0 h[b]	00:00	X	X	X	X		
Week 49	C7D1	D337	0 h[b]	00:00	X	X	X	X		
Week 65	C9D1	D449	0 h[b]	00:00	X	X	X	X		
Week 81	C11D1	D561	0 h[b]	00:00	X	X	X	X		

Table 5.7.3.3-2: PK, Immunogenicity (ADA) and Biomarker Assessment Schedule: Cohort Expansion (except for subjects with MEL or SCCHN) (the Dose Escalation and Cohort Expansion [Part 1; completed])

Collection Timing					Serum				[redacted]	Tumor
Study Week	Study Day	Relative Study Day	Time (Event)	Time (relative)	PK anti-KIR	PK anti-PD-1	ADA anti-KIR	ADA anti-PD-1		Archived Tumor Sample
EOT					X	X	X	X		
Follow-up Visits 1-3					X	X	X	X		

[a] Samples to be collected prior to the infusion of nivolumab.

[b] Samples must be collected immediately following the end of the lirilumab infusion. It is imperative that the actual time that the sample is obtained is recorded. All listed studies should be obtained at this point.

[c] Samples may be collected at any time during the day, but it is imperative that the active time that the sample is obtained is recorded.

C = Cycle; D = Day; EOI = End of Infusion; EOT = End of Treatment.

Table 5.7.3.3-3: Biomarker Assessment Schedule: MEL and SCCHN Cohort Expansions and Subjects Undergoing Tumor Biopsy in the Dose Escalation and Cohort Expansion (Part 1; Completed)

Collection Timing				Plasma	Serum			[redacted]	Tumor	
Study Week	Study Day	Relative Study Day	Time (Event)	ctDNA[a]	PK anti-KIR	PK anti-PD-1	ADA anti-KIR & anti-PD-1		Tumor Biopsy[d,e,f]	Archived Tumor Sample
Screening									X	X
Week 1	C1D1	D1	0 h[f]	X	X	X				
	C1D1	D1	EOI[g]		X	X				
	C1D2	D2	24 h[h]		X					
	C1D8	D8	168 h[h]		X					
Week 3	C1D15	D15	336 h[f]		X	X	X			
Week 5	C1D29	D29	0 h[f]	X	X	X				
Week 9	C2D1	D57	0 h	X						
Week 13	C2D29	D85	0 h[f]	X	X	X				
	C2D29	D85	EOI[g]		X	X				
	C2D30	D86	24 h[h]		X					
	C2D36	D92	168 h[h]		X					
Week 17	C3D1	D113	0 h[d,f]	X	X	X			X[i]	

Table 5.7.3.3-3: Biomarker Assessment Schedule: MEL and SCCHN Cohort Expansions and Subjects Undergoing Tumor Biopsy in the Dose Escalation and Cohort Expansion (Part 1; Completed)

Collection Timing				Plasma	Serum			[redacted]	Tumor	
Study Week	Study Day	Relative Study Day	Time (Event)	ctDNA[a]	PK anti-KIR	PK anti-PD-1	ADA anti-KIR & anti-PD-1		Tumor Biopsy[d,e,f]	Archived Tumor Sample
Week 33	C5D1	D225	0 h[b]	X	X	X				
Week 49	C7D1	D337	0 h[b]	X	X	X				
Week 65	C9D1	D449	0 h[b]	X	X	X				
Week 81	C11D1	D561	0 h[b]	X	X	X				
EOT					X	X	X			
Follow-up Visits 1-3					X	X				

[a] For subjects in MEL cohort expansions only.

[redacted]

[d] A minimum of 10 subjects with MEL in the cohort expansion and a minimum of 10 subjects with SCCHN in the Cohort Expansion (Part 1) will be required to provide pre-treatment and on-treatment biopsies.

[e] Any subject who consents to biopsies is required to collect the biomarker assessments listed.

[f] Samples to be collected prior to the infusion of nivolumab.

[g] Samples must be collected immediately following the end of infusion of lirilumab. It is imperative that the actual time that the sample is obtained is recorded. All listed studies should be obtained at this point.

[h] Samples may be collected at any time during the day, but it is imperative that the actual time that the sample is obtained is recorded.

[i] C3D1 biopsy should be collected prior to Week 17 drug administration.

C = Cycle; CBC = complete blood count; D = Day; EOI = End of Infusion; EOT = End of Treatment.

Table 5.7.3.3-4: Biomarker Assessment Schedule: the SCCHN Cohort Expansion (Part 2; completed)

[redacted]

Collection Timing				Serum			[redacted]	Tumor	
Study Week	Study Day [a]	Relative Study Day	Time (Event)	PK anti-KIR	PK anti-PD-1	ADA anti-KIR & anti-PD-1		Tumor Biopsy [c]	Archived Tumor Sample
Screening								X	X
Week 1	C1D1	D1	0 h	X	X	X			
	C1D1	D1	EOI	X	X				
	C1D2	D2	24 h	X					
	C1D8	D8	168 h	X					
Week 3	C1D15	D15	336 h	X	X	X		X [d]	
Week 5	C1D29	D29	0 h	X	X	X			
Week 9	C2D1	D57	0 h						
Week 13	C2D29	D85	0 h	X	X	X			
	C2D29	D85	EOI	X	X				
	C2D30	D86	24 h	X					
	C2D36	D92	168 h	X					
Week 17	C3D1	D113	0 h	X	X	X			
Week 33	C5D1	D225	0 h	X	X	X			

Table 5.7.3.3-4: Biomarker Assessment Schedule: the SCCHN Cohort Expansion (Part 2; completed)

[redacted]

Collection Timing				Serum			[redacted]	Tumor	
Study Week	Study Day [a]	Relative Study Day	Time (Event)	PK anti-KIR	PK anti-PD-1	ADA anti-KIR & anti-PD-1		Tumor Biopsy [c]	Archived Tumor Sample
Week 49	C7D1	D337	0 h	X	X	X			
Week 65	C9D1	D449	0 h	X	X	X			
Week 81	C11D1	D561	0 h	X	X	X			
EOT				X	X	X			
Follow-up Visits 1-3				X	X				

[a] On days where study drug is administered, samples should be collected before the nivolumab dose unless otherwise specified.

[redacted]

[c] A minimum of 2 cores from a core needle biopsy should be collected at biopsy timepoints (1 core for FFPE, 1 core for nucleic acid analyses [RNAlater]). A minimum of 15 subjects with SCCHN in the SCCHN Cohort Expansion (Part 2) cohort expansion will be required to provide pre-treatment and on-treatment biopsies.

[d] C1D15 biopsy can be collected ± 3 days.

C = Cycle; CBC = complete blood count; D = Day; EOI = End of Infusion; EOT = End of Treatment.

Table 5.7.3.3-5: Biomarker, Pharmacokinetics, and Immunogenicity Assessment Schedule: the SCCHN Randomized Cohorts (Part 3 - closed for enrollment)

[redacted]

Collection Timing				Serum			[redacted]	Tumor	
Study Week	Study Day [a]	Relative Study Day	Time (Event)	PK lirilumab	PK nivolumab	ADA anti-lirilumab & anti-nivolumab		Tumor Biopsy [c]	Archived Tumor Sample
Screening								X	X
Week 1	C1D1	D1	0 h	X	X	X			
	C1D1	D1	EOI	X	X				
	C1D2	D2	24 h	X					
	C1D8	D8	168 h	X					
Week 3	C1D15	D15	336 h	X	X	X		X [d]	
Week 5	C1D29	D29	0 h	X	X	X			
Week 9	C2D1	D57	0 h						
Week 13	C2D29	D85	0 h	X	X	X			
	C2D29	D85	EOI	X	X				
	C2D30	D86	24 h	X					
	C2D36	D92	168 h	X					
Week 17	C3D1	D113	0 h	X	X	X			

Table 5.7.3.3-5: Biomarker, Pharmacokinetics, and Immunogenicity Assessment Schedule: the SCCHN Randomized Cohorts (Part 3 - closed for enrollment)

[redacted]

Collection Timing				Serum			[redacted]	Tumor	
Study Week	Study Day [a]	Relative Study Day	Time (Event)	PK lirilumab	PK nivolumab	ADA anti-lirilumab & anti-nivolumab		Tumor Biopsy [c]	Archived Tumor Sample
Week 33	C5D1	D225	0 h	X	X	X			
Week 49	C7D1	D337	0 h	X	X	X			
Week 65	C9D1	D449	0 h	X	X	X			
Week 81	C11D1	D561	0 h	X	X	X			
Q16W after Week 81 until EOT				X	X	X			
Follow-up Visits 1-3				X	X	X			

[a] On days where study drug is administered; samples should be collected before the nivolumab dose unless otherwise specified.

[redacted]

[c] A minimum of 2 cores from a core needle biopsy should be collected at biopsy timepoints (1 core for FFPE, 1 core for nucleic acid analyses [RNAlater]). In the SCCHN Randomized Cohorts (Part 3), all subjects will be required to provide biopsies during screening and on-treatment if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable.

[d] C1D15 biopsy can be collected ± 3 days.

C = Cycle; CBC = complete blood count; D = Day; EOI = End of Infusion; Q16W = every 16 weeks.

Table 5.7.3.3-6: Biomarker, Pharmacokinetics, and Immunogenicity Assessment Schedule: the Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

Table 5.7.3.3-7: Pharmacokinetics, Immunogenicity, and Biomarker Assessment Schedule: the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed for enrollment) and in the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)

[redacted]

Effective with Revised Protocol 12, PK and ADA samples will continue to be collected but will not be analyzed except as clinically indicated in specific cases such as Grade 3/4 toxicity, infusion reactions, etc.

Collection Timing			Serum				[redacted]	Tumor	
Study Week	Relative Study Day [a]	Time (Event)	PK Lirilumab	PK Nivolumab	PK Ipilimumab	ADA Anti-lirilumab, Anti-nivolumab, and Anti-Ipilimumab		Tumor Biopsy [c]	Archived Tumor Sample
Screening								X	X
Week 1	D1	0 h	X	X	X	X			
	D1	EOI	X	X	X				
	D2	24 h	X						
	D8	168 h	X						
Week 3	D15	336 h	X	X		X		X [d]	
Week 5	D29	0 h	X	X		X			
Week 13	D85	0 h	X	X	X	X			
	D85	EOI	X	X	X				
	D86	24 h	X						
	D92	168 h	X						
Week 17	D113	0 h	X	X	X	X			

Table 5.7.3.3-7: Pharmacokinetics, Immunogenicity, and Biomarker Assessment Schedule: the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed for enrollment) and in the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6 - removed)

[redacted]

Effective with Revised Protocol 12, PK and ADA samples will continue to be collected but will not be analyzed except as clinically indicated in specific cases such as Grade 3/4 toxicity, infusion reactions, etc.

Collection Timing			Serum				[redacted]	Tumor	
Study Week	Relative Study Day [a]	Time (Event)	PK Lirilumab	PK Nivolumab	PK Ipilimumab	ADA Anti-lirilumab, Anti-nivolumab, and Anti-Ipilimumab		Tumor Biopsy [c]	Archived Tumor Sample
Week 25	D169	0 h	X	X	X	X			
Week 37	D253	0 h	X	X	X	X			
Q12W after Week 37 until EOT			X	X	X	X			
Follow-up Visits 1-3			X	X	X	X			

[a] On days where study drug is administered; samples should be collected before the nivolumab dose unless otherwise specified.

[redacted]

[c] A minimum of 2 cores from a core needle biopsy should be collected at biopsy timepoints (1 core for FFPE, 1 core for nucleic acid analyses [RNAlater]). In the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), all subjects will be required to provide biopsies at screening if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable. Subjects in the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) will also be required to provide on-treatment biopsies if a subject has accessible lesions and if the risks associated with obtaining biopsies are deemed acceptable.

[d] For the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5) only, C1D15 biopsy can be collected ± 3 days.

C = Cycle; CBC = complete blood count; D = Day; EOI = End of Infusion.

5.8 Outcomes Research Assessments

No additional QLQ collection is required with Revised Protocol 12.

5.9 Other Assessments

5.9.1 Immunogenicity Assessments

Serum samples for analysis of development of ADA will be drawn in conjunction with analysis of lirilumab, nivolumab, and ipilimumab serum concentrations and will be collected from all as indicated in Section 5.7.3.3. These serum samples will be analyzed for ADA by a validated immunoassay. [redacted] Samples designated for PK analysis (Section 5.5) may be used for immunogenicity analysis in the event of insufficient volume, to complete the immunogenicity assessment, or to follow up on suspected immunogenicity-related AEs. Effective with Revised Protocol 12, PK and ADA samples will continue to be collected but will not be analyzed except as clinically indicated in specific cases such as Grade 3/4 toxicity, infusion reactions, etc.

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered an investigational (medicinal) product 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 investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The casual relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

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

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject 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)
- 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 subject or may require intervention [eg, medical, surgical] to prevent 1 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 6.6 for the definition of potential DILI).

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

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 (eg, routine colonoscopy)
- medical/surgical admission other than remedying ill health state 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 (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- admission for administration of anti-cancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 150 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a

Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Non-serious Adverse Events

A ***Non-serious Adverse Event*** is an AE not classified as serious.

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those that are present at the end of study treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious 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.

Every AE must be assessed by the investigator with regard to whether it is considered immune mediated. For events that are potentially immune mediated, additional information will be collected on the subject's CRF.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject 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).

6.4 Pregnancy

If, following initiation of the investigational product, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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 subject should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 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. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential DILI is defined as:

1) Aminotransferase (ALT or AST) elevation > 3 × ULN

AND

2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

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

6.6.1 Potential Drug-induced Liver Injury for Subjects with HCC

Potential DILI for this study is defined as:

Hepatotoxicity as evidenced by any of the following:

- AST or ALT > 10 × ULN for > 2 weeks,
- AST or ALT > 15 × ULN irrespective of duration,
- Total bilirubin > 8 × ULN irrespective of duration for subjects with elevated total bilirubin at study entry or > 5 × ULN for those with normal total bilirubin at entry,

Clinical deterioration manifested by drug-related hepatic decompensation not identified above.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms (ECGs), x-ray films, any other potential safety assessments required or not required by the protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

6.8 Treatment Algorithms for Drug-related Adverse Events

Treatment algorithms for the management of potential drug-related AEs are located in Appendix 1 of this protocol and in the IB for nivolumab.[19]

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

For all parts of the study, a blinded independent review committee will review all available tumor assessment scans to determine response using RECIST v1.1 criteria. When required, adjudicated events will be submitted to health authorities for review on a specified timeframe in accordance with the adjudication documentation.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation (Part 1; Completed)

As this is a Phase 1/2 dose escalation cohort, the sample size at each dose cannot be determined exactly, as it depends on the number of observed toxicities. Between 3 and 12 subjects approximately are expected to be treated during dose escalation in each Dose Level, and up to 15 subjects may be dosed at selected Dose Levels.

8.1.2 Cohort Expansion (Part 1; Completed)

During cohort expansion, approximately 18 subjects are expected to be enrolled in each of the 3 unknown or low historic response cohort expansions and approximately 35 subjects in the 2 cohorts with higher historic ORR and treated at the previously determined MTD, MAD, or at an alternative dose that is not to exceed the MAD.

CRC, SCCHN, and HCC cohorts: The sample size for each tumor cohort will be guided by a 2-stage Gehan design.[38] In order to determine whether a target ORR is likely in a tumor cohort, 9 subjects will be treated at Stage 1 in each tumor type, as outlined in Table 3.1.1.2-1. For a tumor

type in which no responses are observed, it will be concluded that the true ORR is unlikely to be greater than or equal to the target ORR and no more subjects will be enrolled in these tumor cohorts. Otherwise, for the tumor cohort(s) in which at least 1 response among the first 9 subjects is observed, up to an additional 9 subjects will be enrolled as guided by Table 3.1.1.2-2. With 9 subjects in Stage 1, per tumor there is no more than a 10% chance of declaring that there is no therapeutic effect when actually there is an effect. A total of up to 18 subjects across the 2 stages per tumor will guarantee an estimate of the true ORR with 12% precision.

NSCLC and MEL cohorts: A total of approximately 35 subjects will be enrolled in each of these tumor cohorts based on achieving a higher precision with a reasonable control on the type I error. In a cohort of approximately 35 subjects, if 12, 14, or 16 responses are observed, then the lower limit of the 1-sided 90% CI for the ORR is 24%, 29%, or 34%, respectively. In addition, 19 responses would need to be observed in approximately 35 subjects so that the 90% 1-sided CI for the ORR is entirely above 20%. These calculations are based on the lower limit of the Clopper-Pearson method for exact CIs. If the true ORR in a tumor type is 45%, then with approximately 35 subjects in a cohort there is 96% chance of observing at least 10 responses, and 93% chance of observing at least 11 responses, and there is 7% chance of observing 10 or fewer responses (false negative rate). If the true ORR for a tumor is only 30% rather than 45%, then there is a 35% and 14% chance, respectively, that there will be at least 12 or at least 14 responses in approximately 35 subjects (false positive rate).

The above numbers are approximate, as subjects treated during dose escalation with a tumor under the same setting (eg, dose and population) as in cohort expansion may be included in the total n per tumor.

8.1.3 The SCCHN Cohort Expansion (Part 2; Completed)

A total of approximately 35 subjects will be enrolled in the SCCHN Cohort Expansion (Part 2). The null hypothesis that the true ORR is 25% will be tested against a 1-sided alternative: ORR = 40%. The null hypothesis will be rejected if 12 or more responses are observed in 35 subjects. This design gives a 1-sided type 1 error rate of 0.15 and a power of 0.81.

8.1.4 The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

The SCCHN Randomized Cohorts (Part 3) has a primary endpoint of ORR. A total of 225 subjects will be randomized in a 2:1 ratio to the 2 treatment arms, nivolumab combined with lirilumab (Arm A) and nivolumab monotherapy (Arm B), stratified by PD-L1 $\geq$ 50% expression (yes/no) and prior treatment with cetuximab (yes/no).

Objective Response Rate:

The sample size is calculated to assess the ORR of lirilumab in combination with nivolumab. The type 1 error is set to 0.10 (2-sided) with no planned interim analysis. The final analysis for ORR will take place approximately 6 months after the last subject is randomized and treated. With 150 subjects in Arm A, if 50 responses are observed, the estimated ORR will be 33% and the 90% CI will be [26%, 41%]. In Study CA209041, the 90% CI for the nivolumab arm in PD-L1+ (> 1%) subjects was [9%, 25%].

The above sample size calculation was performed using EAST® 6 and SAS 9.2.

8.1.5 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

[redacted]

8.1.7 The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

8.2 Population for Analyses

- All Enrolled Data set: subjects who signed informed consent and registered in the study.
- All Treated Data set: all subjects who received at least 1 dose of any study drug.
- Response-Evaluable Data Set: all treated subjects who receive any study drug, have a baseline tumor assessment with measurable disease, and 1 of the following:
  - at least 1 evaluable on-treatment tumor assessment,
  - clinical progression, or
  - death prior to the first on-treatment tumor evaluation.
- Lirilumab PK Data Set: all subjects who receive at least 1 dose of lirilumab and have adequate serum concentration data for lirilumab PK.
- Nivolumab PK Data Set: all subjects who receive at least 1 dose of nivolumab and have adequate nivolumab PK.
- Lirilumab Immunogenicity Data Set: all subjects who receive at least 1 dose of lirilumab and have at least 1 ADA sample available.
- Nivolumab Immunogenicity Data Set: all subjects who receive at least 1 dose of nivolumab and have at least 1 ADA sample available.
- Ipilimumab Immunogenicity Data Set: all subjects who receive at least 1 dose of ipilimumab and have at least 1 ADA sample available.
- Biomarker Data Set: all treated subjects who have biomarker data available.
- For the SCCHN Randomized Cohorts (Part 3), Randomized Subjects Data Set: All enrolled subjects who were randomized. This is the dataset for baseline demographics and efficacy analyses for this cohort.
- For the SCCHN Randomized Cohorts (Part 3), PRO subjects: All randomized subjects with baseline and at least 1 post-baseline PRO assessment.

8.3 Endpoint Definitions

Endpoints are defined as follows.

Safety Endpoint Definitions

Safety is the primary endpoint in this study except for the SCCHN Randomized Cohorts (Part 3). All subjects who receive at least 1 dose of study drug will be evaluated for safety as measured by the occurrence of AEs, SAEs, deaths, and laboratory abnormalities, assessed during treatment and for 150 days in follow-up.

Study level endpoints used to assess the safety objective will be based on AE reports and the results of vital sign measurements, ECGs, physical examinations, imaging studies, and clinical laboratory tests. AEs will be categorized using the most current version of MedDRA; both AEs and laboratory tests will be graded using NCI CTCAE v4.03. All subjects who receive study drug therapy will be evaluated for safety as measured by the rate of AEs, and SAEs, and will be assessed during treatment and for 150 days in follow-up.

Safety will be measured by the following:

- Incidence of AEs: all non-serious AEs will be collected from Day 1 until 150 days after the subject's last dose of study drug or until they discontinue the study as per Section 3.5 and all SAEs must be collected from the date of the subject's written consent until 150 days after discontinuation of dosing or until they discontinue the study as per Section 3.5.
- Incidence of clinical laboratory test abnormalities including hematology and serum chemistry, and thyroid panel abnormalities, assessed at specified timepoints as designated in the Time and Events Section (5.1).

Efficacy Endpoint Definitions

Study level endpoints used to assess the anti-tumor activity objective are defined as follows:

ORR is defined as the total number of subjects whose BOR is either CR or PR divided by the total number of subjects in the population of interest.

PFS rate is defined as the probability of a subject remaining progression-free and surviving to 24 weeks. The probability will be computed based on the number of days between the first dose of study drug and PD or death, as defined by each criterion. For those subjects who remain alive and have not progressed, PFS will be censored on the date of the last tumor assessment. The above will be calculated based on tumor measurements occurring Q8W during treatment and at planned timepoints during the clinical follow-up period.

BOR is the best response designation recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation, based on RECIST v1.1 criteria. CR or PR determinations included in the BOR assessment must be confirmed by a consecutive second (confirmatory) evaluation meeting the criteria for response that is performed at least 4 weeks after the criteria for response are first met. The above will be determined based on tumor measurements occurring Q8W (± 7days) during the treatment period (or Q6W (± 7days) for 1 year [48 weeks] and Q12W (± 7days) afterwards for the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 5] and once during the clinical follow-up period.

Other efficacy endpoints include the following:

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drug and every 3 months for up to 3 years following the first dose of study drug via in-person or phone contact after subjects discontinue the study drug.

PFS is defined as the time from randomization to the date of the first documented tumor progression (per RECIST v1.1). Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (confirmed CR or PR) only.

Time to response is defined as the time from randomization to the date of the first confirmed CR or PR. DOR will be evaluated for responders (confirmed CR or PR) only.

DCR is defined as the proportion of subjects with BOR equal to CR, unconfirmed CR, PR, unconfirmed PR, or SD.

Depth of response is defined as the target tumor burden percent change from baseline at nadir for each subject as measured by the percent of subjects with ≥ 50% and ≥ 80% tumor reduction

Pharmacokinetic Endpoint Definitions

PK endpoints (Cmax [µg/mL], Tmax [hr], AUC[0-T] [µg.hr/mL], Ctrough [µg/mL], AUC[TAU] [µg.hr/mL], AUC[INF] [µg.hr/mL], CL [L/day], T-HALF, Vz, and Cmin [µg/mL]) will be evaluated using non-compartmental analysis, where feasible. In addition, nivolumab end of infusion and trough (Cmin) concentrations will be calculated at specified visits for certain study parts [redacted].

Immunogenicity Endpoint Definitions

Endpoints for the study are incidence rates of persistent positive ADA as well as neutralizing positive ADA from initiation of each drug treatment and up to and including the follow-up period of the last study drug dosing. Based on recommendation from BMS Immunogenicity Council, Harmonization of Clinical Immunogenicity Reporting by an Initiative of the Therapeutic Protein Immunogenicity Focus Group of the American Association Pharmaceutical Scientists, and the

FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products, the following definitions will be applied.

ADA Status of a Subject:

- Baseline ADA Positive Subject: A subject with baseline ADA positive sample
- ADA Positive Subject: A subject with at least 1 ADA positive sample relative to baseline at any time after initiation of treatment during the defined observation time period.
- ADA Negative Subject: A subject with no ADA positive sample after the initiation of treatment

Definitions for ADA Status of a Sample (Baseline ADA Positive, ADA Positive, or ADA Negative), as well as sub-categories of ADA Positive Subject such as Persistent Positive, Only the Last Sample Positive, Other Positive and Neutralizing Positive will be provided in the statistical analysis plan.

Biomarker Endpoint Definitions

Measures of TILs, PD-L1, [redacted] expression using IHC, including baseline and changes from baseline outcomes, on mandatory tumor biopsies from the subjects specified in each study part.

[redacted]

Quality of Life Endpoint Definitions

Quality of life endpoints are discussed in detail in Section 5.8.

8.3.1 Primary Endpoint(s)

Refer to Section 8.3 for endpoint definitions.

8.3.1.1 Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

- The primary endpoints are safety measures (the Dose Escalation and Cohort Expansion [Part 1] the SCCHN Cohort Expansion [Part 2]), and assessment of preliminary anti-tumor activity (for the SCCHN Cohort Expansion [Part 2]).
  - For the SCCHN Cohort Expansion (Part 2), assessment of preliminary anti-tumor activity will be based on using irRECIST for the purposes of subject management. Timepoint tumor response evaluations will be recorded on the CRF based on investigators' assessments using irRECIST criteria. Statistical analysis and reporting will be based primarily on RECIST v1.1 criteria.

8.3.1.2 The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

- The primary endpoint is ORR in subjects randomized to lirilumab plus nivolumab.
  - Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, Q8W (± 7 days) until Week 48, and then Q12W (± 7 days) until PD or treatment discontinuation, whichever occurs earlier.

8.3.1.3 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

8.3.1.4 The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)

- The primary endpoints are safety measures and assessment of preliminary anti-tumor activity.
  - The assessment of preliminary anti-tumor activity will be based on using RECIST v1.1. Timepoint tumor response evaluations will be recorded on the CRF based on investigators' assessments using RECIST v1.1 criteria. Statistical analysis and reporting will be based primarily on RECIST v1.1 criteria. Investigator-assessed BOR based on RECIST v1.1 will be listed.

8.3.1.5 The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

8.3.2 Secondary Endpoints

8.3.2.1 The Dose Escalation and Cohort Expansion (Part 1; Completed) and the SCCHN Cohort Expansion (Part 2; Completed)

The secondary endpoints are PK, ADAs, and biomarkers.

- The secondary endpoint of occurrence of specific ADAs to lirilumab and nivolumab will be determined from measurements on Weeks 1, 3, 5, 13, 17, 33, 49, 65, and 81; end of treatment; and all 3 clinical follow-up visits (please see Table 5.7.3.3-1, Table 5.7.3.3-2, Table 5.7.3.3-3, and Table 5.7.3.3-4).
- Biomarker endpoint measures will be taken from a minimum of 10 MEL cohort expansion subjects and a minimum of 10 SCCHN (the Dose Escalation and Dose Expansion [Part 1]) cohort expansion subjects or other additional subjects included in the biomarker analysis data sets.
- Biomarker endpoint measures will be taken from a minimum of 15 subjects in the SCCHN Cohort Expansion (Part 2) or other additional subjects included in the biomarker analysis data sets.

8.3.2.2 The SCCHN Randomized Cohorts (Part 3 - closed to enrollment)

The secondary endpoints are DCR, DOR, time to response, depth of response, OS, PFS, ORR according to investigator-assessed response, and safety measures.

- Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, Q8W (± 7 days) until Week 48, and then Q12W (± 7 days) until PD or treatment discontinuation, whichever occurs earlier.

8.3.2.3 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

8.3.2.4 The Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5 - closed to enrollment)

The secondary endpoints are DOR, depth of response, PK, ADAs, immunomodulatory properties, and biomarkers.

- Tumor assessments are scheduled to be performed at Week 8 (± 7 days) from first dose date, Q8W (± 7 days) for 1 year (48 weeks), and then Q12W (± 7 days) until PD or treatment discontinuation, whichever occurs earlier.
- The secondary endpoint of occurrence of specific ADAs to lirilumab, nivolumab, and ipilimumab, will be determined from measurements specified in Table 5.7.3.3-7).
- Biomarker endpoint measures will be included from all subjects in the biomarker analysis data sets.

8.3.2.5 The Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 6)

Removed with Revised Protocol 12.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, and height will be collected, and body mass index will be derived.

Subject characteristics including demographics, baseline performance status, disease characteristics and baseline laboratory parameters will be summarized by treatment arm and/or tumor types, if applicable, as well as pooled across treatment arm and/or tumor types, if applicable.

8.4.2 Efficacy Analyses

8.4.2.1 The SCCHN Randomized Cohorts (Part 3) Primary Endpoint Analysis

The primary endpoint of ORR in subjects randomized to lirilumab plus nivolumab will be analyzed for the SCCHN Randomized Cohorts (Part 3). Subjects will be enrolled if PD-L1 is expressed in ≥ 1% of tumor cells.

CIs will be provided separately for each treatment arm using the Clopper-Pearson method.

8.4.2.2 Secondary Endpoints Analysis

Individual BOR, DOR, and PFS will be listed using RECIST v1.1 criteria. Summary tables will be presented on efficacy endpoints for each randomized treatment arm. The OS and PFS rates at specific timepoints (eg, at 24 weeks) and corresponding CI will be estimated by KM methodology depending on data availability. ORR, DOR and PFS analyses will include subjects in the cohort expansion phase and subjects in dose escalation matching those in cohort expansion by disease type and treatment. Individual changes in the tumor burden over time will be presented graphically within a disease type.

[redacted]

The number and percentage of subjects in each category of BOR (CR, PR, SD, PD, or unable to determine) will be presented by treatment arm and/or tumor types, if applicable. Finally, a waterfall plot showing the biggest reduction in the sum of target lesions will be produced for response-evaluable subjects.

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Summary tables will be presented on safety parameters for each treatment arm and/or tumor types, if applicable.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for the PK parameters of lirilumab by dose and study day/week. For [redacted] the Signal Detection in SCCHN with Lirilumab, Nivolumab, and Ipilimumab Combination (Part 5), summary tables will also be presented by each treatment arm. To describe the dependency on dose of anti-KIR, scatter plots of Cmax and AUC(TAU) vs dose will be provided for each day measured. Dose proportionality of lirilumab when co-administered with nivolumab will be assessed based on a power model. Dose proportionality of lirilumab when co-administered with nivolumab, and of lirilumab when co-administered with nivolumab and ipilimumab will be assessed based on a power model.

Nivolumab end of infusion and trough (Cmin) concentration will be tabulated by summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be part of a separate report.

8.4.5 Biomarker Analyses

The pharmacodynamic effect of lirilumab on TILs and expression of tumor markers including PD-L1 [redacted] will be assessed by summary statistics, and investigated graphically to explore patterns of change, eg, with drug exposure for corresponding subjects included in the biomarker analysis data set. In addition, the correlation of TIL changes and tumor marker expression with measures of peripheral blood markers will be explored graphically, or by appropriate statistical methods based on data availability, for assessing associations.

[redacted]

8.4.7 Outcomes Research Analyses

Removed with Revised Protocol 12.

8.4.8 Other Analyses

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least 1 positive ADA at any timepoint will be provided by treatment for each analyte. The number (%) of subjects with the following anti-drug responses will be reported for each analyte if applicable, by dose, and overall: Baseline ADA

Positive, ADA Positive (Persistent Positive, Only the Last Sample Positive), ADA Positive with Neutralizing Positive, and ADA Negative.

To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between trough concentrations of lirilumab (or nivolumab or ipilimumab) and corresponding ADA assessments may be explored.

8.5 Interim Analyses

Data emerging from the unblinded parts of this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final lock of the study database. While the study is still ongoing, additional interim analyses may also be performed for administrative purposes or publications. In that case, analyses will only consist of listings, summaries, and graphs of the available data, and no formal inferences requiring any adjustment to statistical significance level will be performed. Efficacy analyses based on interim data may use response-evaluable or all-treated populations depending on the purpose of the analysis.

The Dose Escalation and Cohort Expansion (Part 1; completed) of the study is the dose-escalation study and includes expansion cohorts in specific tumor types. In the dose expansion portion of the Dose Escalation and Cohort Expansion (Part 1; completed), in order to assess if the target response rate is likely for tumor cohorts with unknown or low historic ORR, the tumor response will be initially based on the tumor measurements from the first approximately 9 subjects in each cohort to facilitate decisions on continuing enrollment in that tumor. If no responses are observed in approximately the first approximately 9 subjects with tumor measurements, enrollment in that tumor cohort will not continue. However, accrual to these tumor types may continue, while the Stage I response assessments are performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (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 an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

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.

In addition, the study may be evaluated by BMS 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 BMS.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator 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, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator 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, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. 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 subject, including unique subject identifiers
- amount transferred to another area/study site for dispensing or storage
- non-study disposition (eg, 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.

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

9.2.3 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.

For study sites using the BMS EDC 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC 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 BMS training requirements and must only access the BMS EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

For this protocol, the Signatory investigator will be selected considering the following criteria.

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in study design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life-threatening (defined as an event in which the subject 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, 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 subject or may require intervention [eg, medical, surgical] to prevent 1 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). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
%CV	coefficient of variation
AE	adverse event
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the plasma concentration-time curve in 1 dosing interval
BC	bladder cancer
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BSA	body surface area
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C	Cycle
C30	30-item core
Ca	calcium
CEA	carcinoembryonic antigen
Cavgss	time-averaged concentration at dosing interval
CBC	complete blood count
CD	cluster of differentiation
cHL	classical Hodgkin lymphoma
CI	confidence interval

Term	Definition
CL	clearance
C1	chloride
Cmax	maximum observed concentration
Cmaxss	steady-state peak concentration
Cmin	trough observed concentration
Cminss	steady-state trough concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form, paper or electronic
CRP	C-reactive protein
CT	computed tomography
CTA	clinical trial agreement
CTL	cytotoxic T lymphocyte
ctDNA	circulating tumor deoxyribonucleic acid
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen 4
Ctrough	trough observed serum concentration
D	Day
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
EC50	concentration required for 50% efficacy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture

Term	Definition
EGFR	epidermal growth factor receptor
EOI	End of Infusion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D	EuroQol 5 dimensions questionnaire
ESCC	squamous cell esophageal cancer
Fab	fragment antigen-binding
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Geo	geometric
H&N35	head and neck specific module
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC50	concentration required for 50% inhibition
ICH	International Conference on Harmonisation
ICOS	inducible T-cell co-stimulator
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin

Term	Definition
IO	immuno-oncology
INR	international normalized ratio
ir	immune-related
IRB	Institutional Review Board
IRC	independent review committee
IRT	Interactive Response Technology
IV	intravenous
IVRS	Interactive Voice Response System
K	potassium
KIR	killer cell immunoglobulin-like receptors
KM	Kaplan-Meier
KRAS	Kirsten Ras
[redacted]	
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
Mg	magnesium
mIgG	murine immunoglobulin
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mWHO	modified World Health Organization
Na	sodium
N/A	not applicable
NCI	National Cancer Institute
NK	natural killer
[redacted]	

Term	Definition
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L1+	programmed cell death ligand 1 positive
PD-L2	programmed cell death ligand 2
PE	physical examination
PFS	progression-free survival
[redacted]	
PID	patient identification number
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
QLQ	quality of life questionnaire
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Term	Definition
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SHP-1, -2	Src homology region 2 domain-containing phosphatase-1, -2
sqNSCLC	squamous cell non-small cell lung cancer
T3	triiodothyronine
T4	thyroxine
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCGA	The Cancer Genome Atlas
TF	tumor free
T-HALF	half-life
TIL	tumor-infiltrating lymphocyte
Tmax	time of maximum observed concentration
TRAE	treatment-related adverse event
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
v1.1	version 1.1
v4.03	version 4.03
VAS	visual analog rating scale
Vc	volume of central compartment
Vss	apparent volume of distribution at steady state
Vz	apparent volume of distribution during terminal phase
WBC	white blood cell
WOCBP	women of childbearing potential

12 REFERENCES

1 Leidner R, Kang H, Haddad R, et al. Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck [abstract 456]. SITC Annual Meeting; 2016 Nov 9-13; National Harbor, MD.

2 Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck [published online ahead of print 2016 Oct 8]. N Engl J Med 2016 Oct 8. doi:10.1056/NEJMoa1602252.

3 Galsky MD, Retz M, Siefker-Radtke AO, et al. Efficacy and safety of nivolumab monotherapy in patients with metastatic urothelial cancer (mUC) who have received prior treatment: Results from the phase II CheckMate-275 study [Abstract LBA31]. 2016 ESMO Congress; 2016 Oct 7-11; Copenhagen, Denmark.

4 Poli A, Michel T, Thérésine M, et al. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology 2009;126(4):458-65.

5 Senbabaoglu Y, Winer AG, Gejman RS, et al. The landscape of T-cell infiltration in human cancer its association with antigen presenting gene expression [published online ahead of print 2015 Sep 1]. Available from: URL: http://biorxiv.org/content/early/2015/09/01/025908. doi:http://dx.doi.org/10.1101/025908.

6 Greenwald RJ, Freeman GH, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004;23:515-48.

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

8 Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature Immunol 2007;8:237-45.

9 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;15:7412-20.

10 Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: Releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer J 2012;18:153-9.

11 Effect of anti-Ly49 in Combination with anti-PD-1 or anti-CTLA4 on the rejection of the C1498 AML tumor: Study 1. Bristol-Myers Squibb Company; 2012. Document Control No. [redacted].

12 Segal NH, Infante JR, Sanborn RE, et al. Safety of the natural killer (NK) cell-targeted anti-KIR antibody, lirilumab (liri), in combination with nivolumab (nivo) or ipilimumab (ipi) in two phase I studies in advanced refractory solid tumors [poster 1086P]. 2016 ESMO Congress; 2016 Oct 7-11; Copenhagen, Denmark.

[13] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 6(2):69-90.

[14] NCI SEER Statistics Review. Available from: URL: http://seer.cancer.gov/statfacts/html/oralcav.html. Accessed March 5, 2016.

[15] Leemans CR, Braakhuis B, Brakenhoff R. Molecular biology of head and neck cancer. Nat Rev Cancer 2011;11(1):9-22.

[16] Mehra R, Seiwert TY, Mahipal A, et al. Efficacy safety of pembrolizumab in recurrent/metastatic head neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012 [abstract 6012]. J Clin Oncol 2016:34(Suppl).

[17] Gillison ML, Blumenschein G, Fayette J. Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate141 [abstract CT099]. Cancer Research 2016;76(14 Suppl):CT099-CT099.

[18] Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261-9.

[19] Nivolumab (BMS-936558) Investigator Brochure Version 16. Bristol-Myers Squibb Company; 2017. Document Control No. [redacted]

[20] An open-label, trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum-doublet chemotherapy versus platinum doublet chemotherapy in subjects with stage IV non-small cell lung cancer (NSCLC) (CheckMate 227). ClinicalTrials.gov Identifier: NCT02477826. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02477826.

[21] BMS-986015 (lirilumab) Investigator Brochure, Version 08. Bristol-Myers Squibb Company; 2017. Document Control No. [redacted]

[22] Ipilimumab (BMS-734016) Investigator Brochure Version 19. Bristol-Myers Squibb Company; 2016. Document Control No. [redacted]

[23] Non-clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1). Bristol-Myers Squibb Company. Document Control No. [redacted]

[24] Repeated-dose (q3d x 3, 14-day) toxicity study of anti-CTLA-4/10D1 administered via intravenous injection to cynomolgus monkeys (Study 126-002), Report. Redfield Laboratories; 2000. Document Control No. [redacted]

[25] Study SBi 0919-128: A 2-week toxicity study of human anti-CTLA4 administered by intravenous injection to cynomolgus monkeys. Bristol-Myers Squibb Company; 2000. Document Control No. [redacted]

[26] Covance Study 7114-100: Fourteen day intravenous toxicity study with mAb 10D1 in cynomolgus monkeys. Bristol-Myers Squibb Company; 2000. Document Control No. [redacted]

[27] Study DS06064: BMS-663513 and BMS-734016 (MDX-010): One month intravenous combination toxicity study in monkeys. Bristol-Myers Squibb Company; 2007. Document Control No. [redacted]

[28] Study SBi 1416-128: A repeat dose toxicology and efficacy study MDX-010 or MDX-010-HYB in combination with HBsAg and SKMel vaccines in cynomolgus monkeys. Bristol-Myers Squibb Company; 2003. Document Control No. [redacted]

[29] Study SBi 0992-128: An immunogenic study following combined intravenous/intramuscular administration of MAb10D1/HBsAg, respectively, to cynomolgus monkeys. Bristol-Myers Squibb Company; 2001. Document Control No. [redacted]

[30] Study 01-3460: MDX-CTLA4: A 6-month intravenous toxicology study in cynomolgus monkeys. Bristol-Myers Squibb Company; 2002. Document Control No. [redacted]

[31] Ipilimumab population pharmacokinetics and exposure-response analyses in subjects with advanced melanoma (CA184004, CA184007, CA184008, and CA184022). Bristol-Myers Squibb; 2010. Document Control No. [redacted]

[32] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.

[33] Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-minute infusion: analysis of data from CheckMate 153 [abstract 3059]. American Society of Clinical Oncology 2016 Annual Meeting; 2016 Jun 3-7; Chicago, IL.

[34] Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Abstract 1297O.

[35] Brahmer J, 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 presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

[36] Felip E 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 discussion presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD.

[37] Jin S, Deng Y, Hao J-W, et al. NK cell phenotypic modulation in lung cancer environment. PLoS ONE 2014;9(10):e109976.

[38] Gehan, EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. Therapeutics 1961;13:4,346-53.

[39] Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol 2012;36:945-54.

[40] Umar A, Boland Cr, Terdiman JP, et al. Revised Bethesda Guidelines for Hereditary Non-polyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability. J Nat Cancer Inst 2004;96:261-68.

[41] 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.

[redacted]

APPENDIX 1 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology (I-O) 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 I-O drug-related adverse events (AE). The oral equivalent of the recommended intravenous doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

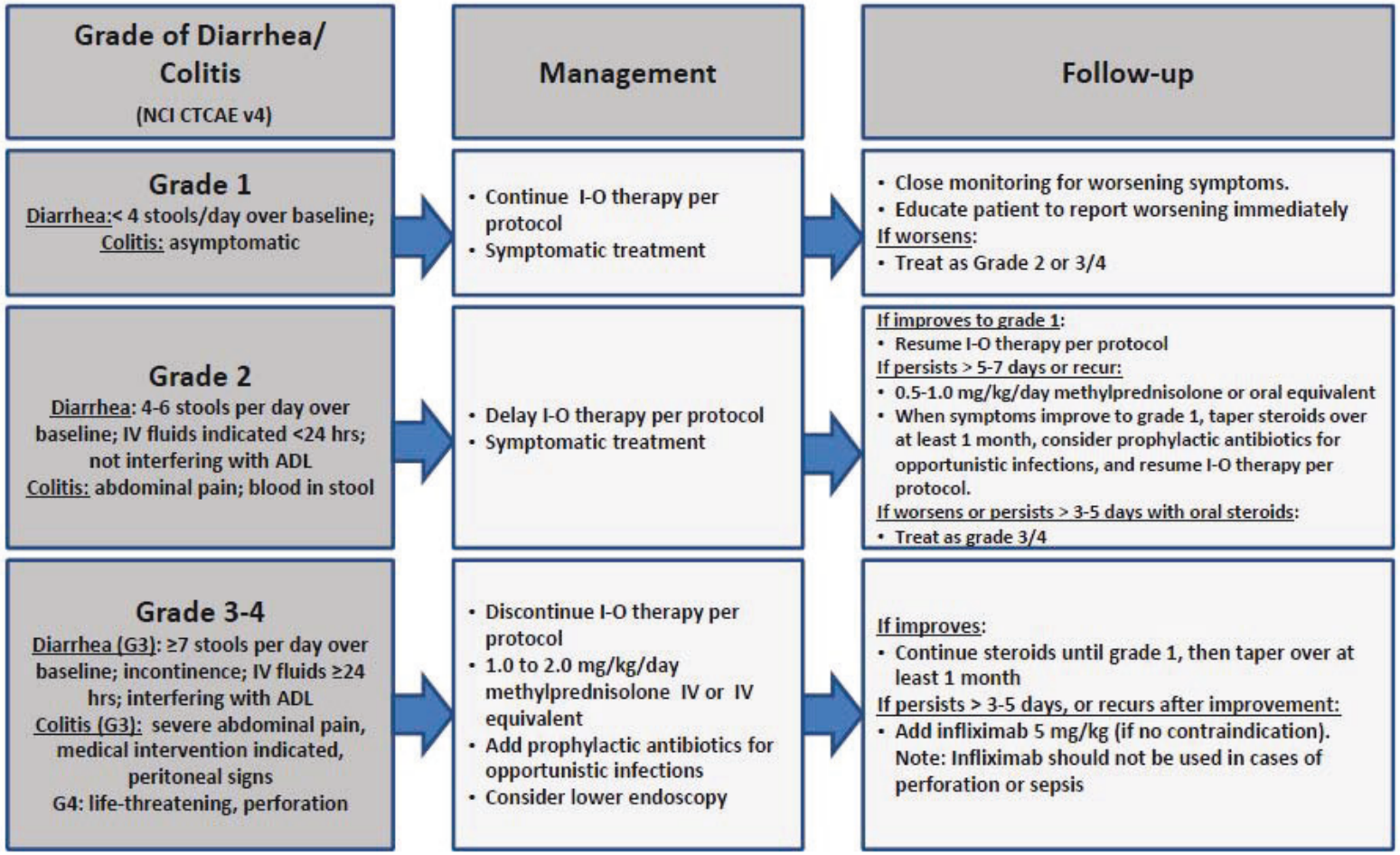
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related AEs covered by these algorithms will depend on the I-O agent or regimen being used.

Source: Appendix 3, BMS936558 IB v15

Figure 1: Gastrointestinal 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.



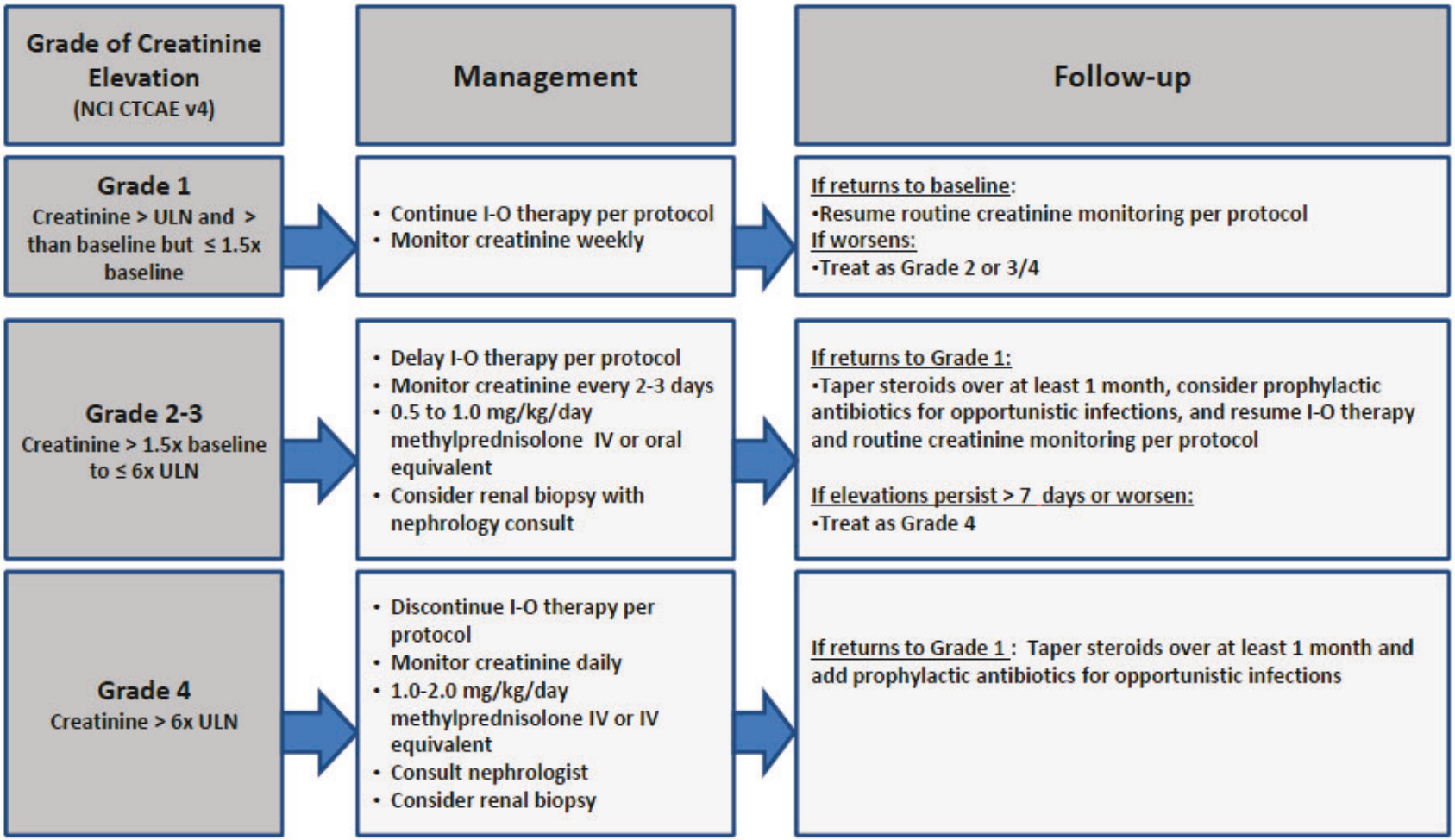
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute.

Source: Appendix 3, BMS936558 IB v15

Figure 2: Renal Adverse Event Management Algorithm

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



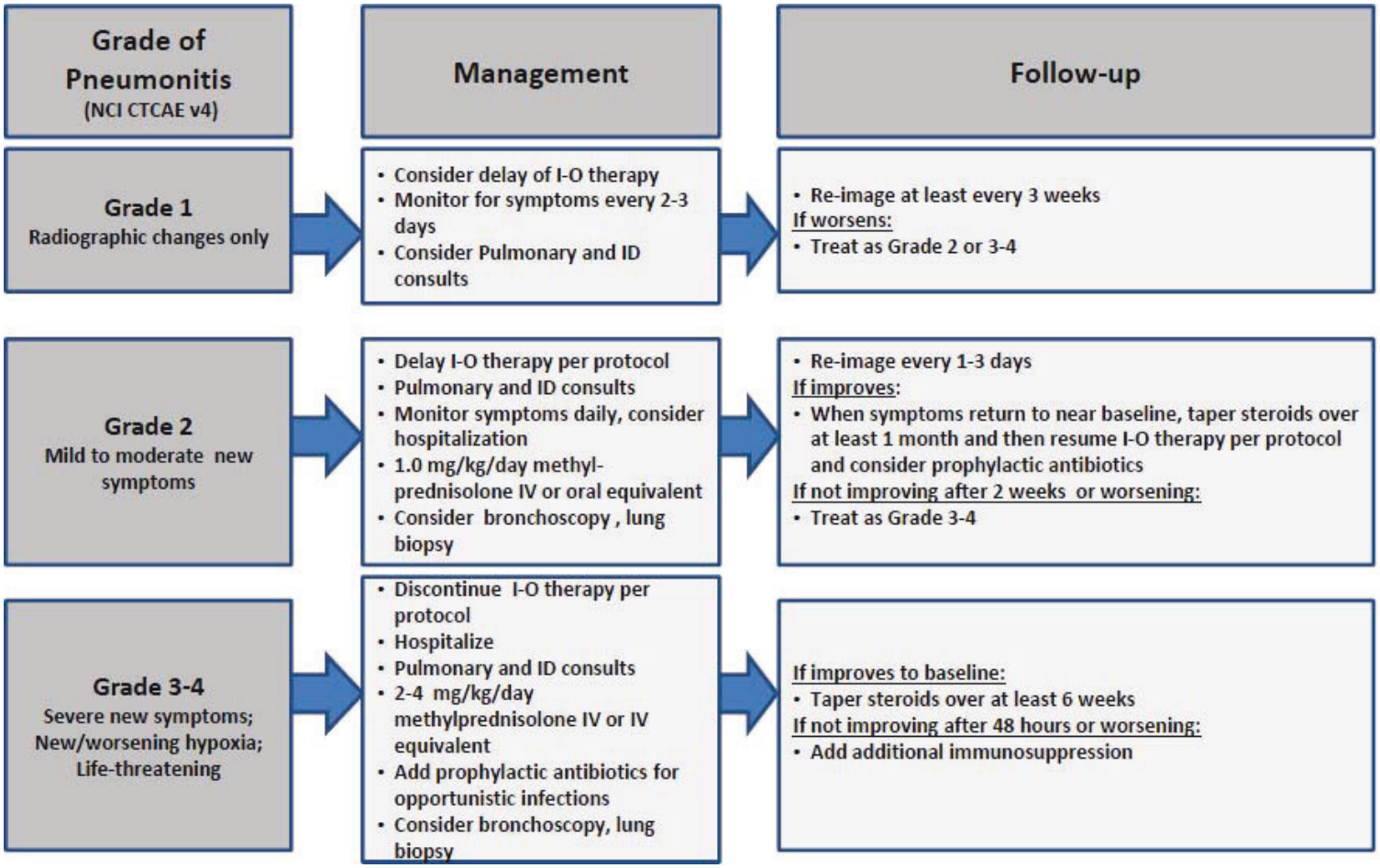
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; ULN = upper limit of normal.

Source: Appendix 3, BMS936558 IB v15

Figure 3: Pulmonary Adverse Event Management Algorithm

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



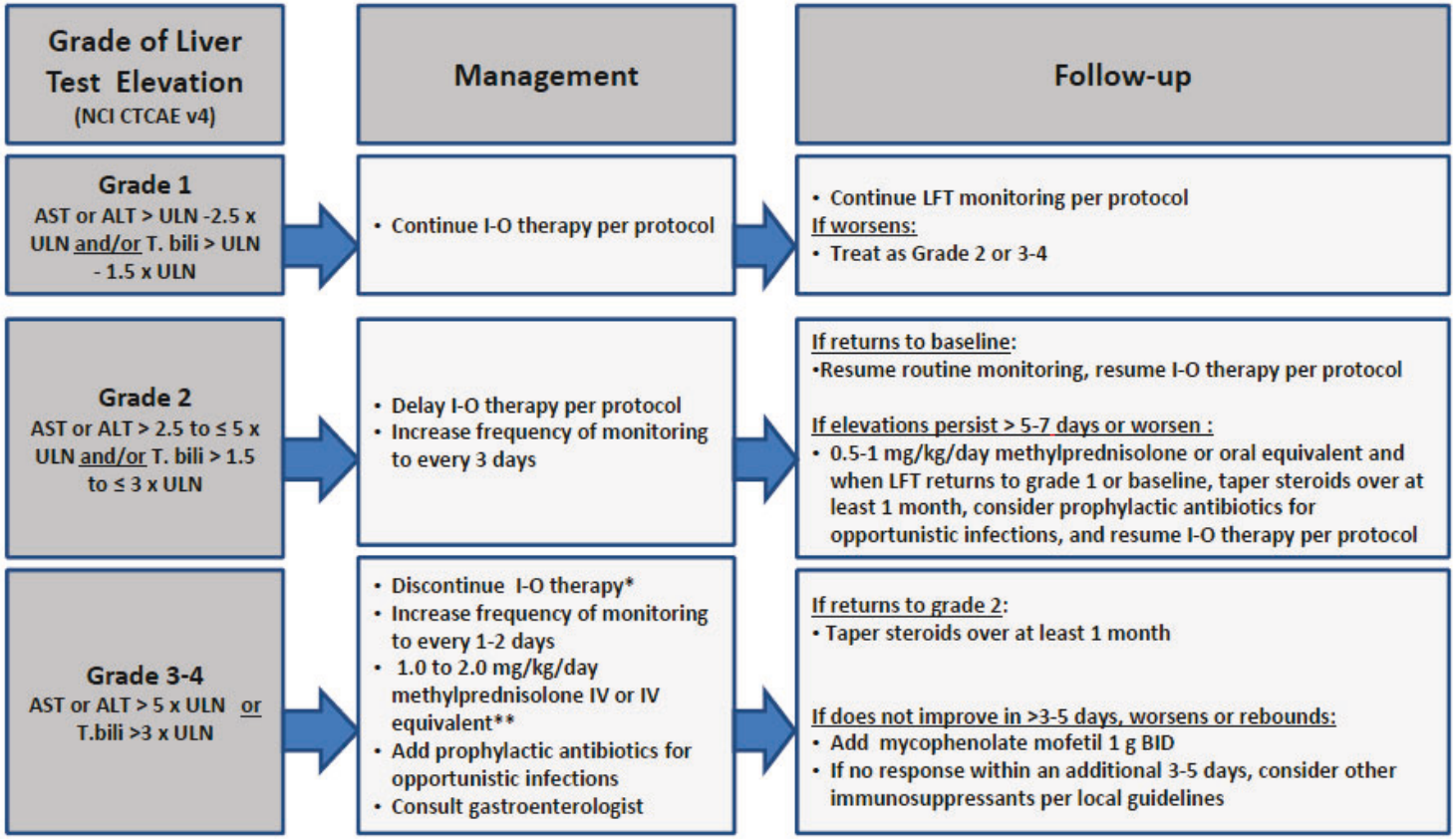
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

CTCAE = Common Terminology Criteria for Adverse Events; ID = infectious disease; IV = intravenous; NCI = National Cancer Institute.

Source: Appendix 3, BMS936558 IB v15

Figure 4: 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 (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 × ULN and total bilirubin ≤ 5 × ULN.**

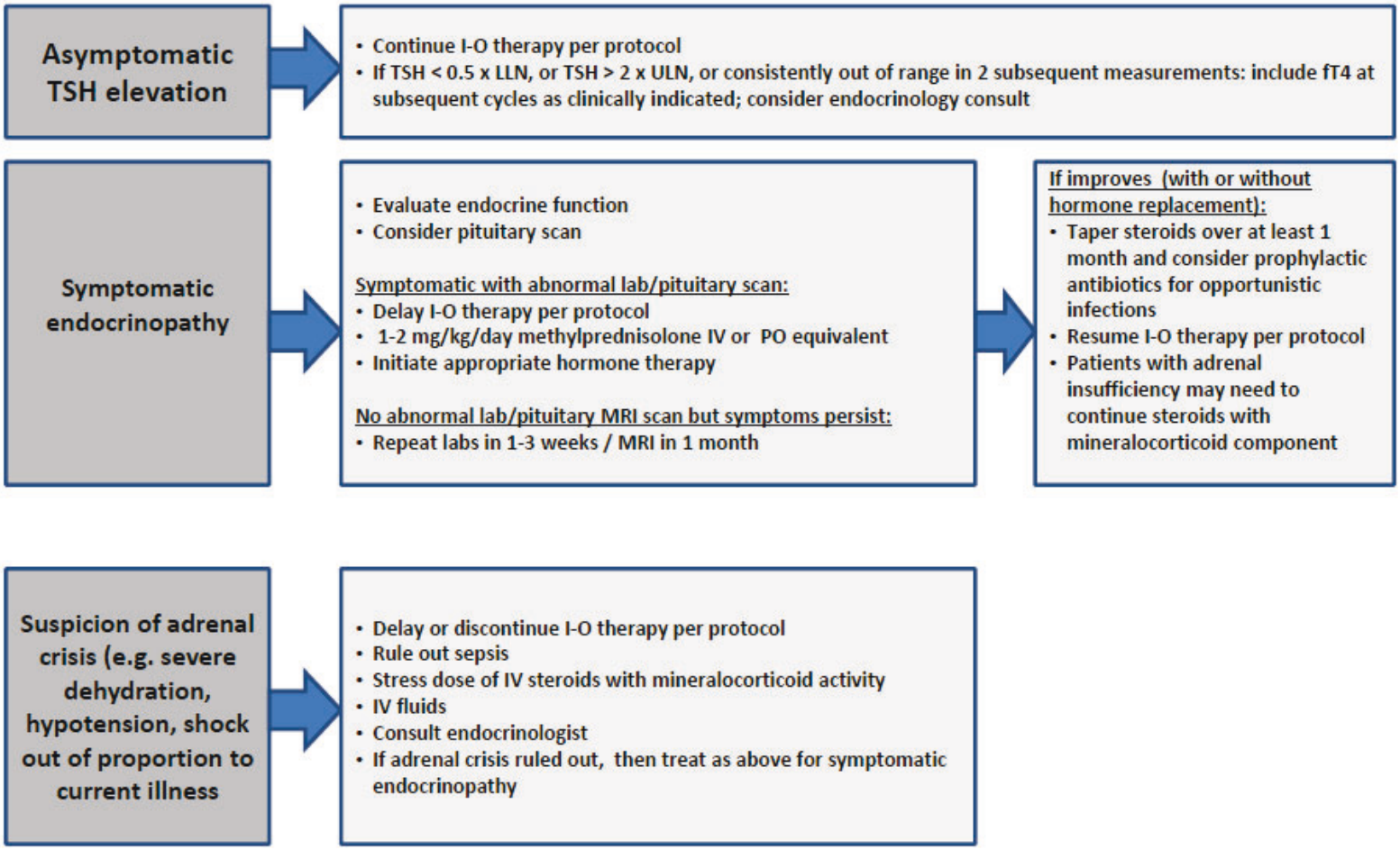
**The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; LFT = liver function test; NCI = National Cancer Institute; ULN = upper limit of normal.

Source: Appendix 3, BMS936558 IB v15

Figure 5: Endocrinopathy Management Algorithm

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



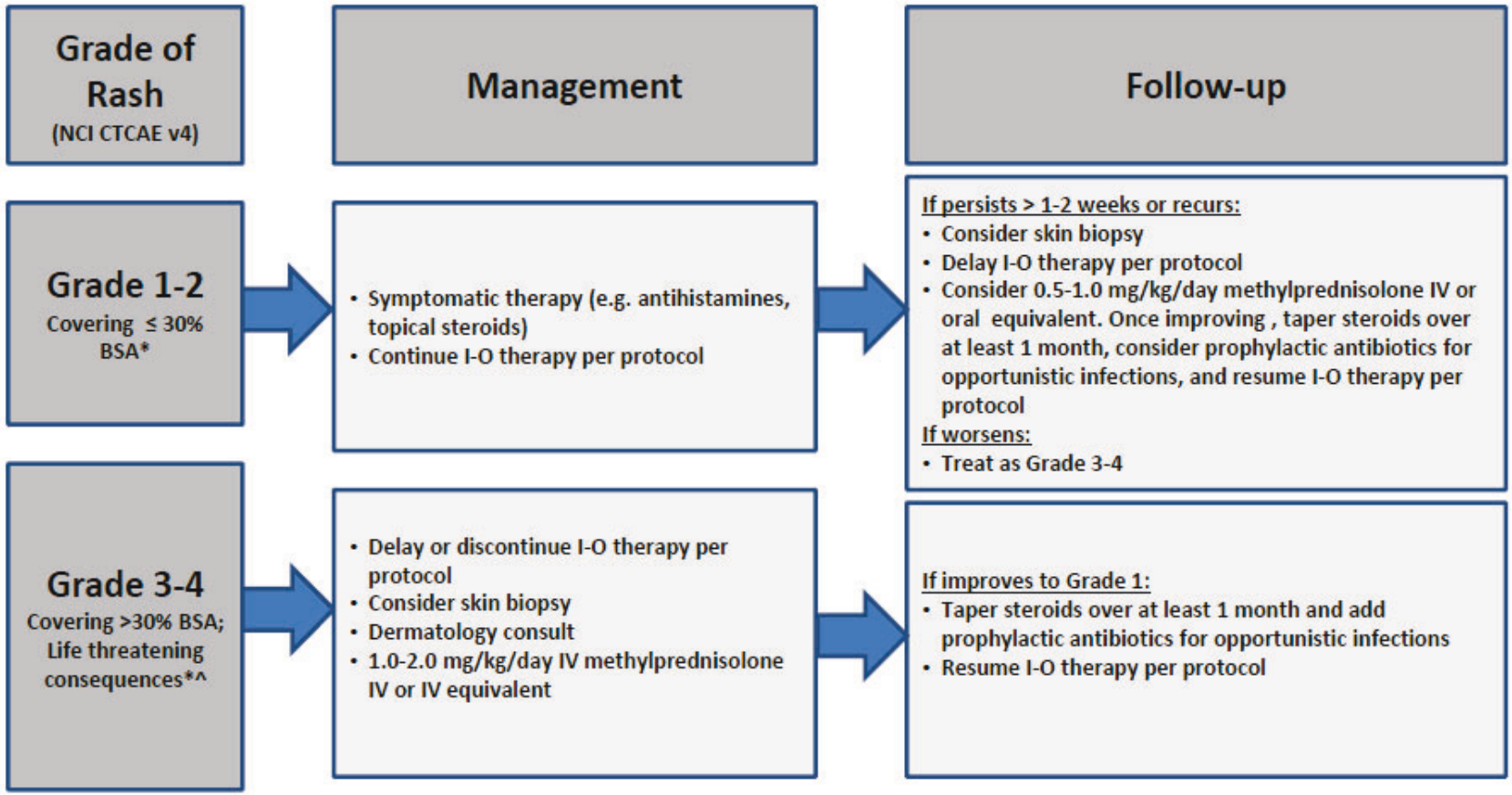
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

IV = intravenous; MRI = magnetic resonance imaging; PO = oral; TSH = thyroid stimulating hormones; ULN = upper limit of normal.

Source: Appendix 3, BMS936558 IB v15

Figure 6: Skin Adverse Event Management Algorithm

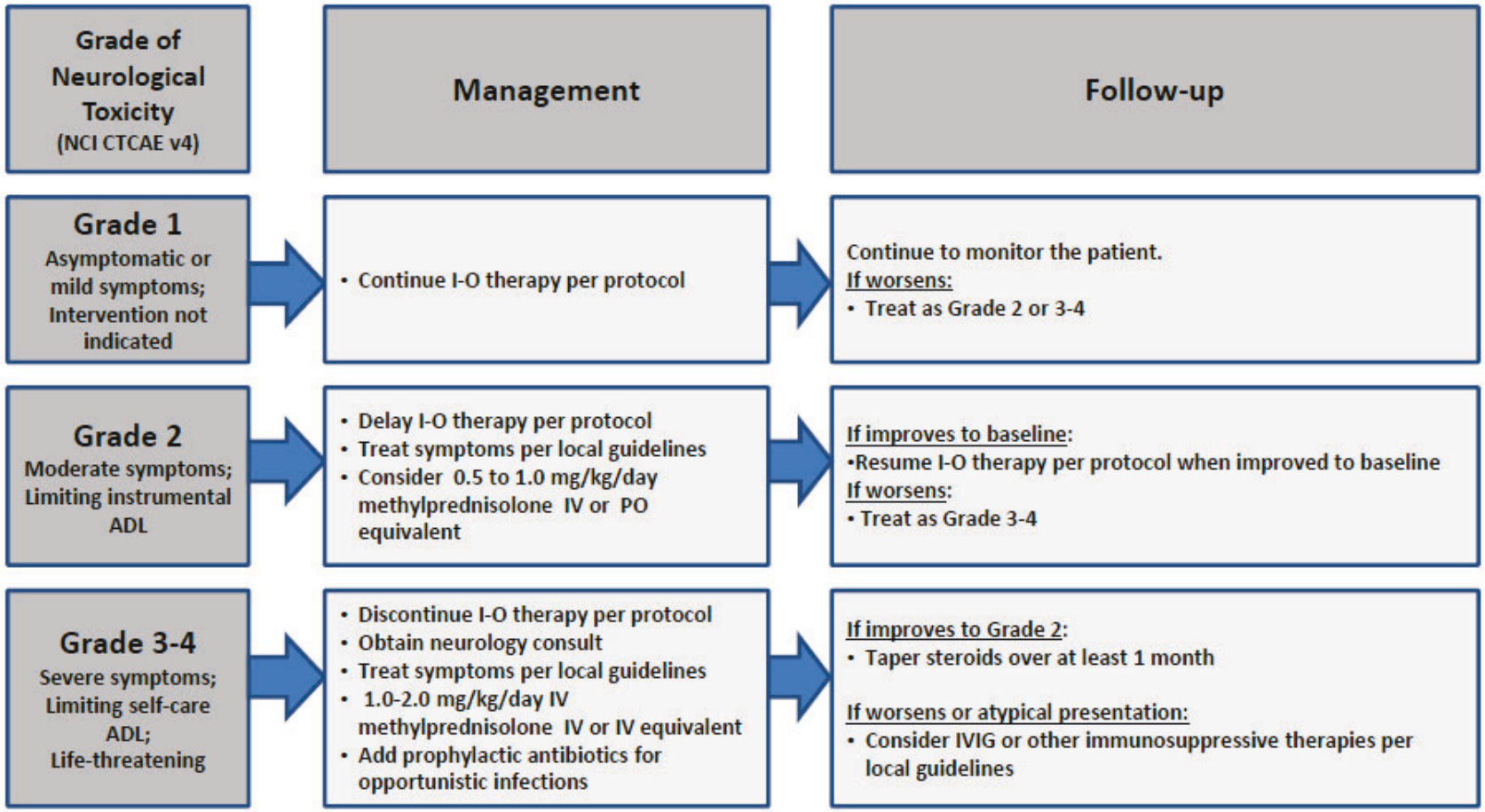
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once 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 v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.
BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; SJS = Stevens Johnson Syndrome; TEN = toxic epidermal necrolysis.
Source: Appendix 3, BMS936558 IB v15

Figure 7: Neurological Adverse Event Management Algorithm

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



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

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; IVIG = intravenous immunoglobulin therapy; NCI = National Cancer Institute; PO = oral.

Source: Appendix 3, BMS936558 IB v15

APPENDIX 2 irRECIST

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Subjects must have measureable disease to be eligible for this study.

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable lesions

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm 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, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or 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.

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Measurable lesions may be in an irradiated field as long as there is documented progression and the lesion(s) can be reproducibly measured.

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements.***

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 below, 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.

2.1.1 Lymph nodes

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 scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

Immune-related Complete Response (irCR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Immune-related Partial Response (irPR): At least a **30% decrease in the sum of diameters of target lesions and all new measurable lesions** (ie Percentage Change in Tumor Burden)**,** taking as reference the baseline sum diameters.

Note: the appearance of new measurable lesions is factored into the overall **Tumor Burden**, but does not automatically qualify as progressive disease until the sum of the diameters increases by ≥ 20% when compared to nadir.

Immune-related Progressive Disease (irPD): At least a **20% increase in Tumor Burden** (ie the sum of diameters of target lesions, and any new measurable 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**. Tumor assessments using immune-related criteria for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old and new lesions as they appear.

Immune-related Stable Disease (irSD): Neither sufficient shrinkage to qualify for irPR nor sufficient increase to qualify for irPD, taking as reference the smallest sum diameters while on study.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

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 scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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 (note: in case of a lymph node believed to be present and 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).

3.1.1.3 Target 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.
- 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'.

3.2 Evaluation 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.

Immune-related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Immune-related Progressive Disease (irPD): Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until **Tumor Burden** increases by 20% (ie the sum of the diameters at nadir of target lesions and any new measurable lesions increases by the required amount)

Note: Non-target lesions are not considered in the definition of Stable Disease and Partial Response.

3.3 New lesions

The appearance of new lesions alone does not denote disease progression. However their contribution to total tumor burden is included in the sum of the diameters which in turn feeds into the irRECIST assessment of tumor response.

4 RESPONSE CRITERIA

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

- **Immune-related Complete Response (irCR)**: Complete disappearance of all tumor lesions (target and non-target), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.

- **Immune-related Partial Response (irPR)**: The sum of the diameters of all target lesions is measured and captured as the sum of diameters at baseline. At each subsequent tumor assessment, the sum of the diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Diameters (irSD). A decrease, relative to baseline of the irSD of 30% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first irPR.

- **Immune-related Stable Disease (irSD)**: irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.

- **Immune-related Progressive Disease (irPD)**: It is recommended in difficult cases (eg, increase in the sum of the diameters accompanied with significant individual lesion regression, "mixed response", or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
  - At least 20% increase in the Sum of the Diameters of all target lesions over the nadir Sum of the Diameters calculated for these lesions.
  - At least a 20% increase in the Sum of the Diameters of all target lesions and new measurable lesions over the nadir Sum of the Diameters calculated for the target lesions.

Table 1. irRECIST Definitions.

Target Lesion Response	Non-target Lesion Response	New Measurable Lesions	New Non-measurable Lesions	% Change in Tumor Burden (including measurable new lesions when present)	Overall ir-response
CR	CR	Any	Any	-100%	irCR
PR	Any	Any	Any	≤ -30%	irPR
				> -30% to < +20%	irSD

Table 1. irRECIST Definitions.

Target Lesion Response	Non-target Lesion Response	New Measurable Lesions	New Non-measurable Lesions	% Change in Tumor Burden (including measurable new lesions when present)	Overall ir-response
				≥ +20%	irPD
SD	Any	Any	Any	> -30% to < +20%	irSD
				≥ +20%	irPD
PD	Any	Any	Any	≥ +20%	irPD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ir = Immune response

4.1.1 Confirmation Scans

- **Verification of Response:** irPR must be confirmed no less than 4 weeks from the initial irPR.

4.2 Best overall response: All timepoints

Best Overall Response and Date of Progression Using irRECIST (irBOR): The investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the investigators.

APPENDIX 3 RECIST V1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Subjects must have measureable disease to be eligible for this study.

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable lesions

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm 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, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or 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.

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Measurable lesions may be in an irradiated field as long as there is documented progression and the lesion(s) can be reproducibly measured.

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 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.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements.***

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 below, 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.

2.1.1 Lymph nodes

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 scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

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'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 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.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

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 scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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 (note: in case of a lymph node believed to be present and

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).

3.1.1.3 Target 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.
- 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'

3.2 Evaluation 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 (< 10 mm 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. (*Note:* the appearance of one or more new lesions is also considered progression).

3.2.1 Special notes on assessment of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows:

3.2.1.1 When the subject also has measurable disease

- 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 quality for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that 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.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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: i.e. 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 a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.

- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers will not be used to assess objective tumor responses.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 subject'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.

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 subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and 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.*

4 RESPONSE CRITERIA

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Table 1. Time point response: subjects 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

Table 1. Time point response: subjects with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
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, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation Scans

- **Verification of Response:** Confirmation of PR and CR is required within 4 weeks to ensure responses identified are not the result of measurement error.

4.2 Best Overall Response: all time points

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject'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.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline.

Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Table 2. Best overall response when confirmation of CR and PR *IS* required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject 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.

4.3 Duration of response

4.3.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Eisenhauer et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009. Vol 45, p 228-247.

APPENDIX 4 HEAD AND NECK SQUAMOUS CELL CARCINOMAS CLASSIFICATIONS

Head and neck squamous cell carcinomas will be classified as follows:

- oral cavity:
  - anterior two-thirds of the tongue
  - tongue unspecified
  - lip
  - gum
  - floor of the mouth
  - hard palate
  - palate unspecified
  - other oral cavity (including buccal mucosa and retromolar area)
  - oral cavity unspecified

- oropharynx:
  - base of the tongue
  - soft palate
  - tonsil
  - uvula
  - other parts of the oropharynx
  - Waldeyer's ring
  - oropharynx unspecified

- larynx:
  - glottis
  - supraglottis
  - subglottis
  - other and unspecified larynx subsites
  - hypopharynx cases are classified as belonging to the larynx, including pyriform sinus

APPENDIX 5 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

APPENDIX 6 GUIDANCE ON CONTRACEPTION

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

For WOCBP

Highly effective methods of birth control include the following:

- Progestogen only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills
- (combination of estrogen and progesterone), vaginal ring, injectables, or implants
- Intrauterine devices (IUDs) (hormonal or non-hormonal)
- Intrauterine Hormone-releasing System (IUS)
- Bilateral tubal ligation
- Vasectomy
- Complete abstinence (complete avoidance of heterosexual intercourse

For male subjects with partners that are WOCBP

- Condom

All male subjects who have partners who are WOCBP must use condoms as their second method of contraception.

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of >1%.

Women of childbearing potential (WOCBP) receiving BMS-936558 (nivolumab) will be instructed to adhere to contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study drug (ie, 30 days [duration of ovulatory cycle] plus the time required for the study drug to undergo approximately 5 half-lives). Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study drug (ie, 90 days [duration of sperm turnover] plus the time required for the study drug to undergo approximately 5 half-lives.)

APPENDIX 7 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[1]	
Grade	**ECOG**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

[1] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.