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

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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

PROTOCOL(S) CA223001

VERSION # 2.1

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1 BACKGROUND AND 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 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 of the protocol).

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.

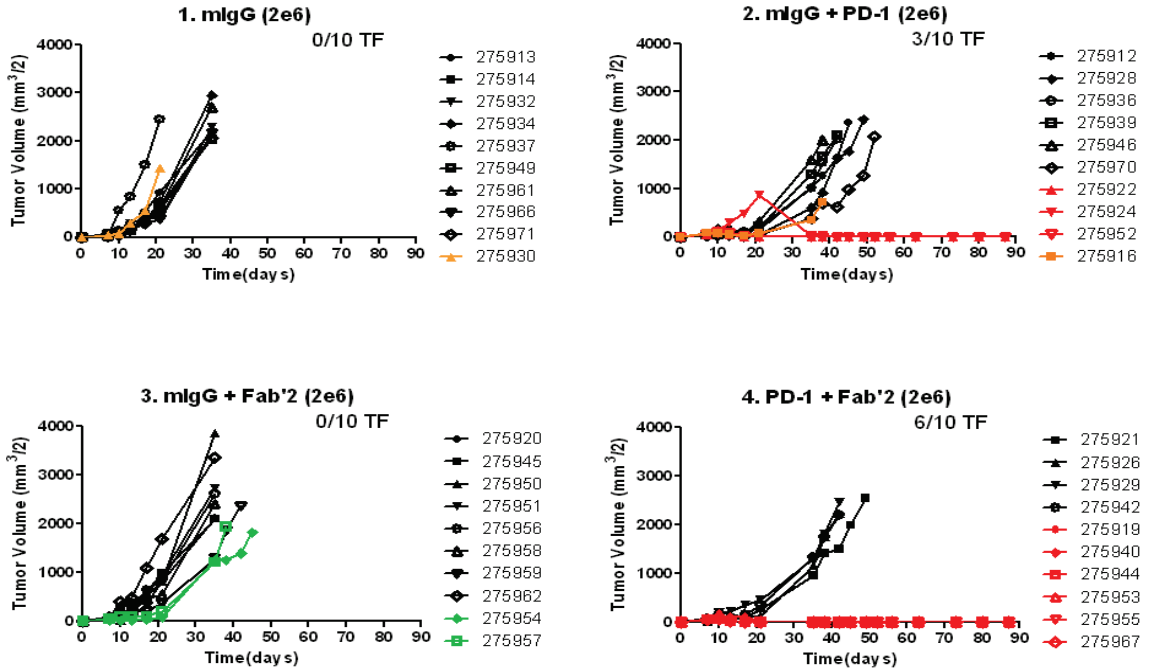
In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (concentration required for 50% efficacy [EC50]: 0.39 to 2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and programmed cell death ligand 2 (PD-L2) (concentration required for 50% inhibition [IC50] ± 1 nM). Nivolumab binds 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" of the protocol body) 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 Schedule of 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.

2 STUDY DESCRIPTION

2.1 Study Design

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

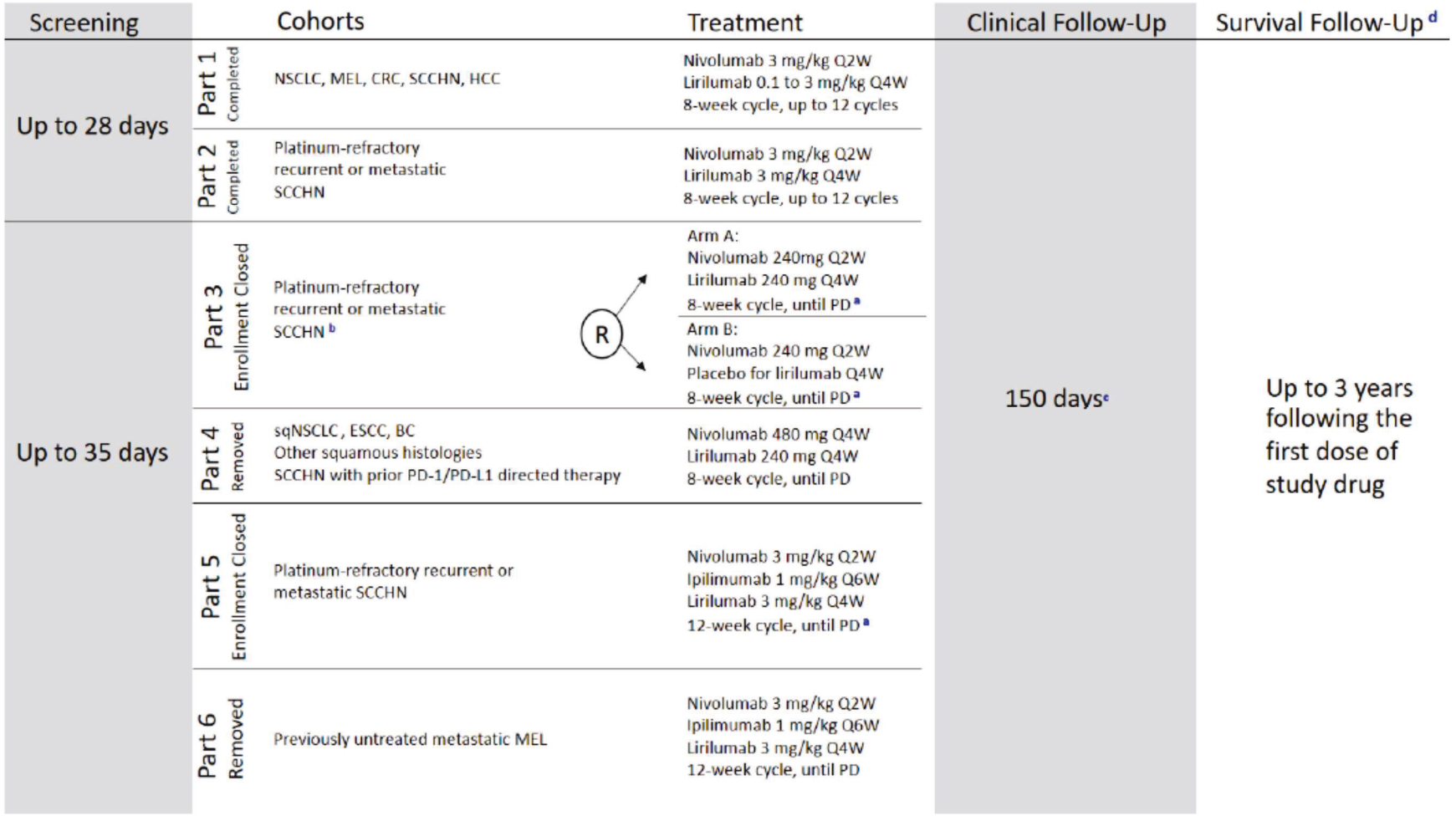
Please note that the Dose Escalation and Cohort Expansion (Part 1) and the SCCHN Cohort Expansion (Part 2) have both completed enrollment and are not applicable starting with Amendment 13 and all subsequent amendments. For preliminary safety results, see Section 1 "Clinical Experience with Lirilumab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

- 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 2.1-1: 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.

2.1.1 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.

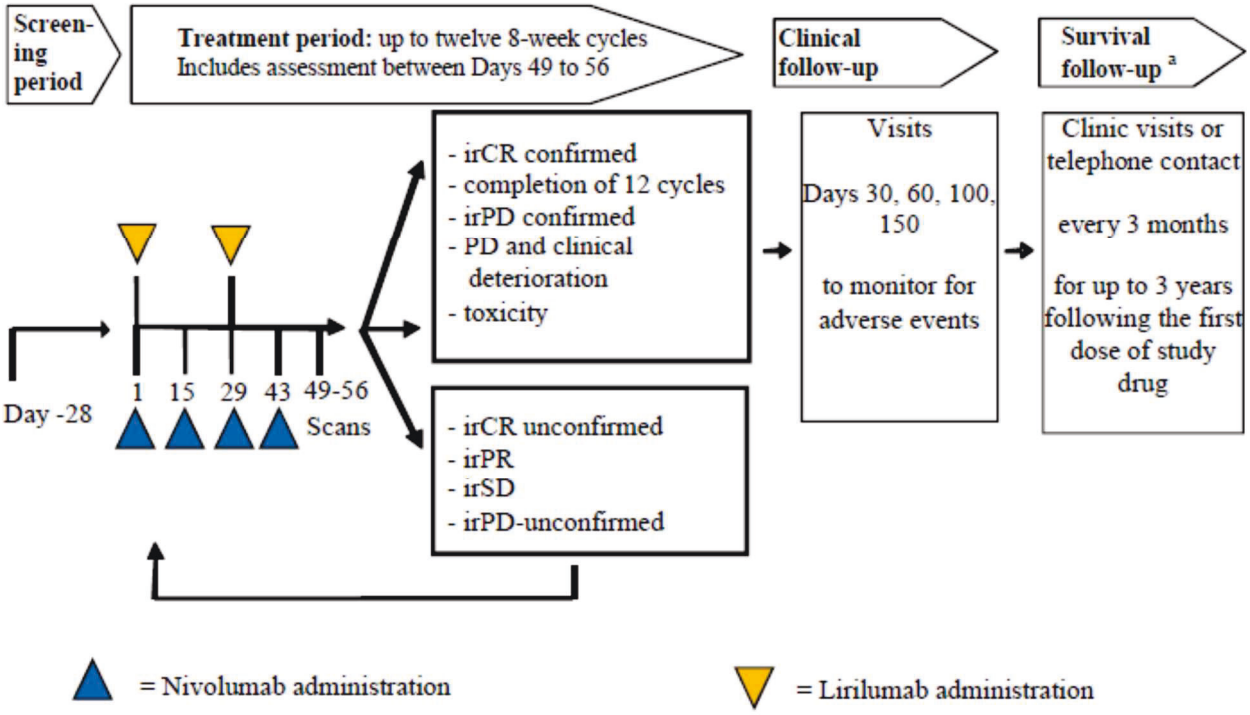
Following each treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next cycle). Treatment decisions related to subject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

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 2.1.1-1.

Figure 2.1.1-1: Study Period Schematic for the Dose Escalation and Cohort Expansion (Part 1; Completed)



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

2.1.1.1 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 2.1.1.1-1. 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 2.1.1.1-1: 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.

2.1.1.2 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 2.1.1.2-1. 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[21] 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 2.1.1.2-1. 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 2.1.1.2-2. 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 2.1.1.2-2 below, using a precision of 12% around the ORR point estimate.

Table 2.1.1.2-1: Table 3.1.1.21: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 2.1.1.2-2), assuming a target ORR of 25% to 30%.

Table 2.1.1.2-2: Table 3.1.1.22: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

Table 2.1.1.2-2: Table 3.1.1.22: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
5	5	14
6	0	9

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

2.1.2 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. 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.

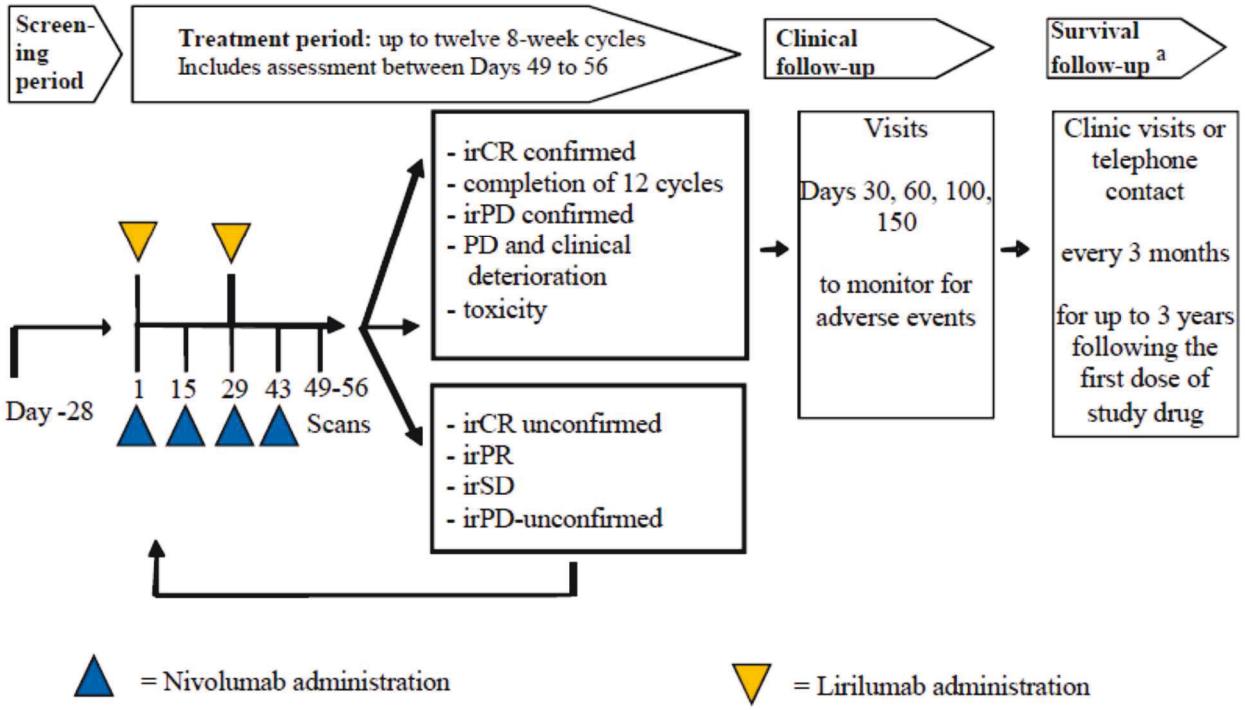
Following each treatment cycle (for all assigned treatments), the decision to treat a subject with additional cycles of study therapy will be based on tumor assessment (evaluation performed between Days 49 and 56 and completed before the first dose in the next cycle). Treatment decisions related to subject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

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 2.1.2-1.

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

Figure 2.1.2-1: Study Period Schematic for Part 2 (Completed)



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

2.1.3 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 of the protocol 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 of the protocol). 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 of the protocol 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 2.1.3-1.

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 2.1.3-2. See Section 3.1 of the protocol for a description of the study phases for this cohort.

Figure 2.1.3-1: Study Design Schematic for the SCCHN Randomized Cohorts (Part 3)

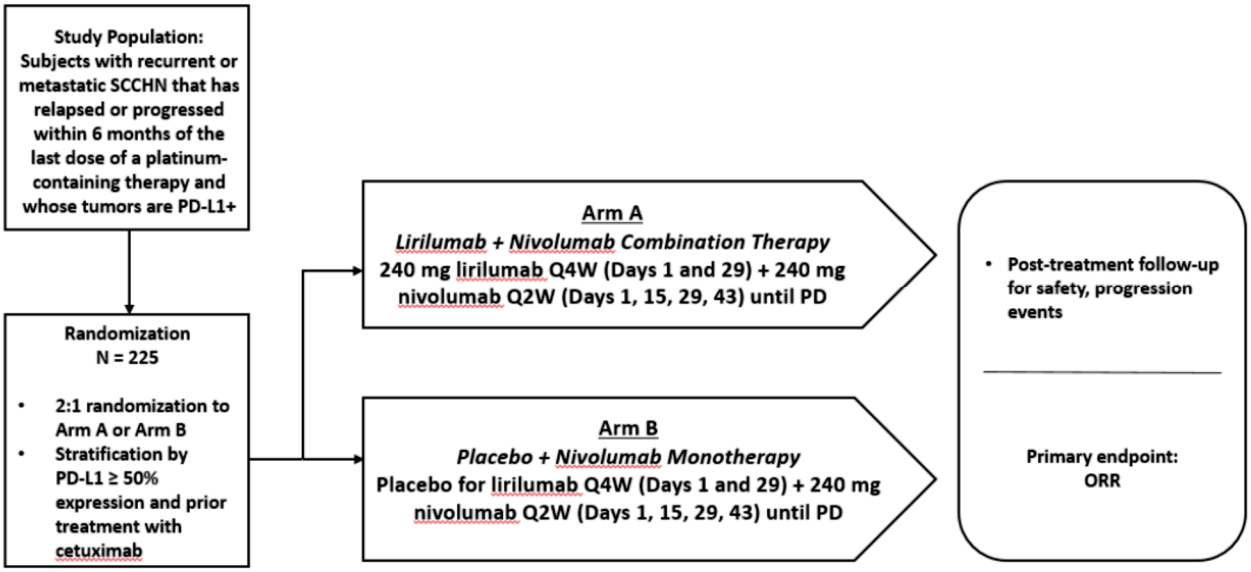
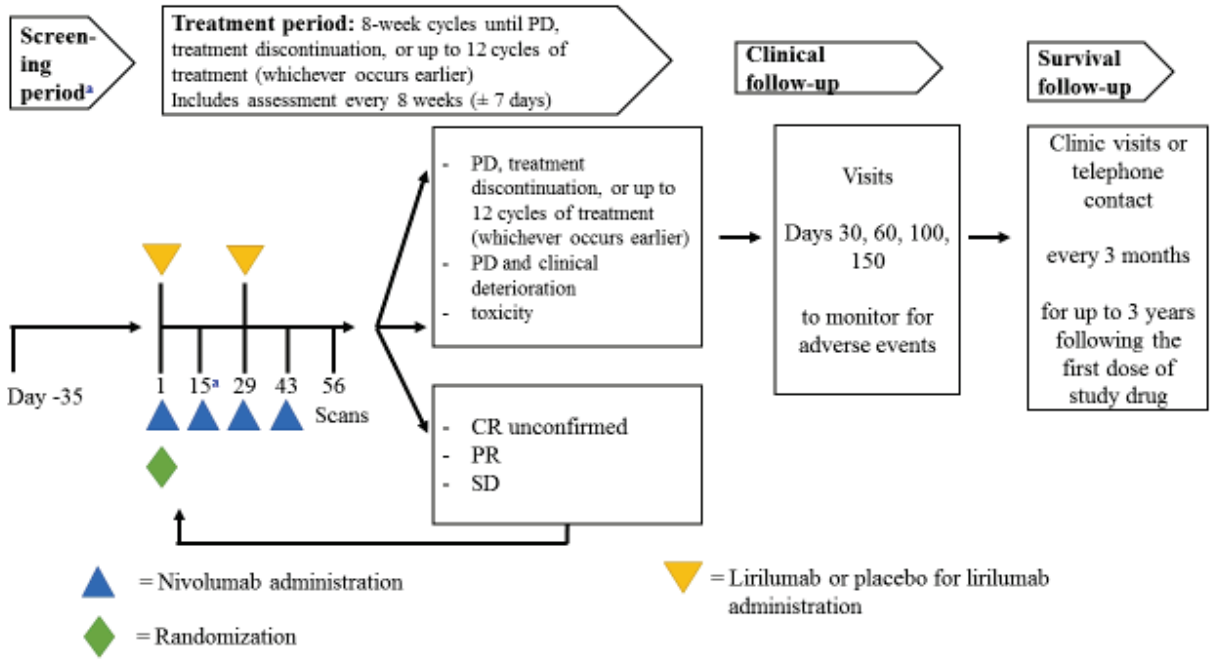


Figure 2.1.3-2: Study Period Schematic for the SCCHN Randomized Cohorts (Part 3)



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

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

2.1.4 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

2.1.5 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] of the protocol). 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 of the protocol 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.

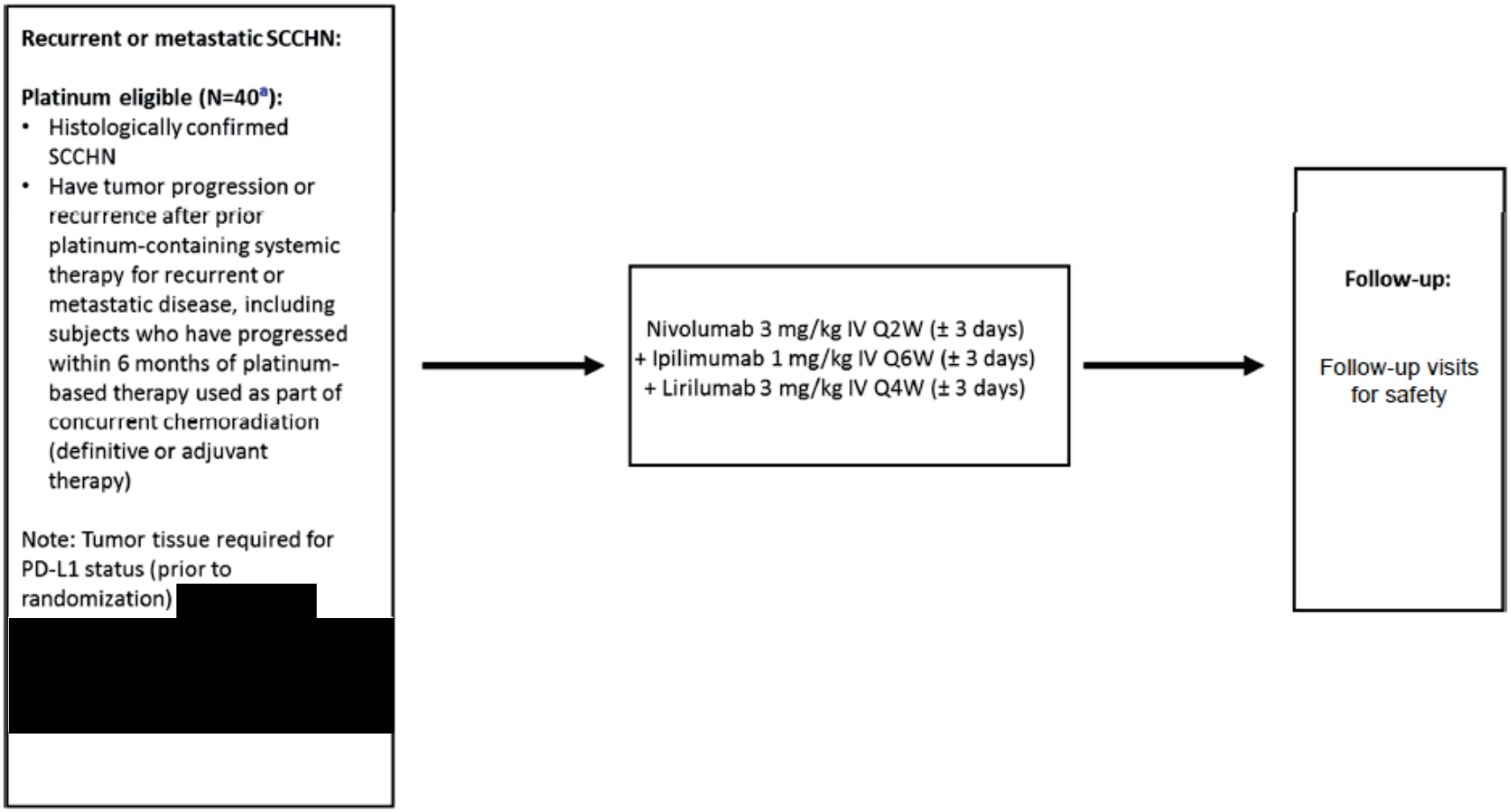
Following each treatment cycle (12 weeks of study therapy consisting of 6 doses of nivolumab given Q2W, 2 doses of ipilimumab given Q6W, and 3 doses of lirilumab given Q4W), the decision to treat a subject with additional study therapy will be based on tumor assessment done Q8W (evaluation performed 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 of the protocol). 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 of the protocol. or 6) maximum treatment duration of 8 treatment cycles (See Section 3.5.1 of the protocol).

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 2.1.5-1 and Figure 2.1.5-2.

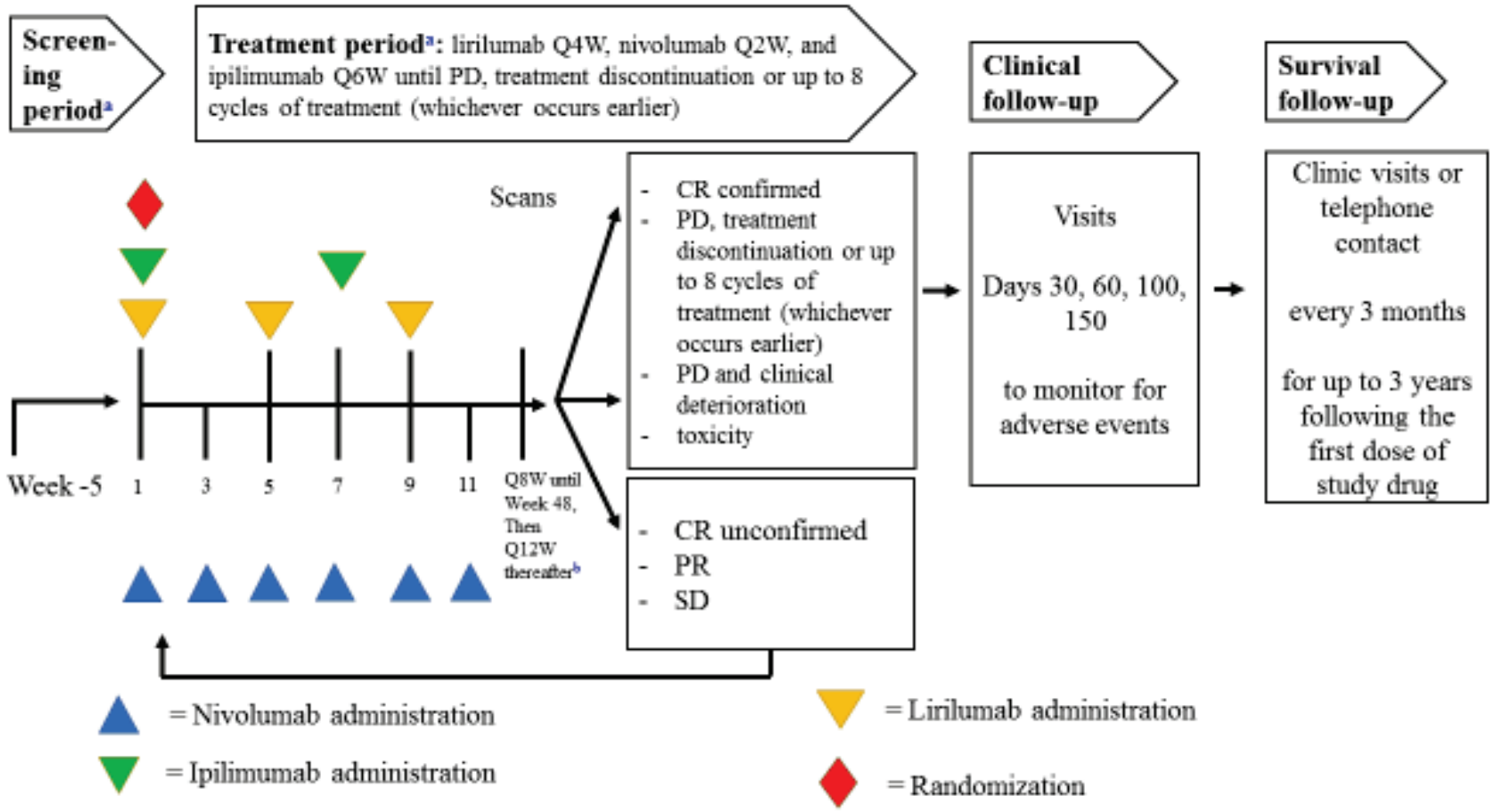
For the purposes of subject management, clinical decision-making will be based on RECIST v1.1. Therefore, timepoint tumor response evaluations will be recorded on the CRF based on investigators' assessments using RECIST v1.1 criteria.

Figure 2.1.5-1: 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 2.1.5-2: 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

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

Removed with Revised Protocol 12.

2.2 Treatment Assignment

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 ≥ 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.

Details regarding the selection and timing of dose for each subject can be found in Section 4.3 of the protocol.

2.3 Blinding and Unblinding

This is only applicable for the single-blinded SCCHN Randomized Cohorts (Part 3). All other parts are open label and non-randomized, thus do not require blinding and unblinding.

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.

2.4 Protocol Amendments

This analysis plan reflects all protocol amendments through Amendment 12, dated 08-May-2018.

2.5 Data Monitoring Committee

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.

3 OBJECTIVES

3.1 Primary Objective

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.

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.

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

Removed with Revised Protocol 12.

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.

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.

3.2 Secondary Objectives

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.

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.

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

Removed with Revised Protocol 12.

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.

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.

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

Safety and preliminary anti-tumor activity are the primary objective for all parts (i.e. Parts 1, 2, 3, and 5) except Part 1, where the primary objective is to assess the safety and tolerability of lirilumab given in combination with nivolumab, and Part 3, where the primary objective is to assess estimate the objective response rate of lirilumab given in combination with nivolumab.

For safety objective, all subjects who receive at least 1 dose of study drug will be evaluated for safety as measured by the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths assessed during treatment and for 150 days in follow-up. In addition, clinical laboratory test abnormalities will be examined.

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 study protocol 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 study protocol Section 3.5. AEs will be categorized

using the most current version of MedDRA. AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

For preliminary-antitumor activity, the primary endpoint will be to estimate ORR by derived BORs per RECIST v1.1 using investigator-provided tumor assessments for all Parts. The BORs for investigator-assessed responses per RECIST v1.1 for Parts 3 and 5 will be listed. Details regarding the definition of ORR will be given in the upcoming Secondary endpoint section for preliminary antitumor activity.

4.2 Secondary Endpoints

4.2.1 Preliminary Antitumor Activity

The following set of study-level efficacy endpoints will be used for comprehensive assessment of antitumor activity.

4.2.1.1 Objective Response Rate (ORR)

ORR is defined as the total number of participants whose best overall response (BOR) is either a complete response (CR) or partial response (PR) divided by the total number of participants in the population of interest. BOR for a participant will be **derived** using investigator-provided tumor measurements per RECIST v1.1 for all Parts. BOR for a participant will also be assessed by the investigator per RECIST v1.1 for Parts 3 and Part 5. All summaries or listings of BOR will be using derived BOR per RECIST v1.1 for all Parts.

BOR for a participant is defined as the best response designation recorded between the date of first dose (or date of randomization) and the date of first objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For participants who continue treatment beyond progression or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial RECIST v1.1 defined progression or subsequent therapy, whichever occurs first.

4.2.1.2 Median Time to Response (mTTR)

The objective response will be further characterized by the time to response. TTR for a participant with a confirmed BOR of CR or PR is defined as the time from the first dosing date to the date of the first documented objective response (CR or PR). TTR will only be evaluated in participants with a BOR of CR or PR.

4.2.1.3 Median Duration of Response (mDOR)

The significance of ORR is assessed by its magnitude and duration of response. DOR for a participant with confirmed response is defined as the time from the date of first response (CR or PR) to the date of first objectively documented tumor progression as determined using RECIST v1.1 or death due to any cause, whichever occurs first. Participant who remain alive and

have not progressed will be censored on the date of their last evaluable tumor assessment. Participants who started subsequent anticancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. Response duration will only be evaluated in participants with a confirmed BOR of CR or PR.

4.2.1.4 Progression Free Survival Rate (PFSR)

The PFSR is defined as the proportion of treated participants remaining progression free and surviving at time T (eg, 24 weeks) since the first dosing date. The proportion will be calculated by the K-M estimate which takes into account censored data.

PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Participants who died without a reported prior progression will be considered to have progressed on the date of their death. Participants who remained alive and have not progressed will be censored on the last evaluable tumor assessment date. Participants who started subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. Participants who did not have any post-baseline tumor assessment and did not die will be censored on the date of first dose of study medication.

Table 4.2.1.4-1: Censoring Scheme for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	First dosing date	Censored
No on-study tumor assessments and no death	First dosing date	Censored
Documented progression	Date of first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to the date of initiation of subsequent anticancer therapy	Censored
Death without progression	Date of death	Progressed

General Efficacy Endpoints Definitions:

Best overall response (BOR) for a subject is the best response designation over the study as a whole, recorded between the date of first dose of study medication and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first, in the study. For subjects without documented progression per RECIST 1.1 or

subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression. Additionally, the following will be applicable for BOR evaluation:

- For a BOR of complete response (CR) or partial response (PR), the response assessment must have been confirmed by a consecutive assessment no less than 4 weeks (28 days) later.
- For a BOR of stable disease (SD), the minimum criteria for SD duration (e.g, 6-8 weeks) must have been satisfied (42 days will be used to derive SD). This time minimum criteria only applies to derived BOR of SD, not to per timepoint evaluation.

Duration of response (DOR) for a subject with confirmed response is defined as the time from first response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. Subjects who remain alive and have not progressed will be censored on the date of their last tumor assessment (prior to subsequent cancer therapy). Response duration will only be evaluated in subjects with objective response of CR or PR.

Time to response (TTR) for a subject is defined as the time from date of first dose of study medication to the date of the first documented objective response (CR or PR). Time to response will only be evaluated in subjects with objective response of CR or PR.

Progression-free survival (PFS) for a subject is defined as the time from the date of first dose of study medication to the date of first documented disease progression or death due to any cause, if death occurred within 100 days after last lirilumab or nivolumab dose of study drug. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS. Subjects who remain alive and have not progressed will be censored on the last tumor assessment date (prior to subsequent cancer therapy). Subjects who did not have any on study tumor assessment and did not die will be censored on the date of first dose of study medication.

Overall survival (OS) for a subject is defined as the time from date of first dose of study medication to the date of death for any cause. A subject who has not died will be censored at last known date alive. OS for a subject who initiated new cancer treatment, will also be censored at the date of the new treatment initiation.

The efficacy endpoints that will used to evaluate BOR, PFS, and OS include:

- Objective response rate (ORR): The proportion of subjects with BOR of either a CR or PR in the population of interest (all treated patients or response evaluable patients).
- Disease control rate (DCR): The proportion of subjects with BOR of either a CR, PR, or SD in the population of interest (all treated patients or response evaluable patients).
- Median duration of response (mDOR)
- Median time to response (mTTR)

- Median overall survival (mOS)
- Median progression-free survival (mPFS)
- Progression-free survival rate (PFSR) at Month 3, 6, and 12: The proportion of subjects remaining progression free and surviving at 3, 6, 9, and 12 months (conditional on availability of a minimum number of subjects with sufficient follow-up) calculated by the product-limit method (Kaplan-Meier estimate)
- Overall survival rate (OSR) at Month 6, 12, 18, 24, and 36: The proportion of subjects surviving at month 6, 12, 18, 24, and 36 (conditional on availability of a minimum number of subjects with sufficient follow-up) calculated by the product-limit method (Kaplan-Meier estimate)

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and every 8 weeks (Q8W and Q12W for subjects in the Signal Detection in Previously Untreated MEL with Lirilumab, Nivolumab, and Ipilimumab Combination [Part 6]) until confirmed disease progression, at the completion of 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[22] (see Appendix 3 of the protocol) 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 of the protocol); all other study parts will use only RECIST v1.1. All radiographic assessments performed for study purposes will be submitted to the third-party radiology vendor for central review. Tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis. At the time of investigator-assessed disease progression, the site must request a BICR from the third-party radiology vendor. For details on the timelines and associated process requirements refer to the imaging manual.

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), the Signal Detection Cohort Expansion (Part 4), [redacted] however, will use only RECIST v1.1 for all assessments. Please refer to Appendix 3 of the protocol for specifics of RECIST v1.1 and Appendix 2 of the protocol for specifics of irRECIST criteria to be utilized in this study.

The SCCHN Randomized Cohorts (Part 3)

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, ORR by investigator (in subjects randomized to

nivolumab monotherapy), 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 later), to determine changes in tumor size. Tumor progression or response endpoints will be assessed by investigator using RECIST v1.1 criteria.

The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

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

Removed with Revised Protocol 12.

4.2.2 Pharmacokinetic Endpoints

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.

Table 4.2.2-1: PK Parameters, Naming Conventions and Definitions

Parameter	Definition
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(TAU)	Area under the concentration time curve in one dosing interval
Ceoinf	End of infusion concentration
Cmin	Trough observed concentration
T-HALFeff	Effective serum half-life
CL	Total body clearance

4.2.3 Biomarker Endpoints

Due to limited numbers of tumor samples collected and limited amount of tumor tissue, PD-L1 IHC is the only biomarker analyzed and reported on for this study.

PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity. PD-L1 expression at baseline (+ or -) will be a key endpoint for assessing associations with efficacy, due to the need to better understand its utility as a potential marker of associations with response in the combination setting. It will be measured in all patients with available archival tumor sample, and in patients with paired pre- and on-treatment biopsies in the expansion cohorts.

4.2.4 Immunogenicity

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 Sample:

- Baseline ADA-Positive Sample: ADA is detected in the last sample before initiation of treatment
- ADA-Positive Sample: After initiation of treatment, (1) an ADA-positive sample in a subject who is baseline ADA-negative, or (2) an ADA-positive sample with ADA titer to be significantly increased (at least 9-fold for lirilumab and at least 4-fold for nivolumab) relative to baseline according to the corresponding analyte assay.
- ADA-Negative Sample: After initiation of treatment, ADA not-positive sample relative to baseline

ADA Status of a Subject:

- Baseline ADA-Positive Subject: A subject with baseline ADA-positive sample
- ADA-Positive Subject: A subject with at least one ADA-positive sample relative to baseline at any time after initiation of treatment during the defined observation time period, such as:
  - Persistent Positive: ADA-positive sample at 2 or more sequential timepoints, where there is an adequate elapse of time between the first and last ADA-positive samples (16 weeks for both BMS-986015 and nivolumab)
  - Only the Last Sample Positive: Not persistent but ADA-positive sample in the last sampling timepoint
  - Other Positive: Not persistent but some ADA-positive samples with the last sample being negative
  - Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected.

- ADA-Negative Subject: A subject with no ADA-positive sample after the initiation of treatment

5 SAMPLE SIZE AND POWER

5.1 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.

5.2 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 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.[21] 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 2.1.1.2-1. 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 2.1.1.2-2. 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: Thirty-five 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 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 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 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 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.

5.3 The SCCHN Cohort Expansion (Part 2; Completed)

More than 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.

5.4 The SCCHN Randomized Cohorts (Part 3)

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.

5.5 The Signal Detection Cohort Expansion (Part 4)

Removed with Revised Protocol 12.

[redacted]

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

Removed with Revised Protocol 12.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of 3 periods: pre-treatment, on-treatment, and post-treatment/follow-up period.

The pre-treatment period covers from the time of signing of the informed consent form to prior to the first dose of study medication.

The on-treatment period starts at the time of the first dose of study medication and extends to the time of decision to discontinue a subject from study therapy or when the subject completes therapy per protocol.

The post-treatment clinical follow-up period begins the day after the on-treatment period ends and extends to up to 150 days after the last dose of lirilumab or nivolumab or ipilimumab, as long as the patients are still enrolled in the study.

Additional follow-up for survival outcomes may extend to up to 3 years after initiation of study drug.

6.2 Treatment Regimens

The treatment group "as randomized/assigned" will be retrieved from the IRT system, if applicable. The treatment group "as treated" will be the same as the arm as randomized/assigned by IRT. However, if a participant received an incorrect treatment for the entire period of treatment, the participant's treatment group will be defined as the incorrect treatment the participant actually received.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent and were registered into IRT;
- All Treated Subjects: All subjects who have received at least one dose of study medication;
- Response-Evaluable Subjects: All treated participants with measurable disease at baseline and one of the following: 1) at least one post-baseline tumor assessment, 2) clinical progression, or 3) death
- All Randomized Subjects: all subjects who were randomized in Part 3. This population will be used for listing of randomization schedule for Part 3 only.
- Lirilumab PK: all subjects who receive at least 1 dose of lirilumab and have adequate serum concentration data for lirilumab PK.
- Nivolumab PK: all subjects who receive at least 1 dose of nivolumab and have adequate nivolumab PK.
- Lirilumab Immunogenicity: all subjects who receive at least 1 dose of lirilumab and have at least 1 ADA sample available.
- Nivolumab Immunogenicity: all subjects who receive at least 1 dose of nivolumab and have at least 1 ADA sample available.
- Biomarker: all treated subjects who have biomarker data available.

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations. S-Plus®, may also be used for graphical presentations.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, i.e., medians, minimums, maximums, and means with standard deviations/(or standard errors of the mean). Categorical

variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.[23]

Unless otherwise specified, the following general rules will be applied:

- Data from Part 1 and Part 2 will be combined, with safety and tolerability data summarized by treatment group, and efficacy data summarized by tumor types.
- All results from Part 3 and Part 5 will be included in listing only.
- Additional outputs may be provided for SCCHN participants as appropriate.

7.2 Study Conduct

7.2.1 Study Information

A listing of batch number and randomization code (Part 3 only) will be provided.

Listing:

- Batch number
- Randomization code by site (include randomization codes, participant ID, treatment assigned) - Part 3 only.

7.2.2 Accrual

The number (%) of participants accrued by country and investigational site will be summarized and listed, using All Enrolled population.

Summary:

- Number (%) of participants accrued by country and investigational site: Include country, site number, (Principal Investigator's name), number of participants enrolled, and number of participants treated

Listing:

- Participants accrued by country and investigational site**.**

7.2.3 Relevant Protocol Deviations

Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) will be reported through ClinSIGHT listings. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations and a listing will be provided. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant (i.e., protocol deviations that could potentially affect the interpretability of the study results).

At Entrance:

Subjects without measurable disease at baseline

Subject who received study medication less than 28 days from the last dose of the prior therapy

Subjects that have received greater than 5 prior treatment regimens

At Entrance for Expansion Cohorts:

Subjects with deviations on baseline or prior therapy related inclusion/exclusion criteria such as:

- NSCLC subjects:
  - who have not received prior platinum chemotherapy
  - with ALK translocation that have not received an ALK inhibitor
  - with an activating EGFR mutation that have not received an EGFR inhibitor
- Melanoma subjects:
  - who have not received prior therapy with ipilimumab
  - with BRAF mutation (V600E or V600K) present who have not received a RAF or MEK inhibitor.
- Colorectal Cancer (CRC) subjects:
  - without Microsatellite instability stable (no alterations) or microsatellite instability low (only one alteration)
  - without DNA mismatch repair gene proficient on tumor immunohistochemistry (IHC)
- Head and Neck Squamous Cell Carcinoma (SCCHN) (oral cavity, pharynx, larynx) subjects:
  - without evidence of progression or recurrence within six months of last dose of platinum therapy
  - with radiation therapy not completed at least 4 weeks prior to study drug administration
- Hepatocellular carcinoma (HCC) subjects
  - without Child-Pugh score of B
  - with hepatitis B infection with hepatitis B DNA viral load greater than 100 IU/mL and not on antiviral therapy
  - with hepatitis B infection with coinfection with hepatitis C or hepatitis D

On-treatment:

- Subjects receiving anti-cancer therapy while on study therapy
- Subjects treated differently than as assigned (subjects who received the wrong treatment for the entire study period, excluding the never treated)
- Subjects receiving greater than 10mg/day of prednisone or equivalent at the time of study drug administration.

7.3 Study Population

All study population related summary tables described in this section will include combined data from Part 1 and Part 2 only. Listings will include all available data from Parts 1, 2, 3, and 5.

7.3.1 Subject Disposition

Status of participants at the end of pre-treatment period will be summarized and listed by including all enrolled participants. Status of participants at the end of treatment period will be summarized by treatment and overall, based on All Treated population. In addition, status of participants at the end of each study period will be summarized as appropriate. A listing will be provided for those

participants who were treated and reason for discontinuation of treatment or not being followed will be described.

7.3.2 Demographic and Other Baseline Characteristics

Summary:

Descriptive statistics will be provided the following baseline characteristics for all treated participants by treatment and overall.

- Age at Consent (in years) ; Age Category (<65, ≥65)
- Gender at Birth
- Race
- Ethnicity (if applicable)
- Height
- Weight
- ECOG PS
- Disease characteristics such as stage and severity of disease, mutation status, cell types, tumor locations (for SCCHN participants only), HPV status (for SCCHN participants only), prior cetuximab use (for SCCHN participants only), and prior therapy.

Listing:

All relevant data, generally variables listed above by treatment.

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of participants exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the All Treated Participants "as treated".

7.4.1 Study Therapy

Summary:

- Duration of therapy summary tables by treatment and total for each study drug: summarize by appropriate numbers of weeks intervals
- Dose information summary tables for each study drug: summary (mean, median, standard deviation, and min and max) of drug dosage, number of doses, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.
  - Duration of therapy (weeks) is (last dose date - first dose date +28)/7 for **lirilumab**, (last dose date - first dose date +14)/7 for **nivolumab**, and (last dose date - first dose date +42)/7 for ipilimumab (for Part 5 listing only).
  - Cumulative dose is the sum of all actual doses that a subject received.
  - Dose intensity is defined as the cumulative dose divided by the duration of treatment.
  - Relative dose intensity is defined as dose intensity divided by planned dose.

Listing:

- By patient listing of drug administered for each study drug by visit
- By patient listing of dosing information for each study drug: Duration of therapy, cumulative dose, dose intensity, and relative dose intensity by study drug.

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by treatment for each study drug.

- Number (%) of subjects with dose delay, omission and discontinuation with reason
- Infusion interruptions
  - Number (%) of subjects with at least one infusion interruption along with the reason
  - Number of infusion interruptions per subject
  - Number (%) of subjects with at least one IV infusion rate reduction along with the reason

Listing: All relevant information on dose modification listed above

7.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. Concomitant medications are defined as medications other than study medications which are taken at any time on-treatment.

Summary:

The number (%) of treated subjects for the following will be provided by treatment:

- Summary table of prior therapy by tumor type and treatment group: include the settings of prior systemic cancer therapy, best responses, and number of prior regimens (0, 1, 2, and >=3), prior ipilimumab therapy and prior nivolumab therapy;
- Summary of non-study medication including prior and concomitant medications
- Concomitant immune-modulating medications for management of AE by medication class and generic term - if applicable

Listing:

- All prior and concomitant medications.

7.5 Efficacy

Efficacy analyses based on Response-evaluable Participants may be performed as supportive analyses. If majority of All Treated Participants is included in Response-evaluable Participants, limited efficacy analyses will be performed on Response-evaluable Participants (eg, ORR). For interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result, efficacy analyses may be performed on Response-evaluable Participants.

Time to event distribution (e.g. progression free survival, overall survival, and duration of response) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology[24] (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. PFSR at 6 months or OS at 12 months) will be derived from the K-M estimate and corresponding confidence interval will be derived based on the Greenwood formula using log-log transformation[25]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

In general, efficacy summaries will be provided by tumor type and treatment group.

Summary:

- ORR and DCR with corresponding 2-sided 95% CI, together with breakdown of BOR
- Duration of response, OS, and PFS with median (95% CI) and range (min, max) by K-M method. The number of subjects still in response at the time of data lock will be indicated
- Time to response with median (95% CI) and range (min, max) by K-M method

Figure:

- Maximum reduction in baseline target lesions (aka waterfall plot)
- Kaplan-Meier (K-M) plot of duration of response for responders only
- Swimmer plot of time to response and duration of response, including time on therapy for responders only
- K-M plot of PFS
- K-M plot of OS

Listing:

The following will be listed by tumor type and treatment group.

- By patient listing of all tumor lesion measurements by visit
- By patient listing of tumor evaluation at each visit
- Subject level efficacy for all treated subjects: tumor best overall response (BOR), maximum reduction in tumor burden from baseline, time to response, duration of response, time to progression, and death indicator

7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by treatment ("as assigned") and overall (if appropriate).

Adverse events (AEs) will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC) according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related. All AEs will be summarized and listed by SOCs and PTs.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include (1) events occurring from the first dose date to 150 days (inclusive) after the last dose of study drug for subjects who are off study treatment and (2) all events occurring from first dose date for subjects who are still on study medication.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.0) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and (1) post-baseline results up to 150 days (inclusive) after the last dose of study drug for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication.

Summary tables will be generated for Part 1 and 2 combined. Listings will include all available data from Parts 1, 2, 3, and 5.

7.6.1 Adverse Events

Summary:

- Overall summary of any AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT
- Overall summary of treatment-related AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT

Listing:

All recorded adverse events occurring in the pre-treatment, on-treatment, and post-treatment period will be listed.

7.6.2 Deaths

Summary:

All deaths during the study within 150 days after the last dose of study drug will be summarized for cause of deaths by treatment.

Listing:

All recorded deaths during the study (after a subject is enrolled and has signed the informed consent), including post-treatment follow-up period, and deaths that resulted from a process that began during the study, will be listed.

7.6.3 Serious Adverse Events

Summary:

- Overall summary of SAEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT

- Overall summary of treatment-related SAEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT

Listing:

A by-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued".

Summary:

- Overall summary of AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT
- Overall summary of treatment-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5, unknown) presented by SOC/PT

Listing:

By-subject AEs leading to discontinuation listing will be provided.

7.6.5 Select Adverse Events

Summary of Select Adverse Events of Hypersensitivity/Infusion Reaction will be provided by ADA Status (Positive, Negative) for all Immunogenicity Subjects by treatment group and overall.

7.6.6 Immune-Mediated Adverse Events

The following summary tables will be generated by treatment group and overall. If needed, by patient listing can be provided to support the summary tables.

Summary:

- Summary of related immune-mediated AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by PT.
- Summary of related immune-mediated AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by PT for SCCHN participants only.

7.6.7 Multiple Events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms[26] in order to collapse adverse event records into unique records based on the preferred term. This data will be presented as the rate per 100 patient-years of exposure (observation period). This analysis will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The patient-years exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as

- Date of last dose of study treatment - date of first dose of study treatment + 100+1 days, for subject who are off study treatment and were followed at least 100 days after last dose of study medication. For patients being followed for 150 days, please use 150 days in above calculation.
- Last known date alive- date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 100 days after last dose of study medication.

When specified, the 95% CI of the rate per 100 patient years of exposure will be derived using normal approximation and variance estimation proposed in Cook and Lawless[27] (optional). Summary tables will be generated for part 1 and 2 combined.

Summary:

The following summary tables will be provided:

- Summary of frequency of unique adverse events
- Total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated across treatments.

Listing:

Unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e., same PT) have been collapsed.

7.6.8 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests, as well as laboratory results outside of the normal range, will be listed. Scheduled laboratory measurements and corresponding change from baseline values will be summarized by treatment and nominal visit for each laboratory test.

The analysis will be based on All Treated Subjects with available laboratory test result on-treatment and up to and including 100 (or 150) days of the last dose of study medication. Laboratory results will be categorized according to NCI CTCAE (version 4) grade.

Summary tables will be generated for Part 1 and 2 combined. Listings will include all available data from Parts 1, 2, 3, and 5.

Summary:

The number (%) of subjects with the following will be summarized by treatment and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline by treatment and study day

Listing:

A by-subject listing of these laboratory parameters will be provided.

7.6.8.1 Abnormal Thyroid Test

Summary:

Elevated TSH value > ULN and

- *with baseline TSH value ≤ ULN*
- *with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test*
- *with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test*
- *with F3/F4 missing within 2-week window after the abnormal TSH test*

Low TSH < LLN and

- *with baseline TSH value ≥ LLN*
- *with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test*
- *with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test*
- *with F3/F4 missing within 2-week window after the abnormal TSH test*

Listing:

A by participant listing of these specific abnormalities will be provided.

7.6.8.2 Vital Signs and Other Safety Evaluation

Summary:

- Vital signs
- ECG measures

Listing:

- Vital signs
- ECG measures and ECG abnormalities
- Diagnostic procedures
- Medical treatment procedures

7.6.8.3 Physical Examination Findings

All physical examination results (e.g., with abnormal findings) will be listed.

7.7 Pharmacokinetics

Cmax (µg/mL), Tmax (hr), AUC(TAU) (µg.hr/mL), AUC(INF) (µg.hr/mL), CL (L/day), Vss, T-HALF, and Cmin (µg/mL) will be evaluated using non-compartmental analysis in all study subjects by study drug for part 1 and 2 combined. In addition, end of infusion (Ceoinf) and trough (Cmin) concentrations will be calculated at specified visits. Ctough will be listed by doses and visit.

The Pharmacokinetic (PK) population will be used for all listings. Evaluable PK population will be used for summaries and statistical analyses. Analysis will include all evaluable PK data for each analyte (BMS-986015 and BMS-986558).

BMS-986015 PK: All individual PK parameters will be listed for each subject including any exclusions and reasons for exclusion from summaries. Summary statistics will be provided for the following parameters by treatment and study day: Cmax, AUC(TAU), AUC(0-T), AUC(INF), Tmax, Cmin, Ceoinf, CL, Vss and T-HALFeff.

Geometric means and coefficients of variation will be presented for Cmax AUC, Cmin, CL, Vss, and AI_{Cmax}, AI_{AUC}. Median, minimum, and maximum will be presented for Tmax. Means and standard deviations will be provided for THALFeff.

Cmin values will be listed and summarized by treatment and study day, and will be displayed graphically.

Dose proportionality of BMS-986015 PK will be assessed for AUC(INF) after single doses and for Cmax and AUC(TAU) at steady state. The dose proportionality analysis will be conducted for participants from Part 1 and Part 2 only.

To assess the dose proportionality the power model described by Gough et al.[28]

$$\text{PK Parameter} = A*\text{Dose}^{\beta}$$

will be estimated by the simple linear regression of the natural log of the PK Parameter (Cmax, AUC) on the natural log of Dose:

$$E[\log(\text{PK Parameter})|\ \text{Dose}] = \alpha + \beta*\log(\text{Dose}).$$

A slope (β) equal to 1 would indicate perfect dose proportionality. For each PK parameters (Cmax, AUC), the point estimates and 90% CI of the slopes will be provided.

Scatter plots or geometric mean plots related to dose proportionality, assessment of steady state or accumulation by dose, vs. study cycle may also be presented.

BMS-986558 PK: All individual PK parameters (Cmin and Ceoinf) will be listed including any exclusions and reasons for exclusion from summaries. Summary statistics will be presented, in terms of geometric means and coefficients of variation for Cmin and Ceoinf.

Results of population PK and exposure-response analyses using sparse or serial PK data for either analyte from this study may be combined with data from other studies and reported separately.

7.8 Immunogenicity (ADA)

The analysis may include the following presentations; modifications may occur based on the evolving understanding of the regulatory or other BMS updates on standards for reporting ADA.

Summary tables will be generated for Part 1 and 2 combined. Listings will include all available data from Parts 1, 2, 3, and 5.

Summary:

- The number (%) of subjects with the following anti-drug responses will be reported by dose, if applicable, and overall, for each analyte:
- Baseline ADA-Positive
- ADA-Positive

- Persistent Positive
- Only the Last Sample Positive
- ADA-Positive with Neutralizing Positive
- ADA-Negative

Listing:

All collected immunogenicity will be listed with flags indicating baseline-positive sample, ADA-positive sample or ADA-negative sample.

7.9 Biomarkers

All analysis of PD-L1 IHC data from archived tumor tissue will be based on All Treated Subjects population unless otherwise stated. Summary statistics will be provided for baseline PD-L1 status. In addition, best overall response summary by baseline PDL-1 status (< 1% vs >= 1%; <5% vs >= 5%) will be provided for SCCHN participants from Part 1 and Part 2 combined.

8 CONVENTIONS

8.1 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

For the summaries of concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

Summary statistics for Ctrough concentrations, analyses of PD-concentrations and ECG-concentrations relationships will be calculated by imputing values less than LLOQ as ½ * LLOQ. This imputation is done for Ctrough concentrations because it is treated like a PK parameter; the imputation is not done for Day 1 pre-dose concentrations. Individual Ctrough listings will display these concentrations as "< LLOQ."

All available concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

10 CONVENTION FOR SELECT AES AND IMAES DATA ANALYSIS

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to onset of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed "clustered" AEs. For example, if a participant (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table 10-1 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs in this category experienced by the participant. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known date alive. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for participants who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the participant started an immune modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table 10-1: Derivation of clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event records is using the following conventions:

For each participant and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

11 DOCUMENT HISTORY

Version Number	Author(s)	Description
0.1 to 0.4	[redacted]	Edits to schedule of analyses, added baseline characteristics, e.g., mutation data, [redacted] ADA updates. Efficacy: removed plot of TTR, clarified presentation of irRECIST results. Duration of therapy clarified. Cleaned up references and other details
0.5, 0.6		Replaced a 'as treated' with 'as assigned' language. Updated relevant protocol deviations. Clarified the 5% for AE summary applying too total, and made optional the CI and figure for multiple event reporting. Defined the BMS-986015 exposure duration by adding 4 weeks to the dosing interval. Added text on handling relevant protocol deviations.
1.0		Clarification of PD-L1 data collection in the first paragraph in Section 4.5.1. Named this vs. no 1 for consistent with CARA
2.0		Update the SAP based on the Revised Protocol Version 12.0
2.1		Minor update the SAP to remove BICR, to include derivation of RECIST v1.1 for all parts, and removal of stratification or summarizing by sub-population for ORR

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