LUDWIG CANCER RESEARCH	**Study Protocol**	**LUD2015-006**	**US-IND# exempt BMS CA209-412**
	Amendment 5	**FINAL**	**12-JUN-2018**

Protocol Title
A Pilot (Phase 1) Study to Evaluate the Safety and Efficacy of Combination Checkpoint Blockade (Ipilimumab and Nivolumab) Plus External Beam Radiotherapy in Subjects with Stage IV Melanoma

Objectives and Synopsis
This is an open-label, multicenter pilot Phase 1 study of the checkpoint antibodies ipilimumab and nivolumab in combination with radiotherapy (RT) in 18 subjects with unresectable stage IV melanoma. All subjects will receive concurrent ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) every 3 weeks for 4 doses, followed by nivolumab monotherapy (240 mg every 2 weeks). Note: per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks. Radiotherapy will be initiated after the first dose and before the second dose of immunotherapy. There will be 2 cohorts in the study. Subjects in Cohort A will initially receive a conventional total palliative dose of 30 Gy delivered over 2 weeks in 10 fractions of 3 Gy each. Once 9 subjects have been accrued to Cohort A and completed the concurrent ipilimumab and nivolumab therapy, if ≤ 7 subjects have Grade 3 or 4 drug- or radiation-related adverse events, the safety of Cohort A will be deemed acceptable and additional subjects will be accrued to Cohort B (see exception in Section 3.1, i.e., asymptomatic amylase and lipase abnormalities are not included). Subjects in Cohort B will receive the high-dose hypofractionated RT for which treatment of a target lesion will comprise a total palliative dose of 27 Gy delivered over 2 weeks in 3 fractions of 9 Gy each. *The primary objective* is the assessment of safety according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. *The secondary objectives* are to evaluate: (1) objective response rate (ORR) at Weeks 12 and 18, (2) disease control rate (DCR) at Weeks 12 and 18, (3) duration of response, (4) progression-free survival (PFS), and (5) overall survival (OS). *The exploratory objectives* are to perform correlative studies investigating the immunological effects of ipilimumab and nivolumab with RT. Assessment methods include the NCI CTCAE (Version 4.03) for safety and the modified Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 (primary) and immune-related RECIST (irRECIST; secondary) for clinical efficacy.

Sponsor: Ludwig Institute for Cancer Research, New York, NY	**Study Chair:** [redacted]
Sponsor representative Signature & Date	Study Chair Signature & Date

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1 Background

1.1 Melanoma

The incidence of malignant melanoma is rising and the mortality rate is increasing.(1) These concerning trends are occurring despite the recent decline in the incidence of several other cancer types. Despite this concerning trend, the overall survival (OS) for all patients diagnosed with melanoma has improved for early stage tumors because of early detection and improved surgical treatment. Nonetheless, many patients who undergo curative-intent surgical treatment of high-risk disease ultimately recur, and recurrent and/or metastatic melanoma remains a largely fatal disease, with a median survival of 3 to 11 months.(2)

The only adjuvant treatment approved by the US FDA after resection of high-risk melanoma is IFN-α. Unfortunately, treatment with high-dose IFN-α is associated with significant side effects, and its role in prolonging survival is not clear. One study showed an OS benefit, but this was not confirmed in a pooled analysis with longer follow-up.(3, 4)

Until 2011, dacarbazine and interleukin-2 (IL-2) were the only US FDA approved treatments for metastatic melanoma. Dacarbazine provides an objective tumor response in only 5% to 20% of subjects, and these responses are short-lived (median duration of response is 6 months). Dacarbazine has also never been shown to improve OS.(2) IL-2 was approved by the FDA in 1998 for treatment of metastatic melanoma. The FDA approval was based on data suggesting a 16% overall objective response rate with a 6% complete response. However, toxicities of high dose IL-2 therapy were severe (e.g., capillary leak, sepsis, and hypotension), and 2% of subjects died from such associated adverse events (AEs).(5)

Since 2011, many new treatments have been approved for patients with melanoma. For patients with BRAF mutations, the BRAF inhibitors dabrafenib and vemurafenib have led to dramatic results with recent demonstration of an overall survival benefit of combining the BRAF inhibitor, dabrafenib with the MEK inhibitor, trametinib.(6) Immunotherapy with immune checkpoint blocking antibodies has similarly led to remarkable advances in advanced melanoma with 3 currently FDA-approved drugs: Ipilimumab, nivolumab, and pembrolizumab.(7-9)

1.2 Ipilimumab

Ipilimumab enhances antitumor immunity by blocking the normally negative regulator of T cell function, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and has demonstrated a survival benefit for subjects with advanced melanoma in two Phase 3 trials.(10, 11) Though ipilimumab can result in impressive long-term tumor control,(12) unfortunately only a subset of patients benefit.

Responses to ipilimumab are often delayed and may be seen after initial apparent disease progression. The unique pattern of disease response seen in subjects with ipilimumab led to a retrospective study analyzing subjects treated across several Phase 2 trials.(13) In this evaluation, improved survival was associated with a variety of disease response patterns such as subjects who initially appeared to have progressive disease but later achieved response and those who had prolonged stable disease.

Though ipilimumab is generally well tolerated, a unique set of side effects, termed immune-related adverse events (irAEs) has been seen during its clinical development. The most severe

irAE is generally considered to be an inflammatory enterocolitis which requires prompt treatment with steroids and, in some cases, anti-TNF-alpha therapy. Unfortunately, a randomized trial evaluating the role of prophylactic budesonide in decreasing the rate of inflammatory colitis showed no benefit to this approach.(14) Other common severe side effects related to ipilimumab include hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated subjects in one study: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.(7)

1.3 Nivolumab

Nivolumab enhances antitumor immunity by blocking another negative regulator of immunity, programmed cell death-1 (PD-1) and has demonstrated high response rates in a number of malignancies and improved OS in subjects with melanoma.(15-17) Since both ipilimumab and nivolumab act upon distinct components of the immune system, several studies are now investigating the combination of both ipilimumab and nivolumab. Impressive early efficacy was seen with an acceptable safety profile in one Phase 1 study.(18) Impressive efficacy has also been seen in phase 2 and 3 trials where the combination of nivolumab and ipilimumab was shown to improve response rates and progression free survival compared to ipilimumab alone.(19, 20)

1.4 Radiotherapy for Melanoma

Radiotherapy (RT) is commonly used to palliate symptoms arising from sites of metastatic melanoma.(21) In one study, 9 of 23 subjects who received RT achieved a complete response in the irradiated area, including 3 of 23 subjects who were rendered free of disease for at least 56 months after RT.(22) RT for melanoma has also been shown to improve symptoms and prevent impending complications from metastatic disease. One prospective study evaluated palliative endpoints for 90 subjects with renal cell carcinoma and melanoma who underwent palliative RT. Improvements in two-thirds of the painful bone or soft tissue lesions were noted by investigators.(23)

The most effective dose and schedule of RT for subjects with metastatic melanoma, however, is not completely clear. In a study conducted by Overgaard et al., there was no difference in response rate between subjects receiving 5 Gy per fraction for 8 fractions versus 9 Gy per fraction for 3 fractions, though subject numbers were small.(24) In another study, Sause et al. reported the results of the Radiation Therapy Oncology Group trial 83-05, which assigned 137 subjects with melanoma to 8 Gy per fraction delivered once weekly for 4 fractions or 2.5 Gy per fraction delivered 5 days per week for 20 total fractions.(25) The response rates for both treatment arms were not statistically significantly different. These results differed slightly from a retrospective analysis of 84 subjects conducted at the Mayo Clinic, which indicated that higher doses of RT were associated with improved palliation and improved survival.(26) Importantly, dose per fraction and location of the irradiated lesions did not appear to correlate with the effectiveness of RT in this study.

It is generally believed that high-dose palliative RT is feasible for subjects with metastatic melanoma,(24) but no rigorous evaluation of dosing schemes has been tested in large, randomized studies. The dose and fractionation may have immunologic implications. Schaue et al. found that immunologic effects and tumor control in a B16 murine melanoma model

depended upon dose and schedule of RT.(27) Tumor control was most effective and immunologic effects were most profound when RT was delivered via 7.5 Gy per fraction. In another study, when RT was delivered with anti-CTLA4 therapy, synergy was not seen when a single fraction of 20 Gy of RT was delivered.(28) A third preclinical study showed that conventionally fractionated RT abrogated the immunologic effects of RT.(29) Many radiation oncologists feel that a higher dose per fraction approach may be preferable, though prospective clinical evaluation of dose and schedule of RT in subjects with metastatic melanoma is necessary.

2 Study Rationale

2.1 Preclinical Rationale for Combining Radiotherapy and Checkpoint Blockade

To increase the numbers of subjects who benefit from ipilimumab and nivolumab, clinical trials have started combining checkpoint antibodies with other therapeutic modalities, such as chemotherapy, targeted therapy, and other immunotherapy. One additional, similarly promising approach involves combining checkpoint antibodies with RT. In a Phase 1/2 study in metastatic castration-resistant prostate cancer, ipilimumab in combination with RT demonstrated clinical antitumor activity and manageable AEs.(30) Other clinical trials exploring RT and checkpoint antibodies are ongoing.

Conceptually, all of these additional therapeutic modalities, including localized RT, could result in increased tumor destruction, releasing tumor antigens that provide further stimulus to T cells disinhibited by checkpoint blockade therapy to enhance durable antitumor immunity. It is also possible that RT may alter the tumor microenvironment and render the tumor cells more susceptible to immunologic-mediated disease regression.

In preclinical models, RT has been shown to enhance antitumor immune responses through multiple mechanisms, including increased antigen presentation in tumor draining lymph nodes and enhanced effector cell migration to the irradiated tumor.(29, 31) In one study, tumors that received RT had improved localization of inflammatory cells into the tumor microenvironment following adoptive cell transfer, which was associated with upregulation of vascular cell adhesion molecules in the tumor microvasculature that may have played a mechanistic role. RT has also been shown to increase MHC-I expression and increase the efficacy of adoptive cell transfer.(32)

In addition to RT's direct immunologic effects, preclinical evaluation has demonstrated synergy with other immunotherapeutic approaches. Specifically, when RT was combined with the immunostimulatory cytokine, FMS-like tyrosine kinase 3 (Flt3), in a lung cancer model, only mice who received RT with Flt3 had improved survival.(33) This survival was associated with the reduced development of distant pulmonary metastatic disease. A functional immune system appeared to be important as the effect was not seen in mice with deficient T cells. Regression of tumors outside of the irradiated field was also seen when Flt3 was combined with RT in a murine breast cancer model but not in mice treated with either modality alone.(34)

The immunologic effects of RT may be further enhanced by concomitant anti-CTLA-4 or anti-PD-1/PD-L1 therapy. In mouse models, CTLA-4 blockade alone resulted in no significant tumor growth inhibition, but when localized RT was administered in combination with CTLA-4 blockade, antitumor effects were seen outside of the irradiated field—a phenomenon known as the abscopal effect.(28, 35) Though the precise mechanisms involved in the abscopal effect are not completely clear, T cells appear to play a central role.(34) This phenomenon has been replicated in multiple solid tumor murine models (Susan Knox, personal communication). RT and PD-1/PD-L1 blockade have also demonstrated synergy in preclinical models.(36, 37) The triple combination of CTLA-4, PD-1, and RT has also been explored in preclinical models and suggests even greater efficacy when all three modalities are combined.(38)

2.2 Clinical Rationale for Combining Radiotherapy and Checkpoint Blockade

To evaluate the potential synergy between RT and immunomodulatory therapy, Formenti et al. conducted a proof of concept study for subjects with multiple solid tumors combining RT and granulocyte-macrophage colony stimulating factor (GM-CSF). They reported that 4 of the 12 evaluable subjects (30%) experienced an abscopal response, defined as a partial response of at least 1 lesion outside of the treatment field.(39) Though subject numbers were low, recent data have additionally shown an unusually high systemic response rate when RT was combined with IL-2 therapy.(40)

Other case reports have suggested synergy between radiotherapy and immunotherapy.(41-44) Retrospective analysis of subjects treated with palliative RT during their induction course of ipilimumab at 3 mg/kg indicates that combination treatment is not associated with a higher rate of irAEs. Only one subject experienced a grade ≥ 3 event (diarrhea), which resolved after infliximab therapy. This side effect could have been related to ipilimumab alone.(45)

Whether the dose or schedule of RT in combination with immunotherapy is relevant remains unknown. Relatively low doses of conventionally fractionated RT (e.g., 30 Gy in 10 fractions) have been shown to be effective palliative therapy for melanoma.(23) Higher doses of hypofractionated RT (e.g., 24 Gy in 3 fractions) are also frequently used in melanoma because of perceived "radio-resistance" due to high levels of sublethal DNA damage repair in melanoma cell lines, although prospective randomized clinical studies have never confirmed this.(24)

However, the dose and fractionation of RT may have immunologic considerations relevant for its combination with immunotherapy. Preclinical studies of CTLA-4 blockade combined with RT have demonstrated the greatest delay in tumor regrowth and highest rates of complete tumor response with a dose of 24 Gy in 3 fractions (versus 20 Gy in 1 fraction or 30 Gy in 5 fractions).(28) Another study analyzing the effect of single doses of radiation from 5-15 Gy found that radiation doses of 7.5 Gy yielded the greatest proportion of tumor-reactive T cells to regulatory T cells.(27) Most importantly, these findings are consistent with our anecdotal clinical observations of abscopal effects in patients undergoing RT (both patients were treated with approximately 27 Gy in 3 fractions) during ipilimumab immunotherapy.

Additional study of the relationship between RT dose and fractionation is warranted, particularly when considering the best strategy to combine with nivolumab and ipilimumab for patients with melanoma. This information would be beneficial for subsequent studies involving combinations of nivolumab and ipilimumab in a variety of diseases and therapeutic settings.

This proposed study is therefore based upon the preclinical evidence suggesting synergy between RT and immunomodulatory therapy and early promising clinical experiences. The current study is designed to be the first prospective evaluation of the combination of ipilimumab, nivolumab, and RT.

3 Experimental Plan

3.1 Study Design

This is an open-label, multicenter pilot Phase 1 study of the checkpoint antibodies ipilimumab and nivolumab in combination with RT in 18 subjects with unresectable Stage IV melanoma. All subjects will receive concurrent ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) every 3 weeks for 4 doses (Weeks 1 through 10), followed by nivolumab monotherapy (240 mg every 2 weeks) through Week 18, with optional extended treatment with nivolumab as described in Section 3.1.12. (Note: per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks, starting on Week 20, followed by Weeks 24, 28, etc.). Radiotherapy will be initiated after the first dose and before the second dose of immunotherapy.

There will be 2 cohorts in the study:

Cohort A:
Subjects in Cohort A will initially receive a conventional total RT palliative dose of 30 Gy delivered over 2 weeks in 10 fractions of 3 Gy each. Once 9 subjects have been accrued to Cohort A and completed the concurrent ipilimumab and nivolumab therapy, if ≤ 7 subjects have Grade 3 or 4 drug- or radiation-related AEs, as per Section 3.1.6, the safety of Cohort A will be deemed acceptable and additional subjects will be accrued to Cohort B.

Note: Grade 3 or 4 amylase or lipase abnormalities that are not associated with clinical symptoms will not be included in the Cohort A safety assessment described above.

Cohort B:
Subjects in Cohort B will receive the high-dose hypofractionated RT for which treatment of a target lesion will comprise a total palliative dose of 27 Gy delivered over 2 weeks in 3 fractions of 9 Gy each.

Radiographic imaging will be performed at Week 12 of therapy. As responses to these immunotherapeutic antibodies do not always occur at the first assessment time point and RT effects may not be apparent at the Week 12 evaluation, repeat radiographic assessment will take place after 6 additional weeks at Week 18. Subjects with symptomatic progression will be removed from the study.

3.1.1 Study Phase

Pilot Phase 1

3.1.2 Enrollment/Randomization

Subjects will be initially enrolled in Cohort A, with subsequent enrollment into Cohort B as outlined in Section 3.1.7. Enrollment will be under ongoing review by an internal data safety monitoring panel (see Section 3.1.14, Safety Monitoring and Study Stopping Rules).

3.1.3 Blinding/Unblinding

This will be an open-label study.

3.1.4 Subject Population

Subjects with unresectable, stage IV metastatic melanoma are eligible for this study, as detailed further in Section 5.

3.1.5 Number of Sites/Subjects

This study will be conducted at 3 sites in the US, with 18 subjects estimated for enrollment.

3.1.6 Sample Size and Statistical Considerations

This study is intended to generate descriptive safety data. Nine subjects are anticipated for each cohort to enable a variety of disease presentations and RT targets.

Prior experience with nivolumab and ipilimumab administered in combination has been associated with a treatment-related grade 3/4 toxicity rate of 53%.(19) A rating of Grade 3/4 drug- or radiation-related toxicity is considered to be acceptable in Cohort A if ≤ 7 of 9 subjects (78%) are affected (see exception in Section 3.1, i.e., asymptomatic amylase and lipase abnormalities are not included). This number was selected to avoid premature closure of exploration of this approach.

As this is the first prospective study of RT plus ipilimumab and nivolumab, no historical controls are available to anticipate the rate of toxicity of this triple combination regimen.

3.1.7 Treatment Arms and Treatment Schema

Table 1 presents the schedule of treatment administration.

Table 1. Treatment Schema

Cohort N	Week	Checkpoint Antibodies (IV)		Radiotherapy
		Ipilimumab[a]	Nivolumab[b]	
Cohort A n = 9	1	3 mg/kg	1 mg/kg	30 Gy delivered over 2 weeks in 10 fractions of 3 Gy each
	2	–	–	
	4, 7, 10	3 mg/kg	1 mg/kg	–
	12, 14, 16, 18	–	240 mg	–
	20+[b]	--	240 mg Q2W or 480 mg Q4W	--
Cohort B n = 9	1	3 mg/kg	1 mg/kg	27 Gy delivered over 2 weeks in 3 fractions of 9 Gy each
	2	–	–	
	4, 7, 10	3 mg/kg	1 mg/kg	–
	12, 14, 16, 18	–	240 mg	–
	20+[b]	--	240 mg Q2W or 480 mg Q4W	--

RT will be initiated after the first dose and before the second dose of immunotherapy.
Abbreviations: Gy = Gray; kg = kilogram(s); mg = milligram(s); N = number; IV = intravenously; Q2W = every 2 weeks; Q4W = every 4 weeks

[a] Administered once every 3 weeks for 4 doses. (3-week cycles)

[b] Administered once every 3 weeks for 4 doses (at 1 mg/kg) and then 240 mg once every 2 weeks.
Note: per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks, starting on Week 20, followed by Weeks 24, 28, etc.
See Section 6.1 for order of infusion.

3.1.8 Dosing Adjustments, Delays, and Discontinuations

Dosing adjustment, delays, and discontinuations of RT should be managed in accordance with standard of care. See Section 6.2 for administration details.

Dosing reductions in response to toxicities of ipilimumab or nivolumab are not permitted. Dosing delays and discontinuations of ipilimumab and nivolumab should be managed in accordance with Section 8.3. The following documents may also be referenced:

- YERVOY® (Ipilimumab) Package Insert: http://packageinserts.bms.com/pi/pi_yervoy.pdf
- YERVOY® (Ipilimumab) Immune-mediated Adverse Reaction Management Guide: https://www.hcp.yervoy.com/pages/rems.aspx
- Opdivo® (Nivolumab) Package Insert: http://packageinserts.bms.com/pi/pi_opdivo.pdf
- Management Algorithms for Adverse Events Associated with Immuno-oncology Agents (see Section 8.3.1).

Note: As durable disease stabilization and/or objective tumor response may be observed after early progression, it is recommended that, in the absence of toxicity requiring discontinuation in accordance with the package insert, all 4 doses of concurrent ipilimumab and nivolumab be administered over the initial 12 weeks, even in the setting of apparent clinical progression, provided the subject's performance status remains stable.

Even in the event of a dose delay, disease assessments should be performed according to standard of care on the originally scheduled study days.

Dose modifications for radiotherapy as a result of toxicity are-allowed per the Investigator's assessment.

3.1.9 Dose-limiting Toxicity

The DLT and MTD will not be defined or determined. A safety review will be conducted when 9 subjects have been accrued to Cohort A and completed the concurrent ipilimumab and nivolumab therapy. If ≤ 7 subjects have Grade 3 or 4 drug- or radiation-related AEs, the safety of Cohort A will be deemed acceptable and additional subjects will be accrued to Cohort B. The Cohort A assessment period for this evaluation will include the first 2 cycles of treatment, up to and including the pre-dose safety assessments scheduled for Cycle 3 (see Section 4.1.2).

Note: Grade 3 or 4 amylase or lipase abnormalities that are not associated with clinical symptoms will not be included in the Cohort A safety assessment described above.

3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Pregnancy or intent to become pregnant.
2. Clinical, symptomatic or radiographic progression warranting alternative treatment.
3. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
4. Initiation of alternative anticancer therapy including another investigational agent.
5. Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up.
6. Withdrawal of consent for further treatment.

7. Best medical interest of the subject (at the discretion of the Investigator)
8. Discontinuation criteria per Section 8.3.

Subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up through 100 days after the last study drug administration (see the Study Flowchart in Section 3.2) and enter the Post Study Follow-up phase (see Section 3.1.16).

A subject will be **withdrawn from the study** for the following reasons:

1. Best medical interest of the subject (at the discretion of the Investigator)
2. Withdrawal of consent for all follow-up.
3. Lost to follow-up
4. Death

3.1.11 Subject Evaluability and Subject Replacement

Subjects in Cohort A are fully evaluable for safety review of the concurrent ipilimumab and nivolumab therapy if:

1) they receive at least 1 dose of ipilimumab, nivolumab, or RT and have a Grade 3 or 4 related AE
2) In the absence of a Grade 3 or 4 related AE, they fulfill the criteria for the Per-protocol population for safety and tolerability as defined in Section 4.1.2.

Subjects in Cohort A who are not fully evaluable for safety review will be replaced.

Subjects are considered evaluable for the secondary efficacy endpoints if they fulfill the Per-protocol and Intent to treat populations described in Section 4.2.2, or if they discontinue from the study due to symptomatic progression, death, or toxicity at any point.

Subjects who discontinue the study and do not meet evaluability criteria may be replaced.

3.1.12 Optional Study Treatment Extension

Treatment extension with nivolumab monotherapy beyond 18 weeks is permitted and will be managed at the Investigator's discretion in accordance with standard practice. Subjects who require additional treatment will continue to be followed for efficacy assessments and On Study Follow-up (see Section 3.1.16 and Section 3.2). Details of extended nivolumab monotherapy administration should be captured on the Drug Administration electronic case report form (eCRF).

3.1.13 Interim Analysis

An interim analysis of safety will be performed after 9 subjects in Cohort A have completed concurrent ipilimumab and nivolumab therapy in order to determine whether to proceed with enrollment into Cohort B (see Section 3.1).

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor's medical

monitor, and drug safety personnel from Bristol-Myers Squibb, the provider of the study drugs. Additional investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board will not be utilized for this open-label study.

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to 1 or more of the study drugs and/or RT.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to 1 or more of the study drugs.
3. Any events that, in the judgment of the medical monitor, are deemed serious enough to warrant immediate review by the data safety monitoring panel.
4. Any other safety finding assessed as related to 1 or more study drugs that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

General criteria for premature trial termination are outlined in the Administrative Section 7.

3.1.15 Duration of Study

Duration of Treatment:	1 year (subjects benefitting from nivolumab treatment may receive continued treatment)
Enrollment Period:	2 years
Length of Study:	3 years
Length of Survival Follow-up	3 years

3.1.16 On Study and Post-Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study as per Section 3.1.10, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

On Study Follow-up will be conducted for 100 days after the last study drug administration according to the flowchart in Section 3.2. Refer to Section 7.1.5 for information on recording AEs during the On Study Follow-up.

In addition to the On Study Follow-up, there will be a Post Study Follow-up, during which clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 12 (± 1) weeks for 3 years after completion of 100-day On Study Follow-up. For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain the data through review of outside records or communication with the subject or his/her physician.

3.2 Study Flowchart

Study Section	Screening	Treatment								Final Assessment and Ongoing Treatment/ Assessments[d]	On Study Follow-up[a,e]	Post-Study Follow-up (Section 3.1.16)
Study Week		**Week 1 (Cycle 1)**	**Week 4 (Cycle 2)**	**Week 7 (Cycle 3)**	**Week 10 (Cycle 4)**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**2 weeks (± 3 days) after last study drug**	**30 (±4), 70 (±4) and 100-107 days after last study drug (AEs and pregnancy tests)**	**(Starts after completion of 100-day On Study Follow-up) Q12W (± 7 d) for 3 years**
Study Day	**-28 to 0** (or as stated)	**1**	**22 (± 3)**	**43 (± 3)**	**64 (± 3)**	**78 (± 3)**	**92 (± 3)**	**106 (± 3)**	**120 (± 3)**			
Drug Administration Cohort A												
Ipilimumab[f] IV		X	X	X	X							
Nivolumab[f] IV		X	X	X	X	X	X	X	X	X[d]		
Radiotherapy[b,f] (30 Gy over 10 fractions of 3 Gy)		X										
Drug Administration Cohort B												
Ipilimumab[f] IV		X	X	X	X							
Nivolumab[f] IV		X	X	X	X	X	X	X	X	X[d]		
Radiotherapy[b,f] (27 Gy over 3 fractions of 9 Gy)		X										
Tumor & Disease Assessments												
Disease Staging (date/stage at first diagnosis and study entry)	X											
Disease Assessment by RECIST 1.1 and irRECIST	X					X			X	X[d] (Week 24, then Q12W ± 7 days)		
Other Procedures & Examinations												
Eligibility Assessment and Informed Consent	X											
Demographics (including DoB, sex, height, race, ethnicity)	X											
Medical History	X											
Physical Exam (including weight)	X	X	X	X	X	X	X	X	X	X[d]		

Study Section	Screening	Treatment								Final Assessment and Ongoing Treatment/ Assessments[d]	On Study Follow-up[a,e]	Post-Study Follow-up (Section 3.1.16)
Study Week		**Week 1 (Cycle 1)**	**Week 4 (Cycle 2)**	**Week 7 (Cycle 3)**	**Week 10 (Cycle 4)**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**2 weeks (± 3 days) after last study drug**	**30 (±4), 70 (±4) and 100-107 days after last study drug (AEs and pregnancy tests)**	**(Starts after completion of 100-day On Study Follow-up) Q12W (± 7 d) for 3 years**
Study Day	**-28 to 0** (or as stated)	**1**	**22 (± 3)**	**43 (± 3)**	**64 (± 3)**	**78 (± 3)**	**92 (± 3)**	**106 (± 3)**	**120 (± 3)**			
Electrocardiogram (baseline and as clinically indicated)	X											
Vital Signs (temperature, HR, BP, RR)	X	X	X	X	X	X	X	X	X	X[d]		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X[d]		
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X	X	X[d]		
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X[d]	X	
Laboratory Measurements & Assays												
Serum Pregnancy Test[e]	X									X[d,e]	X[e]	
Urine Pregnancy Test (collected pre-dose)[e]		X		X		X			X	(Q6W)[d,e]		
Chemistry (Na, K, Cl, CO_2, BUN, creat., gluc., Ca, Mg, total prot., alb., Tbili., AST, ALT, ALP, LDH; blood drawn before dosing[g]	(-14 to 0) X	X	X	X	X	X	X	X	X	X[d,g]		
Free T_3, Free T_4, TSH; blood drawn before dosing[g]	(-14 to 0) X	X	X	X	X	X	X	X	X	X[d,g]		
Amylase, lipase; blood drawn before dosing	(-14 to 0) X	X	X	X	X	X	X	X	X	X[d]		
Blood Hematology (CBC with differential and platelets; blood drawn before dosing)	(-14 to 0) X	X	X	X	X	X	X	X	X	X[d]		
Research Blood Draw (60 mL; blood drawn before dosing)		X		X		X						
Tumor Biopsy (optional)[c]	X	X		X	X	X	X	X	X			

Study Section	Screening	Treatment								Final Assessment and Ongoing Treatment/ Assessments[d]	On Study Follow-up[a,e]	Post-Study Follow-up (Section 3.1.16)
Study Week		**Week 1 (Cycle 1)**	**Week 4 (Cycle 2)**	**Week 7 (Cycle 3)**	**Week 10 (Cycle 4)**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**2 weeks (± 3 days) after last study drug**	**30 (±4), 70 (±4) and 100-107 days after last study drug (AEs and pregnancy tests)**	**(Starts after completion of 100-day On Study Follow-up) Q12W (± 7 d) for 3 years**
Study Day	**-28 to 0** (or as stated)	**1**	**22 (± 3)**	**43 (± 3)**	**64 (± 3)**	**78 (± 3)**	**92 (± 3)**	**106 (± 3)**	**120 (± 3)**			
Progression and Survival Follow-up												X

Abbreviations: alb. = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbili. = total bilirubin; BP = blood pressure; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; Cl = chloride; CO_2 = carbon dioxide; creat. = creatinine; CT = computed tomography; d = day(s); DoB = date of birth; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; gluc. = glucose; Gy = Gray; HR = heart rate; irRECIST = immune-related RECIST; IV = intravenous(ly); K = potassium; mL = milliliter(s); LDH = lactate dehydrogenase; Mg = magnesium; Na = sodium; prot. = protein; Q = every; RECIST = Response Evaluation Criteria for Solid Tumors; RR = respiratory rate; RT = radiotherapy; W = week(s); Q6W = every 6 weeks; Q12W = every 12 weeks

Note: Additional assessments may be evaluated at the Investigator's discretion and per standard of care. Indicated assessments within this chart define clinical data to be captured in the eCRF. Standard of Care procedures may be used for eligibility assessments, provided they meet the criteria specified in either the inclusion criteria or flowchart.

a Subjects will be followed for 100 days after the last dose of study drug as a part of On Study Follow-up; during this time, all AEs will be collected at 30 (±4), 70 (±4) and 100-107 days.

b Radiotherapy will be delivered by standard or high dose palliative RT as per cohort assignment.

c Tumor biopsies are optional but are encouraged. Biopsies are prohibited from compromising the requirement for at least one measurable lesion not undergoing RT.

d **Final Assessment** will be 2 weeks (± 3 days) after last study drug, followed by On Study Follow-up and Post Study Follow-up. A repeat disease assessment scan is not required at the final assessment visit if a scan was done within the previous 6 weeks before the final assessment visit. Subjects who do not continue treatment with nivolumab after Week 18 do not need to have a repeat pregnancy test (if applicable) at the final assessment if the subject had this assessment at Week 18.

For those subjects who are continuing on nivolumab after Week 18 at 240 mg every 2 weeks ±3 days, Study Visits will continue every 2 weeks ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after the last nivolumab treatment.

Per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks ±3 days, starting on Week 20, followed by Weeks 24, 28, etc.

For those subjects who are continuing on nivolumab after Week 18 at 480 mg every 4 weeks ±3 days, Study Visits will continue every 4 weeks ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after the last nivolumab treatment.

Subjects continuing nivolumab monotherapy, subjects who complete study treatment as responders, and subjects who have not progressed (either in irradiated or non-irradiated tumor burden) will have an additional scan (disease assessments by RECIST 1.1/ irRECIST) at Week 24 and subsequent scans Q12W (± 7 days) until progression or start of alternate anti-cancer therapy.

e For females of child-bearing potential (as defined in Section 5.2), pregnancy tests required every 6 weeks and repeated at 30 (±4) days and 70 (±4) days after discontinuation of treatment. Serum pregnancy test is done at screening, final assessment, and during On Study Follow-up; urine pregnancy test is done at all other visits, including during continued nivolumab treatment (Note: For females of child-bearing potential who are continuing on nivolumab after Week 18 at 480 mg every 4 weeks, urine pregnancy tests may be done every 8 weeks). Urine pregnancy test is done and results confirmed pre treatment on Day 1 of study.

f All subjects will receive concurrent nivolumab (1 mg/kg) followed by ipilimumab (3 mg/kg) on the same day every 3 weeks for 4 doses, then followed by nivolumab monotherapy (240 mg every 2 weeks ±3 days) See footnote d for ongoing nivolumab monotherapy after Week 18. Radiotherapy will be initiated after the first dose and before the second dose of immunotherapy.

g Per Amendment 5: After Week 18, LDH testing and TSH (with reflexive free T3/T4) testing during ongoing nivolumab treatment will be done as clinically indicated; other testing will continue per flowchart.

4 Study Objectives & Endpoints

Primary Objective [Endpoints]	*Safety and Tolerability* [According to the NCI CTCAE, Version 4.03]
Secondary Objectives [Endpoints]	• *ORR by RECIST 1.1 and irRECIST* [ORR at Weeks 12 and 18] • *DCR by RECIST 1.1 and irRECIST* [DCR at Weeks 12 and 18] • *Duration of response* • *PFS* • *OS*
Exploratory Objectives [Endpoints]	*Antitumor Immunity* [Immunological Effects of Ipilimumab/Nivolumab/RT]

CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; DCR = disease control rate; irRECIST = immune-related RECIST; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RT = radiotherapy

4.1 Safety and Tolerability

The safety and tolerability of ipilimumab and nivolumab in combination with RT will be determined. Safety will be evaluated by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

4.1.1 Endpoints & Assessment Methods

Clinical laboratory tests, vital sign measurements, physical examinations, and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as AEs. All treatment-emergent, clinically significant abnormalities and deteriorations from the time of informed consent to the End of Study Visit should be recorded in the eCRFs as AEs and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

4.1.2 Subject Evaluation & Statistics

The Intent-To-Treat (ITT) Population for safety and tolerability is defined as all subjects who receive at least one dose of study drug or RT. The *Per-Protocol (PP) Population* for safety and tolerability is defined as all subjects who received at least 75% of the scheduled doses of study drugs and RT over the first 2 cycles, as well as, respective safety assessments (up to and including the pre-dose assessments scheduled for Cycle 3) without major protocol violations over the entire Cohort A concurrent ipilimumab and nivolumab assessment period (as defined in Section 3.1.9).

For both cohorts, the overall analysis of safety and tolerability will be based on the ITT Population.

Appropriate summaries of AEs, laboratory data, and vital sign data will be presented. AEs will be listed individually per subject according to the NCI CTCAE, Version 4.03, and the number of subjects experiencing each AE will be summarized using descriptive statistics.

4.2 Clinical Efficacy

4.2.1 Endpoints & Assessment Methods

Clinical efficacy will be determined by objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS). The primary method of assessment of tumor response will be the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1, and the secondary method of response evaluation will be irRECIST (see Section 8.4)

4.2.1.1 Tumor Response and Overall Response Rate

4.2.1.1.1 Tumor Response outside the Irradiated Fields

ORR will be evaluated at Weeks 12 and 18 as a secondary endpoint of this study.

Tumor imaging assessments (e.g., CT, MRI, PET, etc.) of chest, abdomen, pelvis, and CNS for assessment of tumor size and distribution may be employed as deemed appropriate by investigators. Every attempt should be made to use whichever imaging technique(s) test(s) are used initially for repeat evaluations throughout the study. End of study tumor assessment will be 6 weeks from prior assessment, at the Investigator's discretion, and in accordance with the appropriate evaluation method.

Radiographic imaging evaluations are considered standard of care for subjects treated with ipilimumab/nivolumab. Subjects treated off protocol with apparent progressive disease at Weeks 12 or 18 are encouraged to undergo a repeat radiographic assessment of disease approximately 4 to 6 weeks later to confirm progression.

Study radiologists will be informed as to which lesions are intended to undergo RT. The lesions undergoing RT will not be included in the total tumor burden assessment. A separate calculation of response within the irradiated field will be determined as described in Section 4.2.1.1.2.

4.2.1.1.2 Tumor Response within Irradiated Fields

Since the lesions that undergo RT are not included in the overall tumor burden for purposes of overall response assessments, response within the irradiated field will be separately determined.

The determination of response within the irradiated tumor burden is an independent calculation from the determination of response overall for the tumor burden that does not receive RT.

4.2.1.2 Disease Control Rate

Disease Control Rate (DCR) will be evaluated at Weeks 12 and 18 as a secondary endpoint of this study. DCR is defined as the percentage of evaluable subjects with SD, PR, or CR.

4.2.1.3 Duration of Response

Duration of response will be determined for each subject with time origin at the first occurrence of response until the first occurrence of progression or date of death if the subject dies due to

any causes before progression. Every effort will be made to follow subjects for progression after they discontinue the study.

4.2.1.4 Progression-free Survival

PFS will be defined as the number of days from the date of the first dose of study drug to the date of earliest disease progression based on the appropriate response evaluation method, or to the date of death, if disease progression does not occur. Subjects who do not progress and are still alive will be censored on the date of last follow-up or start of new treatment, whichever comes first. Every effort will be made to follow subjects for progression after they discontinue the study.

4.2.1.5 Overall Survival

OS will be measured for each subject from the date of the first dose of study drug until the recorded date of death or last follow-up. Subjects who are still alive will be censored on the date of last follow-up. Every effort will be made to follow subjects for OS after they discontinue the study.

4.2.2 Subject Evaluation & Statistics

The Intent-To-Treat (ITT) Population for clinical efficacy is defined as all subjects who receive at least one dose of study drug or RT.

The Per-Protocol (PP) Population for clinical efficacy is defined as all subjects who received at least 75% of the scheduled doses of the study drug and RT over the first 2 cycles, as well as, respective disease assessments, without major protocol violations.

The analysis will be based on both ITT and PP populations.

Tumor Response will be summarized and analyzed descriptively for each cohort and analysis population.

Tumor response rates will be assessed overall and for each cohort and tabulated with the 95% confidence intervals assuming binomial distribution.

For time-to-event analyses, Kaplan-Meier methodology will be implemented to estimate the median duration of response, median PFS, and median OS at Weeks 12 and 18.

4.3 Antitumor Immunity

4.3.1 Endpoints & Assessment Methods

Exploratory immunologic objectives will be assessed from peripheral blood and tumor biopsy samples according to the schedule in Section 3.2 to assess the influence of ipilimumab and nivolumab plus RT on assays, which may include but may not be limited to the following:

- Lymphocyte phenotype using markers such as ICOS, PD-1, and CD25;
- Quantities of myeloid-derived suppressor cells (MDSCs), defined as CD14+HLA-DRlow cells;
- Antibody and functional T cell responses to tumor associated antigens (i.e., NY-ESO-1) for relevant subjects;

- Serum cytokine levels such as TNF-alpha, IFN-gamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and TGF-beta;
- Serum and plasma microparticle and exosome nanoFACS and proteomic profiles;
- T cell repertoire diversity in peripheral blood and tumor.

Immunologic characteristics will be summarized descriptively. Antibody, T cell phenotype, and functional T-cell responses will be assessed. Antibody responses will be measured using ELISA and a positive antibody response will be defined as extrapolated reciprocal titers > 100 post treatment. Intracellular cytokine staining will be utilized to assess CD4+ and CD8+ T cell responses. Samples collected after treatment will be considered positive for response if they are higher than baseline values by at least 3 standard deviations. Therefore, for each subject, the standard deviation of the pre-treatment at two separate time points (using 6 replicates each) will be computed, and a positive will be defined as greater than 3 times this value and greater than 0.1% after 10-day in vitro stimulation.

Additional investigational methods may be used to characterize and measure components of the immune response based upon the latest available technology.

4.4 Additional Exploration of Immune Response

The methods used to analyze immune response to cancer antigens used in this study are well established. However, as cellular biology and immune regulation are very active fields of discovery, the opportunity exists to refine and extend the analysis of immune response. Therefore, although most of the blood drawn for the analysis of the immune response is planned for the assays listed, a small part, if still available, may be used to explore other aspects of immunological response. This work may also involve assessing exosomes and markers associated with radiation-induced immunologic cell death, such as expression of calreticulin and extracellular release of HMGB1. There may also be interest in establishing T-cell lines and clones in culture, evaluating tumor antigen-specific immune responses such as those against NY-ESO-1, assessing TCR repertoire diversity, proteomics/seromics analyses, and using samples in collaborations with other investigators and laboratories including those outside of the Ludwig Institute.

5 Subject Eligibility

Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

5.1 Inclusion Criteria

Eligible subjects **must fulfill** all of the following criteria:

1.	Histologic diagnosis of stage IV metastatic melanoma, with 1 melanoma lesion that can be safely irradiated and, in the opinion of the radiation oncologist, is of benefit to the subject to irradiate (note: subjects with primary ocular and mucosal melanoma are permitted). Lesions may include, but are not limited to: a. Symptomatic lymphadenopathy; b. Bothersome cutaneous disease; c. Hepatic metastases; d. Pulmonary metastases.
2.	Excluding the lesion intended to undergo radiation, subjects must have at least 1 unresectable, non-bony lesion that is measurable radiographically (based on RECIST 1.1).
3.	Any number of prior therapies (including none). For subjects who have received prior systemic treatment with CTLA-4, PD-1, and/or PD-L1 therapy, the last monoclonal antibody administration should be no less than 4 weeks prior to start of this protocol therapy and all prior side effects must have resolved to grade 1 or less by the time of the start of this protocol therapy.
4.	Subjects must have: • Completed investigational therapy, other immunotherapy, or prior RT at least 28 days before administration of the first dose of study drug(s) • Completed chemotherapy or targeted therapy at least 14 days before administration of the first dose of study drug(s) • Sufficiently recovered from prior surgery as determined by the treating Investigator. Clinically significant toxicity or pharmacodynamic effects experienced during any prior therapy must be resolved or stabilized before the first dose of study drug(s).
5.	ECOG performance status of 0-1.
6.	Life expectancy ≥ 4 months.
7.	Screening laboratory parameters: a. White blood cell (WBC) count ≥ 2000/µL; b. Absolute neutrophil count (ANC) ≥ 1500/µL; c. Platelets ≥ 100,000/µL; d. Hemoglobin (Hgb) ≥ 9 g/dL; e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); f. Total bilirubin ≤ 1.5 × ULN (< 3 mg/dL for subjects with Gilbert's disease); g. Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

	Female CrCl = [(140 - age in years) x weight in kg x 0.85] / [72 x serum creatinine in mg/dL] *Male* CrCl = [(140 - age in years) x weight in kg x 1.00] / [72 x serum creatinine in mg/dL]
8.	Age ≥ 18 years.
9.	Able and willing to give valid written informed consent.

5.2 Exclusion Criteria

Subjects **may not** enter the study if they fulfill any of the following criteria:

1.	Unresolved irAEs following prior biological therapy. Subjects with asymptomatic endocrinopathy may enroll.
2.	Active autoimmune disease or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
3.	History of motor neuropathy considered to be of autoimmune origin (e.g., Guillain-Barre Syndrome, Myasthenia Gravis).
4.	Other active, concurrent malignancy that requires ongoing systemic treatment or interferes with radiographic assessment of melanoma response as determined by the investigator.
5.	Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for 4 weeks or more after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
6.	Known immunodeficiency or HIV, Hepatitis B, or Hepatitis C positivity. Antibody to Hepatitis B or C without evidence of active infection may be allowed.
7.	History of severe allergic reactions to any unknown allergens or any components of the study drugs.
8.	Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders).
9.	Requirement of RT to treat brain metastases or receipt of any non-study systemic therapy for cancer or any other experimental/investigational treatment.
10.	Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study.
11.	Lack of availability for immunological and clinical assessments or post-study follow-up contact to determine relapse and survival.
12.	Women who are breastfeeding or who are pregnant as evidenced by a positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) performed within 14 days of the first dose of study drug and by a urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours of the first dose of study drug(s).

<table>
<tr><td>13.</td><td>Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 23 weeks after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

[Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).]

Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception from Day 1 and for 31 weeks after receipt of the final dose of investigational product.

Acceptable methods of effective contraception are described in the following table:

<table>
<tr><th>Barrier Methods</th><th>Intrauterine Device Methods</th><th>Hormonal Methods</th></tr>
<tr><td>Male condom plus spermicide, cap plus spermicide, or diaphragm plus spermicide.</td><td>Copper T, or Levonorgestrel-releasing intrauterine system (e.g., Mirena®), also considered a hormonal method.</td><td>Implants, hormone shot or injection, combined pill, minipill, or Patch.</td></tr>
</table>
</td></tr>
<tr><td>14.</td><td>Any condition that, in the clinical judgment of the treating physician, is likely to interfere with the interpretability of the data or prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.</td></tr>
</table>

5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

Subjects **<u>may not</u>** receive the following concomitant therapies during the study, except as allowed in Section 5.3.2:

1.	Systemic treatment with high-dose glucocorticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive treatments (e.g., methotrexate, chloroquine, azathioprine, adalimumab), with a wash-out period of 2 weeks prior to Day 1, unless such treatment is required to treat potential AEs.
2.	Other non-study cancer therapy, with a wash-out period of 4 weeks (2 weeks for chemotherapy, 6 weeks for nitrosoureas, and 12 weeks for antibodies other than CTLA-4, PD-1, and/or PD-L1 antibodies) prior to Day 1.
3.	Any other investigational agents.
The wash-out period prior to Day 1 of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above.	

5.3.2 Permitted Concomitant Therapies

Subjects **<u>may</u>** receive the following concomitant therapies during the study:

1.	At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids to treat study-drug-related immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional international normalized ratio (INR) monitoring is recommended. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
2.	As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in subjects treated with nivolumab-containing regimens.
All prescription and nonprescription drugs must be recorded in the concomitant medications section of the eCRF, listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the eCRF or as AEs.	

6 Study Drug Preparation and Administration

All study drugs are manufactured in accordance with Good Manufacturing Practices (GMP).

6.1 Ipilimumab and Nivolumab

The text within this section is provided for guidance; the current nivolumab and ipilimumab Investigator Brochures should be consulted for complete information regarding the storage, preparation, and administration of the study drugs.

Ipilimumab and Nivolumab Product Descriptions					
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/Label Type**	**Secondary Packaging (Qty)/Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/mL)	10 mL / vial	5-10 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C; Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL / vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C; Protect from light and freezing.

[a]Nivolumab may be labeled as BMS-936558-01 Solution for Injection.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first, as an IV infusion over approximately 60 minutes (or 30 minutes; see note), followed by ipilimumab administered as an IV infusion over approximately 90 minutes (or 30 minutes) that starts approximately 30 minutes after completion of the nivolumab infusion. Note: an infusion time of 30 minutes may also be used for each of the drug infusions (i.e., 30-minute infusion for nivolumab→30-minute interval→30-minute infusion for ipilimumab) as described by Martin-Algarra, et al.(46)

Dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram or as per local institutional standard.

Due to parameters surrounding the use time of nivolumab and ipilimumab, the time of preparation should be noted in the Pharmacy Source documents (accountability logs) or in study files as required for investigator-sponsored research (FDA and GCP).

6.1.1 Nivolumab Storage Conditions & Handling

- Store at 2°C to 8°C (36°F to 46°F); protect from light, freezing, and shaking.

- Please report any temperature excursions encountered during storage to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of IV agents applying aseptic technique.
- Partially used vials should be disposed of at the site following procedures for the disposal of anticancer drugs.
- After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

For details regarding nivolumab preparation, storage, and administration please refer to the pharmacy reference sheets/Investigator Brochure.

6.1.2 Nivolumab Preparation and Administration

For details regarding nivolumab preparation, storage, and administration please refer to the pharmacy reference sheets/Investigator Brochure.

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles. *Note: Mix by gently inverting several times. Do not shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection.
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent*.
4. **Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL**.
5. *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab*.
6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Additional information:

1. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, **and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light**. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

2. Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on subject weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to protein concentrations as low as 0.35 mg/mL. **When the dose is fixed (eg, 240 mg or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.**

6.1.3 Ipilimumab Storage Conditions & Handling

For details regarding preparation, storage, and administration please refer to the pharmacy reference sheets/Investigator Brochure.

Ipilimumab injection may be stored undiluted (200 mg/vial [5 mg/mL]) or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours under refrigerated conditions (2°C to 8°C) or at room temperature. For longer storage, ipilimumab should be kept refrigerated (2°C to 8°C) with protection from light. Ipilimumab injection must not be frozen.

Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

6.1.4 Ipilimumab Preparation and Administration

As this is provided for guidance only, please see Investigator brochure for additional information regarding preparation and administration.

1. As ipilimumab is stored long-term at refrigerated temperatures (2°C to 8°C) and protected from light, allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately 5 minutes.
2. Ensure that the ipilimumab solution is clear, colorless and essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
3. Aseptically transfer the required volume of ipilimumab solution into a syringe. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses.]
4. Do not draw into each vial more than once. Discard partially used vials or empty vials.
5. Ipilimumab solution should be added to an appropriate size infusion container to accommodate the calculated final volume. Total dose should be calculated using the most recent subject weight; if weight on dosing day differs by 10% from prior weight used to calculate dosing, the dose should be recalculated and study drug adjusted accordingly.
6. Mix by GENTLY inverting several times. DO NOT shake.
7. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
8. Visually inspect the final solution. If the initial diluted solution or final solution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.

9. Immediately after the infusion is complete, flush with an adequate amount of 0.9% Sodium Chloride injection (USP) or 5% Dextrose injection (USP) to completely flush the residual fluid (dead space) in your administration set (approximately 30 to 50 mL); this will ensure that all active drug is delivered to the study participant.
10. Safely discard any unused portion of the infusion solution. Do not store for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of IV agents. Ipilimumab is administered as an IV infusion only.

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol be used for this study.

6.2 Radiotherapy

RT will be initiated after the first and before the second dose of ipilimumab/nivolumab.

Target volumes for RT will be defined in accordance with International Commission on Radiation Units and Measurements (ICRU) Report #50: Prescribing, Recording and Reporting Photon Beam Therapy, and ICRU Report #71: Prescribing, Recording and Reporting Electron Beam Therapy.

The target lesion for RT will be defined as the gross tumor volume (GTV). The clinical target volume (CTV) will be the same as the GTV. The planning target volume (PTV) will be a minimum volumetric expansion of the GTV by 2 mm (5 mm recommended), but ultimately will be left to the discretion of the attending radiation oncologist.

CT simulation will be performed for planning purposes. Details of the CT simulation (4D CT, gating, use of contrast, immobilization) will be left to discretion of the attending radiation oncologist.

RT will be planned in 3-D and may be delivered using conventional, IMRT or rapid arc methodology. 6-18 MV photons and/or electron beam RT will be used as determined by the specific clinical situation. 95% of the PTV should receive the prescription radiation dose. Normal tissue constraints (see Section 8.5) will not be exceeded during the planning process.

When photon therapy is used, portal imaging, cone beam CT, or 2D kV on board imaging for QC will occur for each treatment. When electron therapy is used, light field verification of the target will occur at the start of treatment.

6.3 Drug Overdose Management

Any overdoses with the study drugs should be managed according to the appropriate package inserts. All overdoses (excess of 10% or more) must be reported, with or without associated AEs/serious adverse events (SAEs), according to Section 7.1.5 and Section 7.1.6.

7 Administrative, Legal & Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 General AE/SAE Definitions per ICH Guidelines

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods.,

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening[A],
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition[B].

[A] The term "life-threatening" in the definition of "serious" refers to an event in which the patient/subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

[B] Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient/subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.2 Additional SAE Definitions for this Study

For the purpose of this study, the following events are considered medically important conditions and must be treated as SAEs:

1. Pregnancy.
2. Overdose (as defined in Section 6.3).
3. Potential drug-induced liver injury (DILI).

   Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential DILI is defined as:

   - ALT or AST elevation > 3 times upper limit of normal (ULN); AND
   - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); AND
   - No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
4. Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug.

7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious AEs should be assessed according to the NCI CTCAE Scale (Version 4.03).

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious AEs to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)
Probably related (The AE is *likely related* to the investigational agent)
Possibly related (The AE *may be related* to the investigational agent)
Unlikely related (The AE is *doubtfully related* to the investigational agent)
Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in Section 1 (Background) of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

Documentation of serious and non-serious AEs includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as the causal relationship between the event and the study drug in accordance with Section 7.1.4.

All serious and non-serious AEs occurring between the date of signing the informed consent and the off-study date must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship.

During the On Study Follow-up period, all AEs (not only those deemed to be treatment-related) will continue to be collected for 100 days after the last dose of study drug administration.

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

In addition to the General Reporting Requirements specified in Section 7.1.5, all SAEs, irrespective of suspected causation, must be reported by the Investigator to the Sponsor within 24 hours of discovery, using the "Initial Serious Adverse Event Report Form", provided by the Sponsor, or, if Medidata RAVE data capture is utilized, using the respective eCRFs. This includes any deaths that occur after the off-study date, but within 100 days of last study drug administration.

Events meeting the criteria for an SAE as per Sections 7.1.1 and 7.1.2 must be reported to the Sponsor's Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, via email or phone call within 24 hours of becoming aware of the event. The event must also be recorded in the Adverse Event Log electronic CRF and indicated as an SAE within 24 hours. Studies utilizing the Medidata "Safety Gateway", built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below).

In urgent cases, pre-notification via phone or informal e-mail should be considered.

Drug Safety Contact:	*Primary Sponsor Contact:*
[redacted] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted]	[redacted] Director Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted]

SAEs must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned an SAE tracking number by the Sponsor. Institutional Review Boards may have specific rules on which AEs need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor's Medical Monitor. Regulatory authorities and other investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug(s) cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available, using the "SAE Follow-up Report form", provided by the Sponsor.

7.2 Administrative Sponsor Requirements

7.2.1 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

7.2.2 Case Report Form Data Collection

Electronic CRFs will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the CRF and will certify its content.

7.2.3 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. eCRFs must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other sponsor staff will meet with the investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the eCRF at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to subject charts, laboratory reports and other subject records needed to verify the entries on the eCRF ("source data verification").

7.2.5 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects do usually not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

7.2.6 Premature Subject Withdrawal

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from the study. Specific subject withdrawal reasons are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the subject's withdrawal, the appropriate form in the eCRF should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

7.2.7 Early Trial Termination

"End of study" is defined as the last visit of the last subject. Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the

reasons for the termination. The investigator must also notify the appropriate Institutional Review Board accordingly.

7.2.8 Study Drug Shipments & Accountability

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

Initial Orders:

- Following submission and approval of the required regulatory documents, a supply of nivolumab and ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.
- The initial order should be limited to the amount needed for 2 doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not subject specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, in-line filters, and infusion tubing.

Re-Supply:

- Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not subject-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Drug Excursions:

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for the accounting of all used and unused trial supplies. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

7.3 Regulatory, Legal, & Ethical Requirements

7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

7.3.2 Informed Consent

The investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study-specific procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

7.3.3 Institutional Review Board

The investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The investigator must report SAEs to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

7.3.4 Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the eCRF or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed

informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

8 Appendices

8.1 Protocol Version History

Original issue **Issue date: 18-SEP-2015** **Summary of Changes:** n/a

Amendment 001
Issue Date: 05-FEB-2016
Summary of Changes:
Based on recommendations from institutional reviews, the following changes were made:
• Administrative changes
  o Updated footer and synopsis page with new protocol format and logo.
  o General spelling, capitalization, and formatting changes, as needed.
• Synopsis, Section 3.2 and Section 4: all references to Quality of Life Assessments by Functional Assessment of Cancer Therapy-Melanoma (FACT-M) and Brief Pain Inventory-Short Form were deleted. Sections 4.3, 8.7, and 8.8, which were related to these assessments, were deleted and other sections were re-numbered as appropriate. The QoL assessments were removed from the protocol because it was decided that the low subject numbers would preclude a robust statistical analysis.
• Section 3.1.12: added reference to Section 3.2.
• Section 3.1.16: Clarification was added to indicate that Post Study Follow-up will start after completion of the 100-day On Study Follow-up.
• Section 3.2, Study Flowchart:
  o A Final Assessment visit was added, and the assessments from On Study Follow-up were moved to the Final Assessment visit.
  o Clarification was provided that the On Study Follow-up will be assessed at 30, 70 and 100 days after last study drug; AEs and pregnancy tests will be assessed as indicated by footnotes “a” and “e.”
  o 30, 70 and 100 day assessments were added to footnote “a.”
  o The following clarification was provided as footnote “d”: “Final Assessment will be 2 weeks after last study drug, followed by On Study Follow-up and Post Study Follow-up. For those subjects who are continuing on nivolumab, Study Visits will continue Q2W ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after last nivolumab treatment. Disease assessments by RECIST 1.1/ irRECIST will continue Q6W during the continued nivolumab treatment.
  o Clarification was added to indicate that Post Study Follow-up will start after completion of the 100-day On Study Follow-up
  o Chemistry and hematology lab assessments were added for Weeks 14 and 16
  o Amylase and lipase assessments were added on the same days as other chemistry profile assessments
  o Free T3, Free T4 and TSH were separated from the routine chemistry profile and placed on a separate line.
• Section 4.3.1 (previously 4.4.1) and Section 8.6 : Deleted “Whole exome sequencing for mutational load and neoantigens pre- and post-RT” from the list of correlative testing to be

done. In addition, it was clarified that the assays may include but may not be limited to the list provided.

- Section 5.1, Inclusion Criterion #1 was changed as follows (changes in bold): "Histologic diagnosis of stage IV metastatic melanoma, with 1 melanoma lesion that can be safely irradiated **and,** in the opinion of the radiation oncologist, **is of benefit to the subject to irradiate..."**
- Section 5.2, Exclusion Criterion #1 (Any contraindications for ipilimumab (Yervoy®) or nivolumab (Opdivo®) as per the package inserts.) was deleted; remaining criteria were re-numbered.
- Section 5.3.1, #2: Added clarification that washout period is 6 weeks for CTLA-4, PD-1, and/or PD-L1 antibodies and 12 weeks for other antibodies.
- Section 6.1, third paragraph was changed to allow for a time interval for the study drug administration time: a) 60-minute IV infusion was changed to "an IV infusion over approximately 60 minutes"; b) 90-minute IV infusion was changed to "an IV infusion over approximately 90 minutes."
- Section 6.1, next to last paragraph was changed as follows (changes in bold and underlined): "Dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram **or** **as** per **local** institutional standard."
- Section 7.1.6: Changed Primary Sponsor Contact from [redacted].

Amendment 2
Issue Date: 06-MAY-2016
Summary of Changes:

- Cover Page: IND # was deleted, as this study is exempt. BMS reference number was added.
- Section 3.1.15: Enrollment period was changed from 1 year to 2 years; Length of Study was change from 2 to 3 years.
- Section 3.2, Flowchart:
  - "and pre-existing conditions" was deleted from the Medical History line.
  - Added Mg and LDH to list of chemistry assessments
  - Added the following statement to the Note in the footnote: "Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
  - Collection of serum or urine pregnancy tests was clarified in footnotes and flowchart. The following statement was added to footnote e: "Serum pregnancy test is done at screening, final assessment, and during On Study Follow-up; urine pregnancy test is done at all other visits, including during continued nivolumab treatment."
  - Moved Week 14 urine pregnancy test to Week 12.
  - The following clarification was added to footnote "d" (changes in bold): "Disease assessments by RECIST 1.1/ irRECIST will continue Q6W **(starting 6 weeks after last disease assessment)** during the continued nivolumab treatment. **Subjects who do not continue treatment with nivolumab after Week 18 do not need to have a repeat pregnancy test (if applicable) or disease assessment at the final assessment if the subject had these assessments at Week 18."**

- Sections 4.3.1 and 8.6: deleted references to plasma miRNA levels and circulating cell free DNA quantity.
- Section 5: added the following Note to Subject eligibility: "Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
- Section7.2.2: The following statement was added: "All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF."
- Administrative changes: General spelling, grammar, capitalization, and formatting changes, as needed.

Amendment 3
Issue Date: 10-NOV-2016
Summary of Changes:

- Synopsis and Section 3.1 (Study Design): Second sentence was modified (changes in bold): All subjects will receive concurrent ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) every 3 weeks for 4 doses, followed by nivolumab monotherapy (~~**3 mg/kg**~~ **240 mg**) every 2 weeks. **RATIONALE**: monotherapy dose for continuing nivolumab was changed from 3 mg/kg to fixed dose of 240 mg according current BMS prescribing information.
- Section 3.1 (Study Design) and Section 3.1.9 (Dose-limiting toxicity): The following note was added to Cohort A: "Note: Grade 3 or 4 amylase or lipase abnormalities that are not associated with clinical symptoms will not be included in the Cohort A safety assessment described above." A reference to this note was provided in the Synopsis and in Section 3.1.6 (Sample Size and Statistical Considerations).
  RATIONALE: amylase and lipase can increase to Grades 3/4 without serious issues (e.g., pancreatitis) being diagnosed.
- Section 3.1.7 (Treatment Arms and Treatment Schema): The monotherapy dose for continuing nivolumab was changed from 3 mg/kg to fixed dose of 240 mg as indicated above. Footnote b was modified (changes in bold): Administered once every 3 weeks for 4 doses **(at 1 mg/kg)** and then **240 mg** once every 2 weeks. **See Section 6.1 for order of infusion.**
- Section 3.1.8 (Dosing Adjustments Delays and Discontinuations) and Section 8.5.6 (Radiotherapy timing and dose fractionation): the following statement was added: "Dose modifications for radiotherapy as a result of toxicity are allowed per the Investigator's assessment."
- Section 3.2 (Flowchart): For the On Study Follow-up visits, the following windows were added (changes in bold): 30 **(±4)**, 70 **(±4**) and 100-**107** days after last study drug.
- Section 3.2 (Flowchart): Footnote f was added to clarify the dosing for nivolumab and ipilimumab: "All subjects will receive concurrent nivolumab (1 mg/kg) followed by ipilimumab (3 mg/kg) on the same day every 3 weeks for 4 doses, then followed by nivolumab monotherapy (240 mg) every 2 weeks. Radiotherapy will be initiated after the first dose and before the second dose of immunotherapy."
- Section 5.1 (Inclusion Criteria):
  - #3 was changed as follows (6 weeks changed to 4 weeks): Any number of prior therapies (including none). For subjects who have received prior systemic treatment with CTLA-4, PD-1, and/or PD-L1 therapy, the last monoclonal antibody administration should be no

less than ~~6~~ **4** weeks prior to start of this protocol therapy and all prior side effects must have resolved to grade 1 or less by the time of the start of this protocol therapy.

- #4 was changed **FROM:** "Subjects must have completed chemotherapy, targeted therapy, investigational therapy, other immunotherapy, prior RT, or major surgery (requiring general anesthesia) at least 28 days before administration of the first dose of study drug(s). Subjects undergoing minor surgical procedures and biopsies that do not require general anesthesia may begin receiving study therapy if sufficiently recovered as determined by the treating investigator. Clinically significant toxicity experienced during any prior therapy must be resolved or stabilized before the first dose of study drug(s)."
  TO:
  "Subjects must have:
  - Completed investigational therapy, other immunotherapy, or prior RT at least 28 days before administration of the first dose of study drug(s)
  - Completed chemotherapy or targeted therapy at least 14 days before administration of the first dose of study drug(s)
  - Sufficiently recovered from prior surgery as determined by the treating Investigator.

  Clinically significant toxicity or pharmacodynamic effects experienced during any prior therapy must be resolved or stabilized before the first dose of study drug(s)."

- Section 6.1 (Ipilimumab and Nivolumab): the following paragraph was modified (changes in bold): "When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first, as an IV infusion over approximately 60 minutes **(or 30 minutes; see note)**, followed by ipilimumab administered as an IV infusion over approximately 90 minutes **(or 30 minutes)** that starts approximately 30 minutes after completion of the nivolumab infusion. **Note: an infusion time of 30 minutes may also be used for each of the drug infusions (i.e., 30-minute infusion for nivolumab→30-minute interval→30-minute infusion for ipilimumab) as described by Martin-Algarra, et al.(46)**"
  RATIONALE: the reduced infusion times are based on recommendations from BMS and data presented at ESMO 2016 by Martin-Algarra, et al. (46)

Amendment 4
Issue Date: 10-MAY-2017
Summary of Changes:

- Synopsis and Section 3.1.6 (Sample Size and Statistical Considerations): for paragraph 2, sentence 2, the following clarification was added (changes in bold): "(see exception in Section 3.1, **i.e., asymptomatic amylase and lipase abnormalities are not included**).
- Section 3.1.9 (DLT): the following statement was added to provide clarification for the safety evaluation period: "The Cohort A assessment period for this evaluation will include the first 2 cycles of treatment, up to and including the pre-dose safety assessments scheduled for Cycle 3 (see Section 4.1.2)."
- Section 3.1.11 (Subject Evaluability and Replacement): clarification was provided to indicated that the AEs in points 1 and 2 are "related" AEs.

- Section 3.2, Flowchart:
  - The disease assessment frequency after Week 18 was changed from Q6W to Q12W (specifically, "Week 24, then Q12W ± 7 days), based on Investigator input that Q6W scanning is too frequent for patients who have had a response or stable disease after their first 24 weeks on study.
  - Footnote d was changed to align with the change for disease assessment (changes in bold): "Final Assessment will be 2 wee**e**ks (± 3 days) after last study drug, followed by On Study Follow-up and Post Study Follow-up. **A repeat disease assessment scan is not required at the final assessment visit if a scan was done within the previous 6 weeks before the final assessment visit. Subjects who do not continue treatment with nivolumab after Week 18 do not need to have a repeat pregnancy test (if applicable) at the final assessment if the subject had this assessment at Week 18.** For those subjects who are continuing on nivolumab, Study Visits will continue Q2W ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after the last nivolumab treatment. **Subjects continuing nivolumab monotherapy and subjects who complete study treatment as responders will have an additional scan (disease assessments by RECIST 1.1/ irRECIST) at Week 24 and subsequent scans Q12W (± 7 days) until progression or start of alternate anti-cancer therapy. ~~Disease assessments by RECIST 1.1/ irRECIST will continue Q6W (starting 6 weeks after last disease assessment) during the continued nivolumab treatment. Subjects who do not continue treatment with nivolumab after Week 18 do not need to have a repeat pregnancy test (if applicable) or disease assessment at the final assessment if the subject had these assessments at Week 18.~~"**
  - Post Study Follow-up frequency was changed for Q24W to Q12W to align with disease assessment frequency. This was also changed in Section 3.1.16.
  - Added "Electrocardiogram (baseline and as clinically indicated)" to allow for a baseline for cardiac monitoring.
  - Study week row was clarified to indicate week vs cycle (changes in bold):

Study Week		**Week** 1 **(Cycle 1)**	**Week** 4 **(Cycle 2)**	**Week** 7 **(Cycle 3)**	**Week** 10 **(Cycle 4)**	**Week** 12	**Week** 14	**Week** 16	**Week** 18

  - Final Assessment column header was clarified (changes in bold): "Final Assessment **and Ongoing Treatment / Assessments**[d]**"**
- Section 4.1.2 (Subject Evaluation and Statistics): Updated PP Population to clarify evaluation period. (changes in bold): "The *Per-Protocol (PP) Population* for safety and tolerability is defined as all subjects who received at least 75% of the scheduled doses of study drugs and RT over the first 2 cycles, as well as, respective safety assessments **(up to and including the pre-dose assessments scheduled for Cycle 3)** without major protocol violations over the entire Cohort A concurrent ipilimumab and nivolumab assessment period (as defined in Section 3.1.9)."
- Section 5.3.1 (Non-permitted Concomitant Therapies): made corrections to align with language in Section 5.1 (Inclusion Criteria) #4 (changes in bold): "Other non-study cancer therapy **~~(chemotherapy or immunotherapy)~~**, with a wash-out period of 4 weeks (**2 weeks for chemotherapy**, 6 weeks for nitrosoureas **~~and CTLA-4, PD-1, and/or PD-L1 antibodies~~** and 12 weeks for **~~other~~** antibodies **other than CTLA-4, PD-1, and/or PD-L1 antibodies)** prior to Day 1."

Amendment 5
Issue Date: 12-JUN-2018
Summary of Changes:

- For subjects who continue nivolumab treatment after Week 18, a dosing option of 480 mg every 4 weeks was added. Rationale: this option was provided based on current dosing options that are available. This change was added to the following sections:
  - Synopsis, Section 3.1 (Study Design), and Section 3.1.7 (Treatment Arms and Schema), Table 1. "Note: per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks starting on Week 20, followed by Weeks 24, 28, etc.)."
- Section 3.2 (Flowchart):
  - Footnote c was updated to provide clarification and agreement with Inclusion criterion #2 (changes in bold): "Tumor biopsies are optional but are encouraged. Biopsies are prohibited from compromising the requirement for at least ~~**one measurable lesion undergoing RT**~~ and one measurable lesion not undergoing RT."
  - Footnote d was updated to (1) provide clarification that subjects who have not progressed will also have an additional scan at Week 24 and subsequent scans Q12W (± 7 days) until progression or start of alternate anti-cancer therapy; and (2) to add information regarding the 480 mg (every 4 weeks) dosing after Week 18 for nivolumab (changes in bold):

  Final Assessment will be 2 weeks (± 3 days) after last study drug, followed by On Study Follow-up and Post Study Follow-up. A repeat disease assessment scan is not required at the final assessment visit if a scan was done within the previous 6 weeks before the final assessment visit. Subjects who do not continue treatment with nivolumab after Week 18 do not need to have a repeat pregnancy test (if applicable) at the final assessment if the subject had this assessment at Week 18.

  For those subjects who are continuing on nivolumab **after Week 18 at 240 mg every 2 weeks ±3 days**, Study Visits will continue every 2 weeks ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after the last nivolumab treatment.

  Per Amendment 5, nivolumab monotherapy continuing after Week 18 may be given as 480 mg every 4 weeks ±3 days, starting on Week 20, followed by Weeks 24, 28, etc.
  For those subjects who are continuing on nivolumab after Week 18 at 480 mg every 4 weeks ±3 days, Study Visits will continue every 4 weeks ± 3 days during treatment, followed by the Final Assessment Visit, On Study Follow-up, and Post Study Follow-up after the last nivolumab treatment.

  Subjects continuing nivolumab monotherapy, ~~**and**~~ subjects who complete study treatment as responders, **and subjects who have not progressed (either in irradiated or non-irradiated tumor burden)** will have an additional scan (disease assessments by RECIST 1.1/ irRECIST) at Week 24 and subsequent scans Q12W (± 7 days) until progression or start of alternate anti-cancer therapy.
  - Footnote e: the following note was added: "For females of child-bearing potential who are continuing on nivolumab after Week 18 at 480 mg every 4 weeks, urine pregnancy tests may be done every 8 weeks."
  - Footnote f was updated to provide clarification (changes in bold): "All subjects will receive concurrent nivolumab (1 mg/kg) followed by ipilimumab (3 mg/kg) on the same

day every 3 weeks for 4 doses, then followed by nivolumab monotherapy (240 mg every 2 weeks ±**3 days**). **See footnote d for ongoing nivolumab monotherapy after Week 18.** Radiotherapy will be initiated after the first dose and before the second dose of immunotherapy. ○ Footnote g was added to reflect current requirements for LDH and thyroid testing; the change was added only for ongoing treatment period after Week 18 to allow for the core study to have consistent collection of data. • Section 5.1, Exclusion Criterion # 14 was clarified (changes in bold): "Any condition that, in the clinical judgment of the treating physician, is likely to **interfere with the interpretability of the data or** prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk." • Section 6.1.2 (Nivolumab Preparation and Administration). "Additional information" was added per instructions provided by BMS (added last 2 paragraphs). • Administrative changes: General spelling, grammar, capitalization, and formatting changes, as needed. • Section 8.7 (Abbreviations) was updated.

8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information

This information is provided in the Clinical Study File.

8.3 Ipilimumab and Nivolumab Dose Delays and Adjustments

No dose reductions or escalations are permitted.

Criteria for Dose Delay

Because of the potential for clinically meaningful immuno-oncology-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for the following suspected AEs: diarrhea/colitis; elevated creatinine; pneumonitis; elevated liver function tests (LFTs); elevated TSH; rash; and neurological AEs (see Section 8.3.1).

Dose delay criteria apply to all drug-related AEs (regardless of whether or not an event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until criteria for resumption of treatment are met.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related AE.
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the Sponsor for Grade 3 amylase or lipase abnormalities.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.

Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes. Doses may not be skipped. For ipilimumab, the intent is to administer all 4 doses if possible.

If treatment is delayed for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in the discontinuation criteria.

Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic AE, hypersensitivity reactions, and infusion reactions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
        - Any drug-related LFT abnormality that meets the following criteria requires discontinuation:
            - AST or ALT > 8 x ULN.
            - Total bilirubin > 5 x ULN.
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN.
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
    - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing

interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Treatment of Nivolumab- or Ipilimumab-related Infusion Reactions

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

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE, Version 4.03 guidelines.

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

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

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

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

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

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

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

For subjects who are expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage AEs, the following recommendations should be considered.

- Administer antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In subjects who develop recurrent AEs in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

8.3.1 Management Algorithms for Adverse Events Associated with Immuno-oncology Agents

Please refer to the most current version of the nivolumab IB for current recommendations for management of a specific Adverse Event of interest. The following management algorithms are available in the Appendix of the IB:

- GI AE Management
- Renal AE Management
- Pulmonary AE Management
- Hepatic AE Management
- Endocrinopathy Management
- Skin AE Management
- Neurological AE Management

8.4 RECIST 1.1 and irRECIST Guidelines

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.(47) These guidelines have been the widely accepted criteria to assess response and progression in solid tumors; however, limitations have been noted in the use of RECIST 1.1 for immunotherapy trials. With immunotherapeutic agents, clinical trials have shown that complete response, partial response, or stable disease status can still be achieved after an initial increase in overall tumor burden, and regression of initial lesions may occur despite development of new lesions. The Immune-related Response Criteria (irRC) were developed to address the need for response criteria in an immunotherapy setting.(13) The main difference with irRC was that it considered the subject's total tumor burden at each subsequent assessment and required confirmation of suspected disease progression with subsequent imaging, approximately four weeks later. In addition, a greater number of lesions (10 vs. 5) were measured in a bidimensional manner instead of unidimensionally as in RECIST 1.1. In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.(48) Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).(49) The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines. The guidelines for RECIST 1.1 are summarized below, followed by a summary for irRECIST.

RECIST 1.1

The following section outlines the RECIST 1.1 guidelines as published (47) and as summarized by National Cancer Institute for CTEP-involved clinical trials**.**

I. <u>Disease Parameters for RECIST 1.1</u>

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

<u>Measurable disease</u>. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as <u>≥</u>20 mm by chest x-ray, as <u>≥</u>10 mm with CT scan, or <u>≥</u>10 mm with calipers by clinical exam. All tumor measurements must be recorded in <u>millimeters</u> (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

NOTE for irRECIST: During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

NOTE for irRECIST:
Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
Brain lesions detected on brain scans can be considered as both target or non-target lesions depending on the protocol definition.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any non-measureable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

II. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to

the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.(50-52) In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(53)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

III. Response Criteria for RECIST 1.1

A. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

B. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

1. For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

2. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an end-point for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

D. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. (49) are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1. One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

II Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

III Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:** no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

8.5 Recommended Guidelines for Radiation Therapy

8.5.1 Target selection for radiation therapy

The target for radiation therapy will be selected at the discretion of the protocol investigators.

The target should not have been previously irradiated.

In subjects that have had prior radiotherapy, treatment should not be carried out if the target is within 3 cm of the organ below (and criteria in parentheses are met):

Lung (prior v20 ≥25%)
Spinal cord (prior dose >40 Gy within 3 cm of target)
Brain, Globe, Optic nerves, Brainstem (prior dose >50 Gy within 3 cm of target)
Brachial plexus (prior dose >50 Gy within 3 cm of target)
Bowel and stomach (prior dose >40 Gy within 3 cm of target)

The target should be one that is not exclusively within bone (i.e., a bone metastasis with no extraosseous soft tissue component), and therefore cannot be assessed for radiographic response by protocol-defined criteria.

Priority should be given to irradiating symptomatic metastases.

If multiple symptomatic targets are present, the largest target that can safely be irradiated should be chosen.

More than one target can be irradiated, but at least one site of measurable disease must be not be irradiated for response assessment purposes (see protocol).

The radiotherapy target should be described categorically as one of the following:

Lymph node
Bone
Skin
Lung
Liver
Gastrointestinal tract
Muscle
Other

The target for radiation therapy should be anatomically described (including laterality) in order to aid in radiographic response determination by the reference radiologist.

8.5.2 Treatment position, immobilization, and simulation

The treatment position will be comfortable enough to allow the patient to complete treatment, and will be chosen to preserve organ at risk constraints and provide adequate planning target volume coverage.

Immobilization devices will be used to enhance reproducibility of setup.

CT simulation will be carried out for all radiation therapy targets.

The CT simulation should take place with the treatment position, with immobilization devices in place.

The CT scan should include the entire treatment target, and 15 cm of the body superior and inferior to this. This will ensure the entire anatomic structure will be included in the planning CT image for proper evaluation of the normal tissue dose-volume histogram, which is used as treatment planning criteria.

For targets within 5 cm of:	Must be included in simulation CT scan:
Either lung	Thoracic inlet through 5 cm below the diaphragm/lung parenchyma
Either kidney	Entire volume of bilateral kidney parenchyma
Liver	Entire volume of liver
Colon or rectum	Entire abdomen and pelvis (diaphragm dome through ischial tuberosities)

The CT scan slice thickness should be no more than 3 mm.

The use of motion assessment and compensation techniques (including, but not limited to 4D CT, slow CT, breath-hold techniques, compression-belt, and respiratory gating) are permitted for moving targets, but not required.

The use of contrast media for the CT scan is permitted, but not required.

The use of adjunct imaging for simulation (PET, MRI) is permitted, but not required.

8.5.3 Target delineation

Target delineation will be carried out according to International Commission on Radiation Units (ICRU) guidelines 50 and 62.

The gross tumor volume (GTV) is defined as the clinically and/or radiographically apparent site of melanoma chosen as a radiation therapy target.

The clinical target volume (CTV) will be the same as the GTV.

The internal target volume (ITV) will be determined based on motion assessment and compensation strategies applied (if any). If no motion assessment is undertaken, then ITV will be the same as the CTV.

The planning target volume (PTV) will be determined based on the anticipated setup uncertainty, machine tolerance, and intratreatment variation in CTV and/or ITV. This is required to be between 2 and 10 mm and need not be isotropic.

8.5.4 Organ at risk dose (OAR) delineation and dose constraints

The following OARs should be delineated on the CT simulation scan when they are within 10 cm of the PTV:

Organ at risk (OAR)	Definition
Skin	Volume within 5 mm below skin surface or "outer" contour
Brain (not brainstem)	
Lens, left	
Lens, right	
Globe, left Globe, right	
Optic nerve, left	
Optic nerve, right	
Optic chiasm	
Brainstem (not medulla)	
Cochlea, left	http://www.ncbi.nlm.nih.gov/pubmed/15803007
Cochlea, right	http://www.ncbi.nlm.nih.gov/pubmed/15803007
Medulla and spinal cord	Bone limits of spinal canal until L2
Spinal cord subvolume	http://www.ncbi.nlm.nih.gov/pubmed/23864755
Larynx	http://www.ncbi.nlm.nih.gov/pubmed/24673866
Esophagus	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Brachial plexus, left	http://www.ncbi.nlm.nih.gov/pubmed/18448267
Brachial plexus, right	http://www.ncbi.nlm.nih.gov/pubmed/18448267
Ribs, left	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Ribs, right	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Trachea and mainstem bronchi	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
*Lung, left	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
*Lung, right	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Bronchioles	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Great vessels	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Pericardium/Heart	http://www.rtog.org/LinkClick.aspx?fileticket=VyMTDbz25wY%3d&tabid=361
Stomach	http://www.ncbi.nlm.nih.gov/pubmed/24890348
*Liver	http://www.ncbi.nlm.nih.gov/pubmed/24890348
Common bile duct	http://www.ncbi.nlm.nih.gov/pubmed/24890348
*Renal cortex, left	
*Renal cortex, right	
Renal hilum, left	
Renal hilum, right	
Ureter, left	
Ureter, right	
*Colon	http://www.ncbi.nlm.nih.gov/pubmed/24890348
Duodenum	http://www.ncbi.nlm.nih.gov/pubmed/24890348
Jejunum	http://www.ncbi.nlm.nih.gov/pubmed/24890348
Ileum	http://www.ncbi.nlm.nih.gov/pubmed/24890348
Cauda equine	Bone limits of spinal canal below L2
Lumbrosacral plexus, left	http://www.ncbi.nlm.nih.gov/pubmed/22342301
Lumbrosacral plexus, right	http://www.ncbi.nlm.nih.gov/pubmed/22342301
*Rectum	http://www.ncbi.nlm.nih.gov/pubmed/22483697
Bladder wall	http://www.ncbi.nlm.nih.gov/pubmed/22483697
Penile bulb	http://www.ncbi.nlm.nih.gov/pubmed/22483697
Femoral head, left	http://www.ncbi.nlm.nih.gov/pubmed/22483697

Organ at risk (OAR)	Definition
Femoral head, right	http://www.ncbi.nlm.nih.gov/pubmed/22483697
*Both lungs, both kidneys, the liver, colon and rectum must be delineated in their entirety when included in the CT simulation scan.	

OARs should be constrained so that a dose of 27 Gy can be delivered in 3 fractions without exceeding limits below.

OAR	Volume	Volume Max Dose	Max Point Dose**	Endpoint (≥Grade 3)
Skin	<10 cc	30 Gy	33 Gy	Ulceration
Brain	<0.5 cc	18 Gy	23.1 Gy	Necrosis
Lens (right or left)			12 Gy	Keratitis
Globe (right or left)			16.2 Gy	Uveitis
Optic nerves and chiasm (combined)	<0.2 cc	15.3 Gy	17.4 Gy	Neuritis
Cochlea (right or left)			17.1 Gy	Hearing loss
Brainstem (not medulla)	<0.5 cc	18 Gy	23.1 Gy	Cranial neuropathy
Medulla and spinal cord	<0.35 cc <1.2 cc	18 Gy 12.3 Gy	21.9 Gy	Myelitis
Spinal cord subvolume	<10% of subvolume	18 Gy	21.9 Gy	Myelitis
Larynx			26.4 Gy	Laryngitis
Esophagus*	<5 cc	17.7 Gy	25.2 Gy	Stenosis/fistula
Brachial plexus (right or left)	<3 cc	20.4 Gy	24 Gy	Neuropathy
Ribs (each rib)	<1 cc <30 cc	28.8 Gy 30 Gy	36.9 Gy	Pain or fracture
Trachea and main bronchi (combined)*	<4 cc	15 Gy	30 Gy	Stenosis/fistula
Lung (right and left combined)	1500 cc	11.6 Gy		Basic lung function
Lung (right and left combined)	1000 cc	12.4 Gy		Pneumonitis
Bronchioles	<0.5 cc	18.9 Gy	23.1 Gy	Stenosis with atelectasis
Great vessels	<10 cc	39 Gy	45 Gy	Aneurysm
Pericardium/Heart	<15 cc	24 Gy	30 Gy	Pericarditis
Stomach	<10 cc	16.5 Gy	22.2 Gy	Ulceration/fistula
Liver	700 cc	19.2 Gy		Basic liver function
Common bile duct			36 Gy	Stenosis
Renal cortex (right and left combined)	200 cc	16 Gy		Basic renal function
Renal hilum (right or left)	<66% of volume	18.6 Gy		Malignant hypertension
Ureter (right or left)			40 Gy	Stenosis
Colon*	<20 cc	24 Gy	28.2 Gy	Colitis/fistula
Duodenum*	<5 cc <10 cc	16.5 Gy 11.4 Gy	22.2 Gy	Ulceration
Jejunum and Ileum (combined)*	<5 cc	17.7 Gy	25.2 Gy	Enteritis/obstruction
Cauda equine	<5 cc	21.9 Gy	24 Gy	Neuritis
Lumbrosacral plexus (right or left)	<5 cc	22.5 Gy	24 Gy	Neuropathy
Rectum*	<20 cc	24 Gy	28.2 Gy	Proctitis/fistula
Bladder wall	<15 cc	16.8 Gy	28.2 Gy	Cystitis/fistula
Penile bulb	<3 cc	21.9 Gy	42 Gy	Impotence

Femoral heads (right or left)	<10 cc	21.9 Gy	42 Gy	Necrosis
*avoid circumferential irradiation **point defined as 0.035 cc or less				

8.5.5 Beam selection and geometry, planning technique and treatment delivery

In general, beams should be chosen to preserve OAR constraints and provide adequate PTV dosing (D95 ≥95% of the prescription dose), while respecting mechanical constraints of equipment. No minimum number of beams is necessary. Coplanar and non-coplanar beams are permitted.

Any form of external beam radiotherapy is acceptable (high energy photons, electrons, or protons), provided the dose is expressed in cobalt-Gy equivalent (CGyE) or Gy equivalent. Beam energy should be chosen in consideration of penetration depth, neutron contamination, etc. To account for the radiobiologic effectiveness of electrons, investigators are encouraged to prescribe the radiation dose to the 90% isodose line that encompasses the PTV.

Radiotherapy must be planned in 3-dimensions, and dose-volume analyses are required to ensure OAR constraints and PTV coverage is adequate. For 3D conformal planning, both physical and dynamic wedges can be used. Both MLC and block could be used for beam confinement when using photons.

Planning and treatment delivery can be carried out using any technique (non-conformal, conformal, intensity-modulated, volume modulated arc, etc) using any mechanism of external beam radiation delivery (linear accelerator, CyberKnife™, etc).

Use of tissue equivalent bolus to ensure adequate build-up is permitted for the treatment of superficial targets.

Verification of accurate subject positioning for treatment must occur through the generation and assessment of imaging (MV port films, kV images, cone beam CT, etc) or direct inspection of light fields (for electron beam therapy). Conventional subject setup with skin tattoos or optical surface imaging can only be used as initial subject alignment, but not final positioning.

8.5.6 Radiotherapy timing and dose fractionation

Treatment will be initiated after the first dose of immunotherapy, but before the second dose of immunotherapy.

Subjects receiving 27 Gy in 3 fractions should be scheduled to receive treatment on non-consecutive weekdays, no more than 2 days/week, over no more than 14 days. Ideally, treatment will be given with 2 days between treatment (Monday/Thursday/Monday, Tuesday/Friday/Tuesday, Monday/Friday/Tuesday, or Tuesday/Friday/Wednesday schedule).

Subjects receiving 30 Gy in 10 fractions should be scheduled to receive treatment on consecutive weekdays, no more than 5 days/week, over no more than 14 days.

Dose modifications for radiotherapy as a result of toxicity are allowed per the Investigator's assessment.

8.6 Exploratory Assessment of Correlative Immunologic Research

Peripheral blood and optional tumor samples (when available) will be collected as outlined in Section 3.2 and banked for testing at the end of the study. Separate instructions will be provided regarding the processing, storage and testing of these samples. Testing may include but may not be limited to the following:

- lymphocyte phenotype using markers such as ICOS, PD-1, and CD25
- the quantities of myeloid derived suppressor cells (MDSCs), defined as CD14+HLA-DRlow cells
- antibody and functional T cell responses to tumor associated antigens (i.e. NY-ESO-1) for relevant subjects
- serum cytokine levels such as TNF-alpha, IFN-gamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and TGF-beta
- Serum and plasma microparticle and exosome nanoFACS and proteomic profiles
- T cell repertoire diversity in peripheral blood and tumor.

Additional investigational methods will be used to characterize and measure components of the immune response based upon the latest available technology.

8.7 Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DCR	Disease control rate
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HLA	Human Leukocyte Antigen
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IL	interleukin
IND	Investigational new drug
irAE	Immune-related adverse event
irRC	immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous
IRB	Institutional Review Board
LICR	Ludwig Institute for Cancer Research
mAb	Monoclonal antibody
MDSC	myeloid derived suppressor cells
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
OAR	Organ at risk
ORR	Objective Response Rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PFS	Progression free survival

PK	Pharmacokinetics
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Standard Deviation
TME	Tumor microenvironment
TIL	tumor-infiltrating lymphocyte
ULN	Upper limit of normal

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