MSK PROTOCOL COVER SHEET

A Prospectively Designed Study to Assess the Relationship between Tumor Mutation Burden and Predicted Neo-antigen Burden in Patients with Advanced Melanoma or Bladder Cancer Treated with Nivolumab or Nivolumab plus Ipilimumab (CA209-260)

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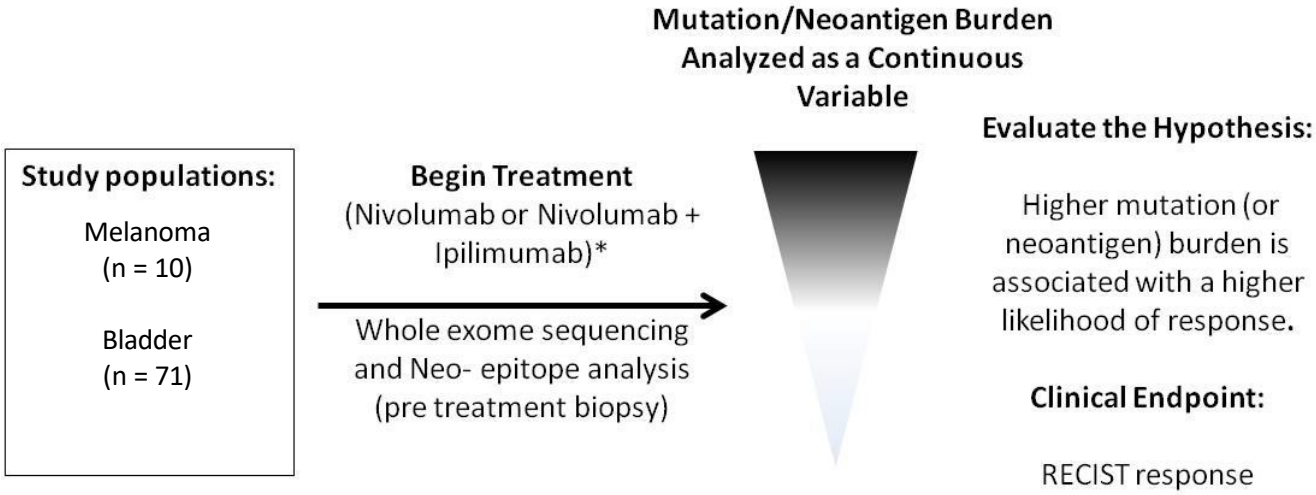
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a prospectively designed, open label study of nivolumab monotherapy or nivolumab plus ipilimumab in patients with advanced cancers designed to test the hypothesis that tumors with a higher frequency of mutations (or neo-antigens) will have a higher response rate to checkpoint blockade than those with lower mutation (or neo-antigen) burden. Patients must have at least one lesion that is safe to undergo biopsy and at least one additional measurable lesion not intended to be biopsied. A biopsy will be performed prior to treatment on study and whole exome and whole transcriptome sequencing will be performed on the biopsied material. All patients will have imaging to evaluate disease response (by RECIST 1.1) every 6 weeks for the first 6 months of treatment. Patients with bladder cancer who receive nivolumab monotherapy and who have disease progression may be eligible to subsequently receive ipilimumab in combination with nivolumab.



Treatments: For patients with melanoma, the planned treatment will be ipilimumab (3 mg/kg) in combination with nivolumab (1 mg/kg) administered every 3 weeks for 4 doses followed by nivolumab administered every 2 weeks at 240mg, or every 4 weeks at 480mg. Treatment may continue for up to 2 years, if the patient is clinically benefitting, the PI and treating investigator may elect to continue beyond two years. For patients with bladder cancer, the planned treatment will be nivolumab administered every 2 weeks at 240mg, or every 4 weeks at 480mg. Treatment may continue for up to 2 years, if the patient is clinically benefitting, the PI and treating investigator may elect to continue beyond two years. Patients who have disease progression after their 6 week scan may continue to receive nivolumab monotherapy, at the discretion of their treating physician and the study PI. Patients who have disease progression at 6 weeks that is confirmed to be progression on a second scan(by RECIST 1.1 criteria) may be eligible to subsequently receive ipilimumab (3 mg/kg) in combination with nivolumab (1 mg/kg) administered every 3 weeks for 4 doses followed by nivolumabadministered every 2 weeks (240mg) or every 4 weeks

(480mg). The crossover treatment may begin approximately 12 or more weeks after initial treatment on study. Treatment may continue for up to 2 years from the initial dose of nivolumab, if the patient is clinically benefitting, the PI and treating investigator may elect to continue beyond two years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Correlative Objective: Obtain preliminary prospective data on whether mutational load is associated with RECIST 1.1 response to immunotherapy.

Primary Clinical Objective: Obtain prospective data on the overall response Rate (per RECIST 1.1) to 1) nivolumab monotherapy and 2) ipilimumab and nivolumab combination therapy in patients progressing on initial nivolumab monotherapy.

Secondary Clinical Objectives:

1. Evaluate duration of response (DOR), progression free survival (PFS), overall survival (OS), rate of grade 3/4 toxicity.
2. Evaluate ORR, DOR, PFS, OS according to the immune related RECIST criteria.

Secondary Correlative Objectives:

1. Obtain preliminary prospective data on whether neo-antigen score is associated with RECIST 1.1 response to immunotherapy.
2. Compare tumor characteristics (mutation burden, neo-antigen score, PD-L1, TCR repertoire, immune infiltrate) between pre-treatment and on-treatment (optional) tumor biopsies.
3. Evaluate tumor PD-L1 expression across range of mutation burden/predicted neo- antigens.
4. Evaluate TCR repertoire across a range of mutation burdens/predicted neo-antigen scores.
5. Evaluate for the presence of predicted neo-antigen specific T cells in peripheral blood samples.
6. Compare IMPACT assay to whole exome sequencing for the evaluation of patients according to mutation burden.

3.0 BACKGROUND ANDRATIONALE

Mutations, Cancer and Anti-Tumor Immune Responses

Tumors harbor a diverse range of unique, tumor specific mutations, from dozens to thousands per tumor.[1-3] *In silico* analyses predicts that a subset of these mutations are detectable by the immune system as tumor- specific neo-antigens (Figure1).[4,5] The repertoire of neo-antigens for any individual tumor has been dubbed the “immunome”, to highlight the vast diversity of potential epitopes. In preclinical models, utilizing syngeneic transplantable murine tumors, it is clear that tumor-specific neo-antigens can be functional “tumor rejection” antigens.[6-9] In murine models, responses to neo-antigens in combination with checkpoint blockade can generate potent tumor rejection.[10]

Figure 1. Converting the TCGA into an Immunome database
(Srivastava *et al.* unpublished data).

There is longstanding evidence that tumor specific neo-antigens may be relevant in human cancers with over 40 publications describing T cells specific for tumor neo-antigens derived from a mutated proteins documented since 1993. (http://cancerimmunity.org/peptide/mutations/) In pioneering work by Ton Schumacher and colleagues, T cell responses to neo-antigens were temporally associated with the activity of the checkpoint blocking antibody ipilimumab in a patient with melanoma.[11] For adoptive T cell therapies, these neo-antigen specific T cells can also have potent anti-tumor activity, as demonstrated in a compelling case report by Steve Rosenberg.[12] More recently, important work by Jedd Wolchok, Tim Chan and Alex Snyder at MSKCC suggests that the benefit of ipilimumab for patients with advanced melanoma may be associated with the frequency of mutations in the tumor and the presence of mutations that function as neo-antigens.[13] Moreover, differences in the mutational profiles of 3 distinct tumors in a patient treated with the combination of ipilimumab and nivolumab were linked to differences in clinical responses in case study under development by Maggie Callahan, Jedd Wolchok and Pramod Srivastava (manuscript in preparation).

Nivolumab, Ipilimumab, and Combination Therapy

Nivolumab enhances antitumor immunity by blocking the co-inhibitory molecule expressed on T cells, programmed death 1 (PD-1), thereby interrupting its interaction with its ligand programmed death ligand 1 (PD-L1). Nivolumab has shown anti-tumor activity in advanced solid tumors including melanoma, renal cell cancer, non-small cell lung cancer, head and neck cancers, and ovarian cancer. In addition, several other drugs blocking either PD-1, or its binding partner PD-L1, have been developed and have demonstrated activity in additional tumor types including bladder cancer and gastric cancer (Table 1). Tumor PD-L1 expression has been explored as a potential biomarker for nivolumab, however PD-L1 expression alone lacks both the positive predictive value and negative predictive value to be a useful clinical tool.

Hundreds of patients with advanced solid tumor have been treated with nivolumab, and its safety and tolerability have been well established. Although nivolumab is generally well tolerated, a unique set of side effects, termed immune-related adverse events (irAEs) has been seen during its clinical development. CA209003 (MSKCC IRB 09-102) is a Phase 1 open label, multiple dose escalation study of nivolumab in patient with previously treated advanced solid tumors.[14]Patients received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy, if the patient is clinically benefitting, the PI and treating investigator may elect to continue beyond two years. No maximal tolerated dose was identified. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3-4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%), and pneumonitis (1%).

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 patients with advanced melanoma in two phase 3 trials.[15,16] The objective response rate to ipilimumab is unfortunately quite low and identifying which patients are expected to benefit from

this treatment is an area of ongoing research.

Responses to ipilimumab are often delayed and may be seen after initial apparent disease progression. The unique pattern of disease response seen in patients with ipilimumab led to a retrospective study analyzing patients treated across several phase 2 trials. In this evaluation, improved survival was associated with a variety of disease response patterns such as patients who initially appeared to have progressive disease but later achieved response and those who had prolonged stable disease. To better reflect the distinct kinetics of response, the immune-related response criteria (irRC) were proposed.[17] The irRC are undergoing prospective validation in ongoing clinical trials. IrRC may also have utility in nivolumab treated patients. A recent abstract at ASCO 2014 presented by F. Stephen Hodi described a survival benefit in patients treated with nivolumab who achieve responses by irRC, but not by traditional response criteria, compared to those who have disease progression by irRC.

Thousands of patients have been treated with ipilimumab and its toxicity profile is well described. The most severe irAE is generally considered to be an inflammatory colitis, which requires prompt treatment with steroids and, in some cases, anti-TNF-alpha therapy. Other side effects related to ipilimumab consist of hypophysitis, hepatitis, and dermatitis. Other rarer side effects have also been reported including peripheral neuropathy and uveitis. Published algorithms for the treatment of ipilimumab-related irAEs are available (https://www.hcp.yervoy.com/pages/rems.aspx).

Due to the distinct mechanisms of action of CTLA-4 and PD-1 blockade, combined blockade of both CTLA-4 (ipilimumab) and PD-1 (nivolumab) has been tested as a therapeutic approach in patients with advanced melanoma, RCC, and NSCLC.[18-20] At the time of initial publication, the objective response rate by for patients treated with the concurrent combination of ipilimumab and nivolumab across all doses tested was 40%, with a response rate > 50% in patients treated at the doses (3 mg/kg ipilimumab, 1 mg/kg nivolumab) chosen for further clinical development. The rate of grade 3/4 treatment-related adverse events related to therapy was 53% of patients in the concurrent-regimen group. This rate is numerically higher than that typically described for monotherapy with ipilimumab at 3 mg/kg, nivolumab, or pembrolizumab. However, it is important to consider that the majority of grade 3/4 adverse events that composed the 53% number from this trial were asymptomatic, elevated laboratory values. These included patients with elevations in lipase (13%), none of whom had clinical pancreatitis, as well as aspartate aminotransferase (13%) and alanine aminotransferase (11%), none of whom were symptomatic. There appeared to be no new toxicities attributed to the combination of ipilimumab and nivolumab that have not been seen with ipilimumab or nivolumab alone.

This combination also appears promising in RCC where a small study comprising 21 patients treated with 3 mg/kg nivolumab plus 1 mg/kg ipilimumab and 23 patients treated with 1 mg/kg nivolumab plus 3 mg/kg ipilimumab described response rates of 43% and 48% respectively. These numbers compare favorably to the ORR of 21% described for nivolumab monotherapy. This combination has also been tested in NSCLC where a lower response rate (13-20%) and relatively high toxicity rate were observed. The activity of the combination of nivolumab and ipilimumab in bladder cancer is presently being tested in a Phase 2 study CA209-032 (MSKCC IRB 13-187), presently open to accrual at MSKCC. Up to date data on the safety and activity of the combination of ipilimumab and nivolumab in bladder cancer will be available prior to its use in this study.

Table 1. Established Clinical Activity of PD-1 and PD-L1 blocking antibodies.

Drug	Sponsor	Target	Disease Type	Response (n)	Reference
Nivolumab	BMS	PD-1	Solid Tumors	21% (42)	Topalian et al. NEJM 2012
			Melanoma	32% (44)	Weber et al. JCO 2013
			NSCLC	14% (63)	Antonia et al. WCLC 2013
			RCC	21% (168)	Motzer et al. ASCO 2014
			Ovarian	17% (18)	Hamanishi ASCO 2014
MDX - 1105	BMS	PD-L1	Solid Tumors	17% (135)	Brahmer et al. NEJM 2012
Pembrolizumab	Merck	PD-1	Melanoma	40% (113)	Daud et al. AACR 2014
			NSCLC	19% (146)	Gandhi et al. AACR 2014
			Melanoma	34% (411)	Ribas ASCO 2014
			NSCLC*	26% (45)	Rizvi ASCO 2014
			Head & Neck	18% (55)	Selwert et al. ASCO 2014
			Solid Tumors	21% (103)	Herbst et al. ASCO 2013
MPDL3280a	Genentech	PD-L1	Melanoma	23% (30)	Hamid et al. ASCO 2013
			NSCLC	23% (53)	Sorial et al. ECC 2013
			Bladder	26% (65)	Powels et al. ASCO 2014
			Solid Tumors	11% (179)	Segal et al. ASCO 2014
MEDI4736	Medimmune	PD-L1	NSCLC	16% (58)	Brahmer et al ASCO 2014
			Head & Neck	14% (22)	Segal et al. ASCO 2014
			Gastric	19% (16)	Segal et al. ASCO 2014

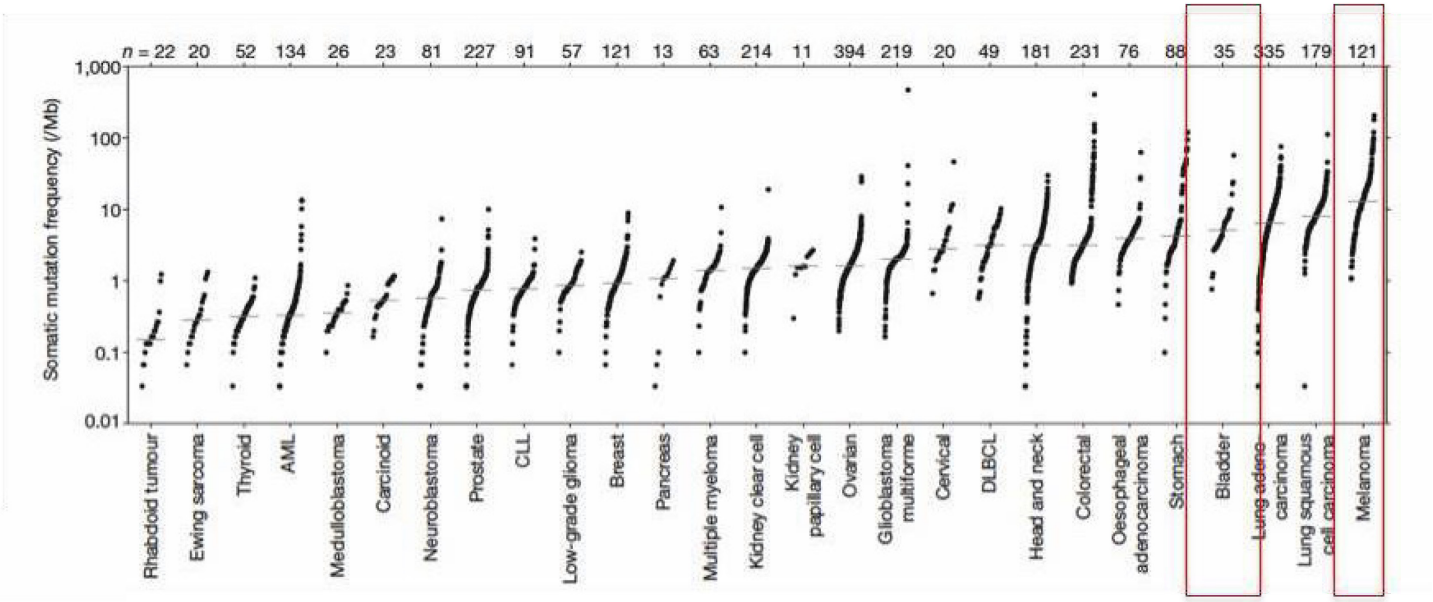
Rationale for Tumor Types Selected

The selection of melanoma and bladder cancer was driven primarily by the biology of these diseases. In reviewing the literature, we sought to identify tumors that had a relatively high mutation burden and a diverse frequency of mutations (see Figure 1). Further, we reasoned that, in a 2-disease study, it would be prudent to choose one disease type that has a well established response rate for nivolumab (melanoma) and one that has high potential, but is more exploratory (bladder). Additionally for melanoma, data retrospectively linking mutation burden to response to checkpoint blockade (ipilimumab) has already been reported by our group at MSKCC and has been used to approximate the differences that we may anticipate between “high” and “low” mutation burden tumors in this setting.

For bladder, we anticipate that results from the upcoming CA209-032 (MSKCC IRB 13-187) bladder cohort may serve as a reference and a recent abstract reports a response rate of 50% for the PD-L1 blocking antibody MPDL3280A in metastatic urothelial bladder cancer highlighting the promise of checkpoint blockade for this tumor type. Other tumor types that could also be considered promising in this setting, would include gastric, head and neck, RCC, ovarian, NSCLC, breast, and CRC, however, in order to assure that the study is adequately powered to address the primary endpoint, we have limited the study to 2 disease types at this time. Additionally, studies addressing similar questions in CRC (focusing on patients with MSI high disease), in NSCLC, and

in RCC are either open or under development.

Figure 1. Frequency of Mutations Across a Diversity of Tumor Types (Lawrence et al. 2013)



Clinical Rationale for Evaluating Mutations in Checkpoint Blockade

This analysis will allow us to shed light on several important biological and mechanistic questions: Does tumor mutation burden (or predicted neo-antigen burden) related to responses to nivolumab monotherapy or to the combination of nivolumab and ipilimumab ? Does this relationship explain differences in response to checkpoint blockade between tumor types or within tumor types? How does the mutation burden relate to other tumor specific predictive markers (PD-L1)?

Data presented at ASCO in 2014, reflecting the work of Alex Snyder, Tim Chan and Jedd Wolchok, suggested that mutation burden correlates with response to ipilimumab in a retrospective study of patients with metastatic melanoma. Using a cutoff of 250 mutations (~ the median of the population), tumors can be divided into a “high” mutation burden group and a “low” mutation burden group with rates of long term benefit of 58% and 23% respectively. If the cases that fall closest to the median (250 +/- 20%) are eliminated from the analysis, then the high mutation group, defined as > 300 mutations comprises ~ 40% of the group and the low mutation burden group (< 200 mutations) comprises 44% of the group (eliminating the middle ~20% of the population as “medium” mutation burden). With this approach, tumors with a high mutation burden have a 60% long term benefit rate, and those with a low mutation burden have an 18% long term benefit rate, a difference of 42%.

Ultimately, it is our hope that mutation burden, predicted neo-antigen burden, or both, offer some utility as biomarkers to guide patient selection for nivolumab or nivolumab/ipilimumab combinations.

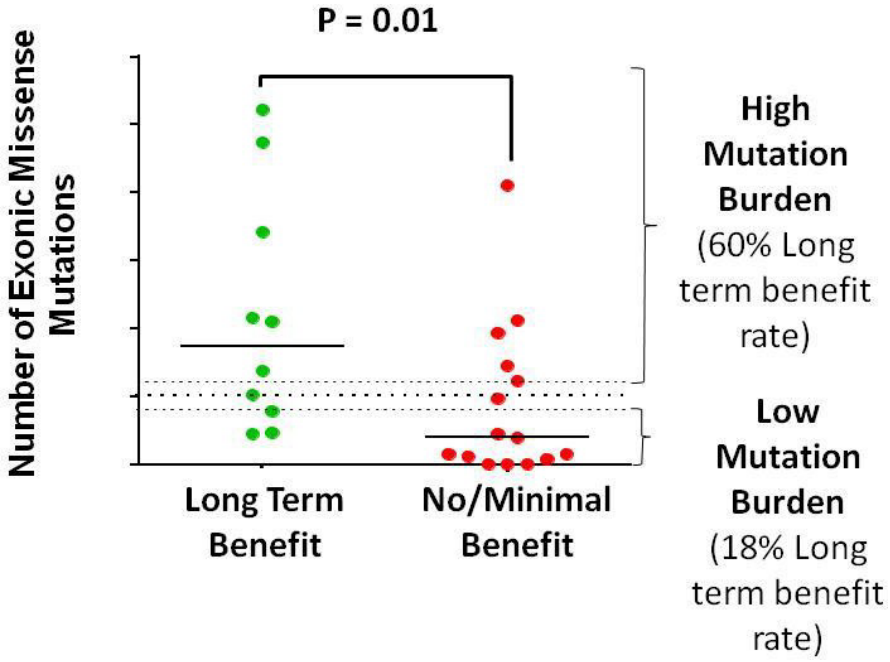
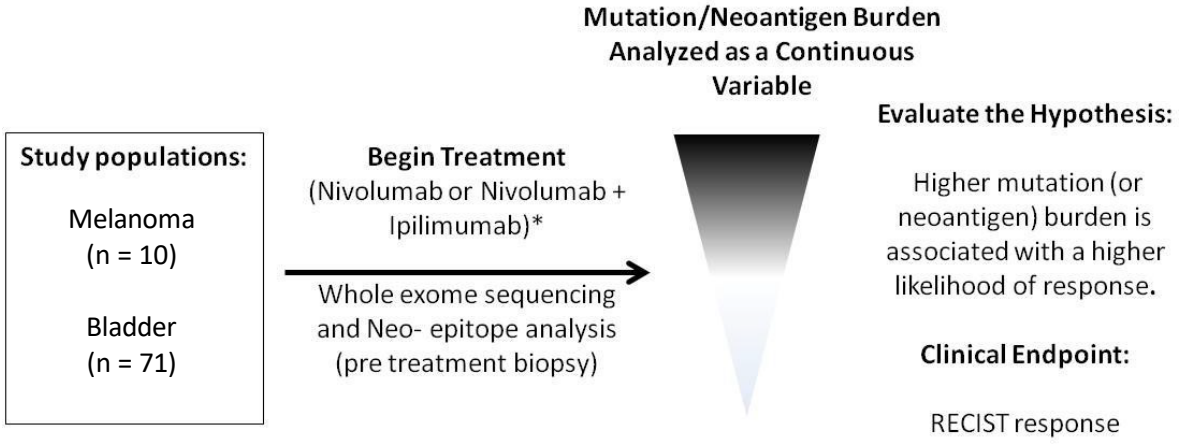


Figure 2. Patients with Long term benefit after treatment with ipilimumab have a higher mutational burden than those with minimal or no benefit. (Snyder *et al.* NEJM *in press*).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design



The study design will include 2 independent study populations (melanoma and bladder). The bladder cohort will be analyzed for the primary and secondary endpoints. The melanoma cohort will be analyzed in a descriptive fashion. All patients enrolled on study who meet eligibility criteria, including pre-study biopsy, will be treated as described in section 4.2. Tumor biopsy material will be used for whole exome sequencing and whole transcriptome sequencing to evaluate the tumor mutation burden and neo-antigen score for each individual patient/biopsy sample.

Statistical Plan for Evaluation of Primary and Secondary Objectives

Patients who receive at least 1 dose of nivolumab will be considered evaluable for the primary clinical objective and patients who have adequate biopsy material for whole exome sequencing and adequate sequencing data for determination of mutation burden will be considered evaluable for the primary correlative objective (1). Tumor mutation burden and neo-antigen score will be determined for each patient enrolled as described in Appendix 3.

The primary clinical objective is to determine the confirmed objective response rate defined as the proportion of patients who achieve a complete or partial response to protocol therapy. The primary correlative objective is to obtain information on mutational load and obtain preliminary prospective data on whether this factor is predictive of response to immunotherapy. Patients mutational load will be assessed using tissue obtained prior to treatment and the number of mutations will be calculated. We will perform a nonparametric receiver operator characteristic (ROC) curve analysis with mutational load as a continuous measure and estimate the area under the curve (AUC) to assess the detectability of responders. ***This will allow us to prospectively test the hypothesis that a higher mutational burden is associated with a higher likelihood of response and also estimate the strength of the relationship between mutational burden and response rate.***

Patients who develop early clinical progression or death related to disease progression (i.e. before initial imaging) will be evaluated as non-responding patients for the purpose of study

analysis. Patients who develop early toxicities that require treatment delay or discontinuation will continue to be evaluated for response on study and response will be determined based upon radiographic evaluation. In the unlikely scenario where a patient is lost to followup in the first 12 weeks on study and a determination of response by either radiographic findings, clinical progression, or death related to disease cannot be made, this patient would be considered non-evaluable.

This analysis of the relationship between mutation burden and response rate will be performed for each tumor type (melanoma vs. bladder) independently. A responder is defined as someone who achieves a confirmed complete or partial response based on RECIST 1.1 criteria. The cutoff point will be identified using Youden's index. These results will be examined in a descriptive manner in order to identify potential predictive measures. In addition, we will run the same analysis using the predicted neo-antigen score (as described in Appendix 3) and test if predicted neo-antigen burden is predictive of response.

4.2 Intervention

Patient Population

Patients with histologically confirmed locally advanced or metastatic disease of the following tumor types who meet the eligibility criteria:

(1) melanoma

(2) bladder cancer

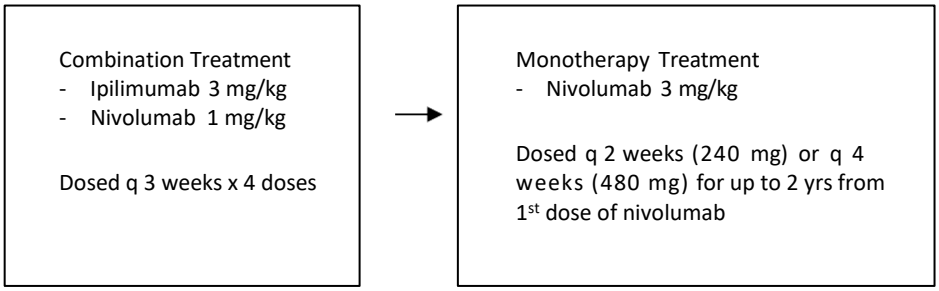
Sample Size

Up to 81 patients will be enrolled in two separate arms: one for melanoma and one for bladder cancer. It is estimated that approximately 85% of enrolled patients will be considered evaluable for both the clinical and research (WES, RNAseq) study endpoints, with an approximate 10% failure rate related to the biopsy, biopsy sample preparation and sequencing, and an approximate 5% failure rate for clinical reasons (i.e. patient replaced for clinical reasons and non-evaluable for response). Based upon these calculations, we estimate that we will have approximately 60 bladder patients and approximately 8 melanoma patients with both clinical and research (genomic) data for anlysis, consistent with the protocol statistical plan.

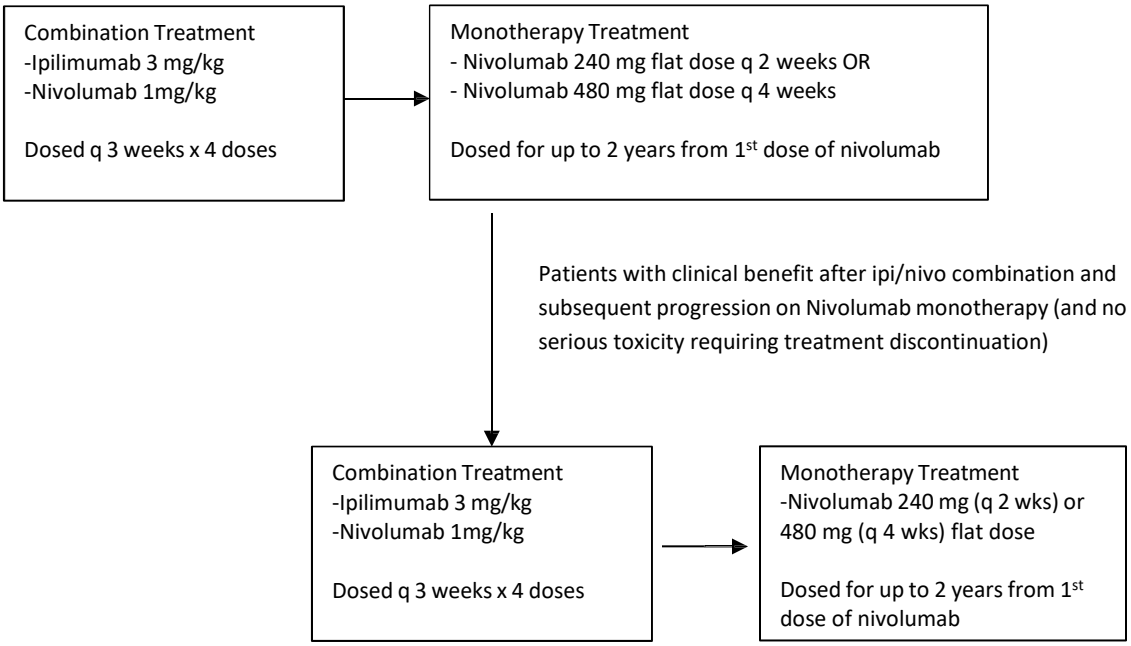
Treatment Schema

All eligible patients with melanoma will receive ipilimumab at a dose of 3 mg/kg combined with nivolumab at a dose of 1 mg/kg. The ipilimumab and nivolumab will be dosed every 3 weeks for 4 doses. Thereafter, patients may be eligible to continue to receive nivolumab monotherapy at a dose of 240 mg administered every 2 weeks, or at a dose of 480mg administered every 4 weeks, for up to 2 years. If the patient is clinically benefitting, the PI and treating investigator may elect to continue treatment beyond 2 years..

Schema for Melanoma (prior to Amendment 11)



Schema for Melanoma (after Amendment 11)



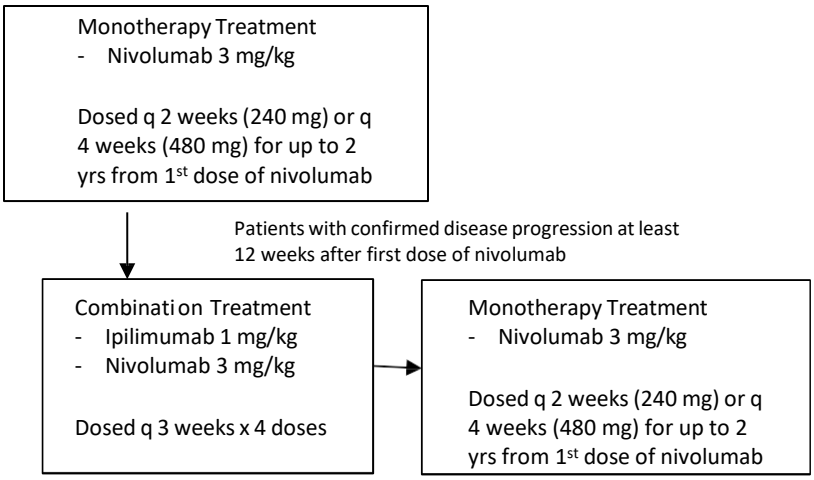
All eligible patients with bladder cancer will receive nivolumab at a dose of 240 mg administered every 2 weeks, or at a dose of 480 mg administered every 4 weeks,for up to 2 years. If the patient is clinically benefitting, the PI and treating investigator may elect to continue treatment beyond 2 years.

Patients with bladder cancer who have confirmed disease progression after treatment with nivolumab monotherapy may be treated with the combination of nivolumab and ipilimumab provided all of the following conditions are met:

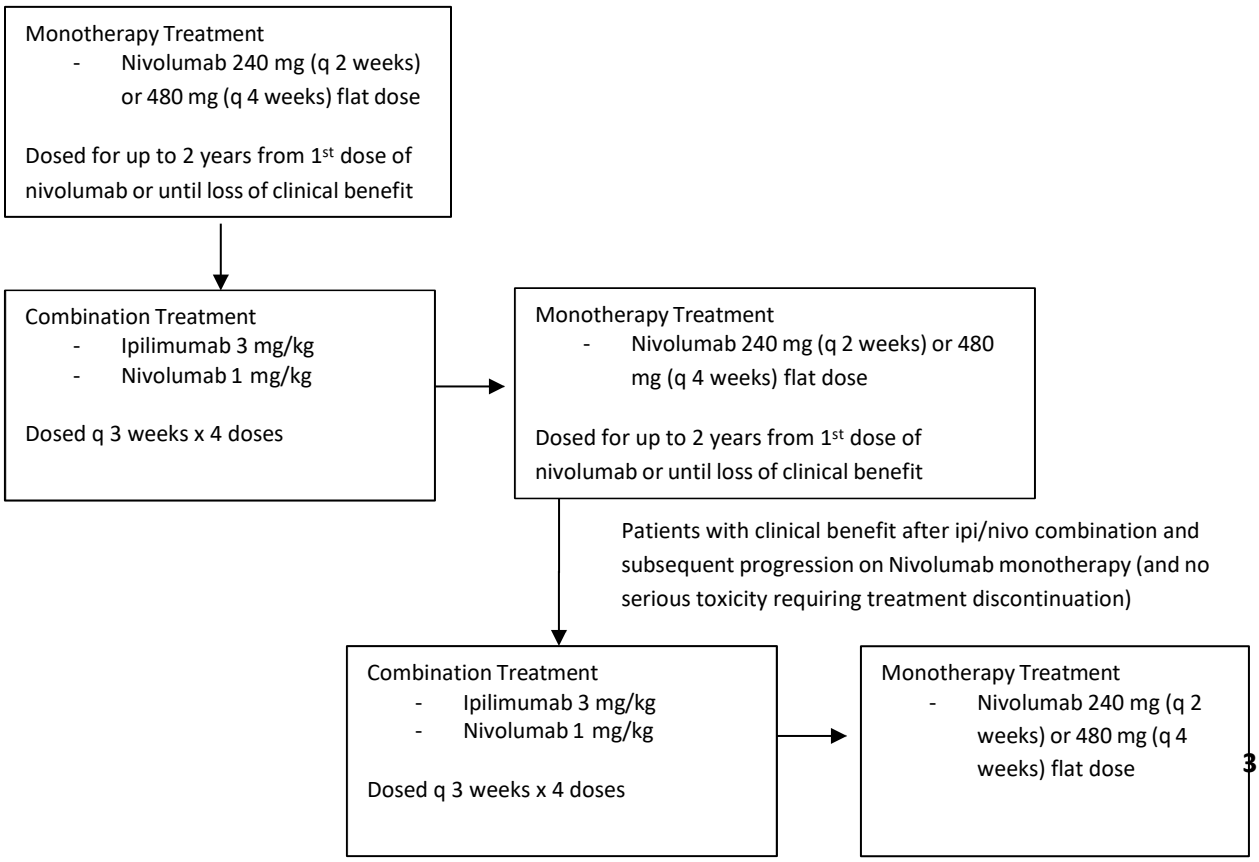
- Progressive disease should be confirmed on a second imaging study at least 4 weeks later and should demonstrate at least 10% or greater additional increase in disease burden. Alternatively, if the reviewing radiologist and the treating physician feel that there is unequivocal progression, then the patient may be eligible for crossover after discussion with the principal investigator.
- The patient has not experienced a nivolumab related adverse event(s) leading to permanent discontinuation.
- The patient should have completed at least one cycle of treatment before crossing over the combination treatment. It is not required that the patient receive all scheduled doses of nivolumab during this time; a minimum of 4 doses of nivolumab monotherapy must be given before crossover. Patients may crossover before 4 doses of nivolumab after discussion with the MSK principal investigator.
- The patient must have an ECOG of 0-1.
- In the opinion of the treating investigator, treatment with the combination of ipilimumab and nivolumab represents a reasonable treatment option for the patient.

For patients with bladder cancer, the combination treatment will be 3 mg/kg ipilimumab plus 1 mg/kg nivolumab. The first dose of the combination treatment will be administered at least 2 weeks, but no more than 6 weeks, after the most recent dose of nivolumab. The combination treatment will be administered once every 3 weeks for 4 doses and thereafter, patients will be treated with nivolumab every 2 weeks (240 mg) or every 4 weeks (480 mg) for up to 2 years, if the patient is clinically benefitting, the PI and treating investigator may elect to continue beyond two years.

Schema for Bladder Cancer (prior to Amendment 11)



Schema for Bladder Cancer (after Amendment 11)



See the study flowcharts (Section 10) for a depiction of study event scheduling.

Dosing Adjustments, Delays and Discontinuations

Dosing reductions/adjustments in response to toxicities of nivolumab or ipilimumab are not permitted. Patients who delay or discontinue treatment for toxicities should continue followup as per study calendar (i.e. imaging, study visits, laboratory followup).

Dose Delay Criteria/Criteria to Resume Treatment

Dose delay criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both. All study drugs must be delayed until treatment can resume. Because of the potential for clinically meaningful ipilimumab/nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. See appendix 2 for specifics.

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin adverse event
- 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 AEs, 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 timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

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

Treatment Discontinuation

Discontinuation criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both. 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 adverse event lasting > 7 days, with the following exceptions

for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, 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 liver function test (LFT) abnormality that meets the following criteria require 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 adverse event 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 and decrease to < Grade 4 within 1 week of onset.
    - 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 adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principle 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 Princip le Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
    - Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Principle Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

Post-Treatment Follow-up

Patients who discontinue treatment early due to toxicity, should continue follow up with their study physician as clinically appropriate until the resolution or stabilization of the toxicity. Thereafter, they should continue to follow the study calendar until week 12 (i.e. study visits) and thereafter they should continue with tumor imaging (scans) q 6 months or every other scan, visits and labs.

If patients discontinue treatment due to toxicity after they have been on treatment for 12 weeks, then the q 12 week follow up will begin after the patient's end of treatment. If the patient did not have an end of treatment visit, the q 12 week follow up will begin after the patient's last dose. Patients who experience progression of disease after discontinuing

treatment early due to toxicity should move to survival follow-up. Patients in toxicity follow-up who initiate treatment with a new therapy will be immediately moved to survival follow-up.

For melanoma and bladder cancer patients receiving nivolumab or nivolumab plus ipilimumab, there is one follow up visit scheduled 6 weeks after the end of treatment. Additional follow up visits may be necessary at the discretion of the treating physician (i.e. for follow up of study related toxicities). All patients will be followed as per institutional guidelines in accordance with the usual standard of care principles.

Subjects who decline to return to the site for evalutations will be offered follow-up by phone every 3 months as an alternative. This will be documented in the patient's medical record.

As of MSK Amendment 21, all patients on active follow up should be taken off study as we prepare for study closure.

Survival Follow-up

Patients will be followed up by telephone (or by office visit) every 12 weeks (+/- 2 weeks) for 4 years from the start of treatment or until death. Follow-up calls or visits should begin 12 weeks (+/- 2 weeks) from the last study contact. Follow up calls must be documented in the patients' medical records.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

PRODUCT INFORMATION TABLE: Please also see Pharmacy manual in Appendix 1.

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	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	Protect form 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.

*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.

For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer section 8.8 and to the BMS-936558 (nivolumab) and Ipilimumab Investigator Brochure section for "Recommended Storage and Use

Conditions"

Estimated Requirements for Study Drug:

Drug	***Source***	***Required Quantity***
For melanoma cohort:		
Nivolumab	BMS	Up to 667,200 mg Induction - 19,200 mg (60 pt x 80 kg x 1 mg/kg x 4 doses) Maintenance – 648,000 mg (60 pt x 80 kg x 3 mg/kg x 45 doses)
Ipilimumab	BMS	Up to 57,600 mg (60 pt x 80 kg x 3 mg/kg x 4 doses)
For bladder cohort:		
Nivolumab	BMS	Up to 705,600 mg Induction – 57,600 mg (60 pt x 80 kg x 3 mg/kg x 4 doses) Maintenance/ Monotherapy – 648,000 mg (60 pt x 80 kg x 3 mg/kg x 45 doses)
Ipilimumab	BMS	Up to 19,200 mg (60 pt x 80 kg x 1 mg/kg x 4 doses)

Drug Dosing

For patients receiving nivolumab monotherapy, the drug shall be dosed at a dose of 240 mg (every 2 weeks) or 480 mg (every 4 weeks).

For patients initiated on treatment, or initiated on crossover treatment after the approval of Amendment 11, the dosing for the combination of ipilimumab and nivolumab will be ipilimumab 3 mg/kg and nivolumab 1 mg/kg for both bladder and melanoma patients. For patients who initiated treatment with the combination of ipilimumab and nivolumab prior to Amendment 11, they will maintain their current dosing/schedule.

For patients receiving the combination of nivolumab and ipilimumab, the dosing calculations should be based on the actual body weight at screening (within 28 days of starting therapy). For Bladder crossover patients, the baseline weight for crossover should be used for dosing calculations instead of the weight collected during screening for monotherapy. For all patients receiving the combination of nivolumab and ipilimumab, if the subject's weight within 5 days of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All subsequent dosing should use the baseline weight unless the patients weight has changed by > 10% from the weight used to calculate the original dose. If the patients dose differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed. See appendix 1 for additional details.

Drug Storage, Preparation and Administration

See appendix 1.

Ipilimumab and Nivolumab will both be provided by BMS to the study sites. An IND for each agent will be cross filed and will be held by MSKCC, the data coordinating center.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

*For entry into the study, **all** of the following criteria must be met:*

1. Subjects must have signed and dated an IRB approved written informed consent in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.
2. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.
3. Pathologically confirmed locally advanced or metastatic disease per the treating institution's standard of care of the following tumor types:
    a. Subjects with histologically confirmed locally advanced/unresectable or metastatic ***melanoma*** who meet all of the following criteria:
        i. Subjects have received any number of prior lines of therapy or may be treatment naïve
        ii. If the subject has been treated with a prior line of therapy, they must have had disease progression or be refractory to treatment

    OR

    b. Subjects with histologically or cytologically confirmed locally advanced/unresectable or metastatic urothelial carcinoma (including mixed histologies of urothelial carcinoma with elements of other subtypes) of the renal pelvis, ureter, bladder or urethra (referred to broadly in this protocol as "***bladder cancer***") who meet the following criteria:
        i. Subjects must have disease progression or refractory disease after their prior line of therapy. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of metastatic or locally advanced unresectable disease. Subjects may have received any number of prior lines of therapy

        OR

        ii. Subjects with disease recurrence within 1 year of a platinum based neoadjuvant or adjuvant therapy for bladder cancer.

        OR

        iii. The subject actively refuses chemotherapy for the treatment of metastatic or locally advanced disease considered as standard treatment for this disease stage (i.e. a patient who has relapsed >1 year after treatment with neoadjuvant or adjuvant chemotherapy), despite being informed by the investigator about the treatment options. The subject's refusal must be documented.
4. Subjects must have measurable disease by CT scans or MRI per RECIST 1.1 criteria. Radiographic tumor assessment must be performed within 28 days prior to first dose of study drug.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
6. Age ≥ 18 years.

7. Subjects must consent to allow for the acquisition of tumor sample prior to starting treatment on study (in most cases patients will require a tumor biopsy). This biopsy site may be the only site of measurable disease if the site is > 2 cm. The biopsy site must, in the opinion of the investigator, be likely to yield acceptable tumor sample for core biopsies as described in Appendix 3. It is also acceptable if tumor sample is obtained by excision biopsy or during surgery (i.e. if procedure was previously planned), provided the tumor sample can be processed as described in Appendix 3. In the case that a patient had a tumor sample acquired prior to consenting to the study and this tumor sample is acceptable for processing as described in Appendix 3 (i.e. frozen sample stored) and the tumor sample was acquired within 60 days of starting treatment, this is acceptable and a new biopsy will not be required.
8. Willingness to adhere to the study visit schedule and prohibitions as specified in this protocol.
9. Expected survival of at least 4 months.
10. At the time of day 1 of the study, patients must have completed chemotherapy, targeted therapy, investigational therapy, other immunotherapy, radiation therapy or major surgery (requiring general anesthesia) at least 28 days before administration of the first dose of nivolumab. Patients 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. Patients may have received prior focal radiotherapy for palliation of an isolated site of disease, which must be completed at least 14 days prior to day 1 of the study.

    Palliative (limited-field) radiation therapy is permitted during treatment with study drug(s).

11. All baseline laboratory requirements will be assessed and should be obtained within 14 days of the first dose of study drug. Screening laboratory values must meet the following criteria:

    - White blood cells (WBCs) ≥ 2000/μL
    - Neutrophils ≥ 1000/μL
    - Platelets ≥ 100 x 103/μL
    - Hemoglobin ≥ 9.0 g/dL
    - Serum creatinine ≤ 1.5 x ULN (or glomerular filtration rate ≥ 40mL/min)
    - Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's syndrome who must have total bilirubin ≤ 3.0mg/dL)
    - AST and ALT ≤ 3 x ULN
    - Albumin ≥ 3.0 g/dL

6.2 Subject Exclusion Criteria

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

1. Active brain metastases or leptomeningeal metastases. Subjects with treated brain metastases are eligible if they meet all of the following criteria:
    a. Must be at least 28 days since craniotomy and resection, stereotactic

radiosurgery, or whole brain radiotherapy.
   b. Must have no evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration.
   c. Must have no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy or interfere with the interpretation of study results.

3. Other prior malignancy active within the previous 2 years except for local or organ confined early stage cancer that has been definitively treated with curative intent or does not require treatment, does not require ongoing treatment, has no evidence of active disease and has a negligible risk of recurrence and is therefore unlikely to interfere with the endpoints of the study.

4. Subjects with active autoimmune disease, symptoms or conditions. Subjects with vitiligo, type I diabetes, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, asymptomatic laboratory evidence of autoimmune disease (e.g.: +ANA, +RF, antithyroglobulin antibodies), or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

6. Subjects who have received prior therapy with any T cell co-stimulation or checkpoint pathways such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4, anti-CD137; or other medicines specifically targeting T cells are prohibited. Prior therapy with BCG is permitted. Prior IL-2 is permitted.

7. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy and which are not

expected to resolve and result in long lasting sequelae such as neuropathy after platinum-based therapy, are permitted to enroll.

8. Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.

9. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

10. History of allergy to study drug component or history of severe hypersensitivity reaction to any monoclonal antibody

11. Women who are breast feeding or pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) done within 14 days of first dosing and urine test within 72 hours of first dosing.

12. Women of childbearing potential (WOCBP) not using a medically acceptable means of contraception throughout the study treatment and for at least 23 weeks following the last dose of study treatment (5 half-lives of study drug plus 30 days duration of ovulatory cycle).

    WOCBP are defined as those who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post-menopausal is defined as:

    -Amenorrhea ≥ 12 consecutive months without another cause, or

    -For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

13. Male subjects who are unwilling to use contraception during the treatment and for at least 31 weeks after the last dose of study treatment (5 half-lives of study drug plus 90 days duration of sperm turnover).

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

Restricted Concomitant Treatments

1. Immunosuppressive agents (except to treat a study-drug related adverse event)
2. Systemic corticosteroids > 10 mg daily prednisone equivalent (except to treat a study-drug related adverse event or as per section 4.2)
3. Any concurrent antineoplastic therapy, chemotherapy, immunotherapy, biologic therapy, except for palliative radiotherapy as described in section 6.1.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research teams at Memorial Sloan-Kettering Cancer Center and participating institutions. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The MSKCC Principal Investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

This limited waiver will apply only to MSK. Any participating sites that require a limited waiver must obtain it from their own local IRB/Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSK staff to confirm the participating data collection site(s) have a limited waiver approved by their local IRB(s)/PBs.

8.0 PRETREATMENT EVALUATION

Disease Staging
Disease Assessment by RECIST 1.1
Tumor Biopsy
Other Examinations
Eligibility Assessment and Informed Consent
Demographics
Medical History

Vitals
ECOG & Physical Exam
Adverse Events Assessment
Labs & Assays
Pregnancy Test (see Section 6.2, serum based.)
Urine pregnancy test (within 3 days prior to dosing)
Chemistry: Sodium, Potassium, Chloride, CO2, BUN, Creatinine, Glucose, Calcium, Magnesium, AST, ALT, Alkaline Phosphatase, Total Bilirubin, LDH, TSH, Free or Total T3[1], Free or Total T4[1], albumin
Blood Hematology (CBC with differential)
Research Blood Draw
HIV, Hepatitis B and Hepatitis C tests

1. Total T3 or Free T3 and Total T4 of Free T4 may be collected according to treating physician preference and institutional availability.

9.0 TREATMENT/INTERVENTION PLAN

Treatment of protocol eligible patients with nivolumab or nivolumab and ipilimumab will follow the treatment plan described in section 4.2. Treatment with nivolumab or nivolumab and ipilimumab are deemed experimental treatments. Treatment with nivolumab or nivolumab and ipilimumab will occur in the outpatient setting.

The following interventions on treatment are considered routine and will be performed according to the schedules in section 10.0 with indicated time windows.

- Disease assessment by RECIST 1.1 (CT scan CAP, or alternative imaging as needed for disease assessment and MRI or CT brain, if applicable)
- Medical History
- Vitals (including Height and Weight)
- Physical Exam
- Pregnancy test (serum or urine)- only if WOCBP
- Chemistry Panel Comprehensive Metabolic Panel (including AST, ALT, total bilirubin) LDH, TSH, Total or Free T3, Total or Free T4, albumin
  Note: 1. Total T3 or Free T3 and Total T4 of Free T4 may be collected according to treating physician preference and institutional availability.
- Hematology Panel – CBC with differential
- HIV, Hepatitis B and Hepatitis C tests

The following interventions on treatment are considered research and will be performed according to the schedules in section 10.0 with indicated time windows. Additional details are available in Appendix 3.

- Tumor Biopsy
- Research Blood draw for collection of PBMCs and serum (6 time points for bladder crossover cohort and melanoma cohort, 8 time points for bladder monotherapy cohort)

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Standard Evaluation

Flowchart 1 - Nivolumab Monotherapy for Patients with Bladder Cancer

Study Section	**Screening**	**Baseline**	**Initial Treatment**							**Treatment beyond Week 12 (up to 2 yrs)[h]**	**End of Nivolumab Treatment [e]** If patient has not proceeded to Crossover Theraoy	
Study Week			**0**	**2 (+/-3 d)**	**4 (+/-3 d)**	**6 (+/-3 d)**	**8 (+/-3 d)**	**10 (+/-3 d)**	**12 (+/-3 d)**		Last Day (EOT Only)	Last Day + 6 Weeks (+/- 1 wk, EOT only)
Study Day	**-28 to -1**	**-14 to -1** (or as stated)	**1**	**15**	**29**	**43**	**57**	**71**	**82**	(+/- 3 d)		
Drug Administration												
Nivolumab (240 mg or 480 mg) [a]			X	X	X	X	X	X	x	q 2 wks (240 mg) **OR** q 4 wks (480 mg)		
Tumor Assessments												
Disease Staging	X											
Disease Assessment by RECIST 1.1(including MRI or CT brain at screening)	X		Every 6 weeks (+/- 7 days) from first dose for the first 24 weeks and then every 12 weeks (+/- 7 days) thereafter until study discontinuation. [i] MRI or CT brain required at screening, but only necessary for subsequent disease assessments in patients with known disease metastatic to the CNS [f]									
Tumor Biopsy	X		2 weeks (- 5, +5 days) from first dose and before 2nd dose of therapy [g]							At tumor progression (+ 14 days) [g]		
Other Examinations												
Eligibility Assessment and Informed Consent	X											
Demographics	X											
Medical History	X											
ECOG, Vital Signs (including Height, Weight), Physical Exam & collection of concomitant medications	X		X	X	X	X	X	X	X	q 2 weeks/ q 4 weeks [j]	X	X
EKG	X											
Adverse Events Assessment	X		X	X	X	X	X	X	X	q 2 weeks/4weeks [j]	X	X
Labs & Assays												
Pregnancy Test (see Section 5.2.17, serum based. [b]		3mL									X	X
Urine pregnancy test (within 3 days prior to dosing) [b]			X	X	X	X	X	X	X	q 2 weeks/4 weeks [j]		
Chemistry (Comprehensive Metabolic Panel, LDH, TSH) [c]		X	X	X	X	X	X	X	X	q 2 weeks/4 weeks [j]	X	X
Blood Hematology (CBC with differential) [c]		X	X	X	X	X	X	X	X	q 2 weeks/4 weeks [j]	X	X
Research Blood Draw [mL] [c]	60mL		60mL	60mL	60mL	60mL	60mL	60mL	60mL		60 mL	
HIV, Hepatitis B and Hepatitis C	X											
Survival Follow-up [d]											X	X

a. Nivolumab may be dosed no less than 11 days from the previous dose of drug.
b. Pregnancy tests are not required if the patient is a male or a woman not of child-bearing potential
c. Blood drawn prior to dosing drug. Blood must be drawn at all required timepoints. Results of thyroid functions tests are not required prior to dosing drug.
d. Patients will be followed up by telephone (or by office visit) every 12 weeks (+/- 2 weeks) for 4 years from the start of treatment or until death. Follow-up calls or visits should begin 12 weeks +/- 2 weeks from the last study contact.
e. If the patient will not initiate treatment with the combination, end of treatment should be initiated as per Study Flowchart 3
f. Patients who discontinue treatment due to toxicity will continue to follow the study procedures (without treatment) for 12 weeks from the start date. They will require all disease assessments according to study protocol, however, after 12 weeks, all other study assessments (PE, Laboratory assays) will be performed every 12 weeks (+/-7 days). If patients discontinue treatment due to toxicity after they have been on treatment for 12 weeks, then the q 12 week follow up will begin after the patient's end of treatment. If the patient did not have an end of treatment visit, the q 12 week follow up will begin after the patient's last dose. Patients who experience progression of disease after discontinuing treatment early due to toxicity should move to survival follow-up. Patients in toxicity follow-up who initiate treatment with a new therapy will be immediately moved to survival follow-up.
g. Optional
h. Patients with a proven ability to tolerate treatment who have been on study for longer than one year will have visits with physicians every 4 weeks and treatment-only visits in between.
I. Patients who have completed 26 weeks of treatment may elect to complete disease assessment scans every 6 months (24 weeks). This will continue until study discontinuation, under the treating investigator's discretion
j. Frequency of ECOG, Vital Signs, Physical Exam, AE Assessments and all lab panels should follow the frequency of Nivolumab treatment (q 2 weeks or q 4 weeks) and should occur simulataneously within the same visit

Flowchart 2 - Nivolumab plus Ipilimumab Combination Treatment for Patients with Melanoma

Study Section	**Screening**	**Baseline**	**Initial Treatment**				**Treatment beyond Week 12 (up to 2 yrs)** [e,h]	**End of Treatment**	
Study Week			**0**	**3 (+/-3 d)**	**6 (+/-3 d)**	**9 (+/-3 d)**		**Last day**	**Last day +6 weeks (+/- 1 wk)**
Study Day	**-28 to -1**	**-14 to -1** (or as stated)	**1**	**22**	**43**	**64**	(+/- 3 d)		
Drug Administration									
Nivolumab 1 mg/kg			X	X	X	X			
Nivolumab 240 mg or 480 mg [a]							q 2 wks (240 mg) **OR** q 4 wks (480 mg)		
Ipilimumab 3 mg/kg			X	X	X	X			
Tumor Assessments									
Disease Staging	X								
Disease Assessment by RECIST 1.1 (including MRI or CT brain at screening)	X		Every 6 weeks (+/- 7 days) from first dose for the first 24 weeks and then every 12 weeks (+/- 7 days) thereafter until study discontinuation. [i] MRI or CT brain required at screening, but only necessary for subsequent disease assessments in patients with known disease metastatic to the CNS [f]						
Tumor Biopsy	X		2 weeks (- / +5 days) from first dose and before 2nd dose of therapy [g]				At tumor progression (+ 14 days) [g]		
Other Examinations									
Eligibility Assessment	X								
Demographics	X								
Medical History	X								
ECOG, Vital Signs (including Height, Weight), Physical Exam & collection of concomitant medications	X		X	X	X	X	q 2 weeks / q 4 weeks [j]	X	X
EKG	X								
Adverse Events Assessment	X		X	X	X	X	q 2 weeks / q 4 weeks [j]	X	X
Labs & Assays									
Pregnancy Test (see Section 5.2.17, serum based.) [b]		3 mL						X	X
Urine pregnancy test (within 3 days prior to dosing) [b]			X	X	X	X	q 2 weeks / q 4 weeks [j]		
Chemistry (Comprehensive Metabolic Panel, LDH, TSH) [c]		X	X	X	X	X	q 2 weeks / q 4 weeks [j]	X	X
Blood Hematology (CBC with differential) [c]		X	X	X	X	X	q 2 weeks / q 4 weeks [j]	X	X
Research Blood Draw [mL] [c]	60mL		60mL	60mL	60mL	60mL		60mL	
HIV, Hepatitis B and Hepatitis C tests	X								
Survival Follow-up [d]								X	

a. Nivolumab may be dosed no less than 11 days from the previous dose of drug.
b. Pregnancy tests are not required if the patient is male or a woman of child-bearing potential.
c. Blood drawn prior to dosing drug. Blood must be drawn at all required timepoints. Results of thyroid functions tests are not required prior to dosing drug.
d. Patients will be followed up by telephone (or office visit) every 12 weeks (+/- 2 weeks) for 4 years from the start of treatment or until death. Follow-up calls or visits should begin 12 weeks +/- 2 weeks from the last study contact.
e. *First dose of nivolumab monotherapy is on week 12 (+/- 3 days)*
f. Patients who discontinue treatment due to toxicity will continue to follow the study procedures (without treatment) for 12 weeks from the start date. They will require all disease assessments according to study protocol, however, after 12 weeks, all other study assessments (PE, Laboratory assays) will be performed every 12 weeks (+/-7 days). If patients discontinue treatment due to toxicity after they have been on treatment for 12 weeks, then the q 12 week follow up will begin after the patient's end of treatment. If the patient did not have an end of treatment visit, the q 12 week follow up will begin after the patient's last dose. Patients who experience progression of disease after discontinuing treatment early due to toxicity should move to survival follow-up. Patients in toxicity follow-up who initiate treatment with a new therapy will be immediately moved to survival follow-up.
g. Optional
h. Patients with a proven ability to tolerate treatment who have been on study for longer than one year will have visits with physicians every 4 weeks and treatment-only visits in between.
I. Patients who have completed 26 weeks of treatment may elect to complete disease assessment scans every 6 months (24 weeks). This will continue until study discontinuation, under the treating investigator's discretion
j. Frequency of ECOG, Vital Signs, Physical Exam, AE Assessments and all lab panels should follow the frequency of Nivolumab treatment (q 2 weeks or q 4 weeks) and should occur simulataneously within the same visit

Flowchart 3 - Nivolumab plus Ipilimumab Combination Treatment for Patients with Bladder Cancer Eligible for Crossover (or Reinduction with Combination Treatment for Bladder or Melanoma Patients)

Study Section	**Baseline[a]**	**Initial Treatment**				**Treatment beyond Week 12 (up to 2 yrs) [f, i]** (+/- 3 d)	**End of Treatment**	
Study Week		**0**	**3 (+/-3 d)**	**6 (+/-3 d)**	**9 (+/-3 d)**		**Last day**	**Last day +6 weeks (+/- 1 wk)**
Study Day	**-28 to 0**	**1**	**22**	**43**	**64**			
Drug Administration								
Nivolumab 1 mg/kg [b]		X	X	X	X			
Ipilimumab 3 mg/kg		X	X	X	X	Re-induction (if applicable)		
Nivolumab 240 mg or 480 mg						q 2 wks (240 mg) **OR** q 4 wks (480 mg)		
Tumor Assessments								
Disease Assessment by RECIST 1.1 (MRI or CT brain only necessary in patients with known disease metastatic to the CNS)	X	Every 6 weeks (+/- 7 days) from first dose for the first 24 weeks and then every 12 weeks (+/- 7 days) thereafter until study discontinuation MRI or CT brain only necessary in patients with known disease metastatic to the CNS [g, j]						
Tumor Biopsy	X [h]	2 weeks (- 5, +5 days) from first dose and before 2nd dose of therapy [h]				At tumor progression (+ 14 days) [h]		
Other Examinations								
Eligibility Assessment	X							
Demographics	X							
Medical History	X							
ECOG, Vital Signs (Height, Weight), Physical Exam & collection of concomitant medications	X	X	X	X	X	q 2 weeks / q 4 weeks [k]	X	X
EKG	X							
Adverse Events Assessment	X	X	X	X	X	q 2 weeks / q 4 weeks [k]	X	X
Labs & Assays								
Pregnancy Test (see Section 5.2.17, serum based.) [c]	3 mL						X	X
Urine pregnancy test (within 3 days prior to dosing) [c]		X	X	X	X	q 2 weeks / q 4 weeks [k]		
Chemistry (Comprehensive Metabolic Panel, LDH, TSH) [d]	X	X	X	X	X	q 2 weeks / q 4 weeks [k]	X	X
Blood Hematology (CBC with differential) [d]	X	X	X	X	X	q 2 weeks / q 4 weeks [k]	X	X
Research Blood Draw [mL] [d]	60mL	60mL	60mL	60mL	60mL		60mL	
HIV, Hepatitis B and Hepatitis C tests								
Survival Follow-up [e]							X	

a. Baseline procedures do not need to be repeated for reinduction combination treatment for bladder or melanoma patients.
b. For patients with melanoma, ipilimumab will be dosed at 3 mg/kg and nivolumab at 1 mg/kg, for patients with bladder cancer ipilimumab will be dosed at 3 mg/kg and nivolumab at 1 mg/kg. Nivolumab may be dosed no less than 11 days from the previous dose of drug.
c. Pregnancy tests are not required if the patient is male or a woman not of child-bearing potential
d. Blood drawn prior to dosing drug. Blood must be drawn at all required timepoints. Results of thyroid functions tests are not required prior to dosing drug.
e. Patients will be followed up by telephone (or office visit) every 12 weeks (+/- 2 weeks) for 4 years from the start of treatment or until death. Follow-up calls or visits should begin 12 weeks +/- 2 weeks from the last study contact.
f. *First dose of nivolumab monotherapy is on week 12 (+/- 3 days)*
g. Patients who discontinue treatment due to toxicity will continue to follow the study procedures (without treatment) for 12 weeks from the start date. They will require all disease assessments according to study protocol, however, after 12 weeks, all other study assessments (PE, Laboratory assays) will be performed every 12 weeks (+/-7 days). If patients discontinue treatment due to toxicity after they have been on treatment for 12 weeks, then the q 12 week follow up will begin after the patient's end of treatment. If the patient did not have an end of treatment visit, the q 12 week follow up will begin after the patient's last dose. Patients who experience progression of disease after discontinuing treatment early due to toxicity should move to survival follow-up. Patients in toxicity follow-up who initiate treatment with a new therapy will be immediately moved to survival follow-up.
h. Optional
i. Patients with a proven ability to tolerate treatment who have been on study for longer than one year will have visits with physicians every 4 weeks and treatment-only visits in between.
j. Patients who have completed 26 weeks of treatment may elect to complete disease assessment scans every 6 months (24 weeks). This will continue until study discontinuation, under the treating investigator's discretion
k. Frequency of ECOG, Vital Signs, Physical Exam, AE Assessments and all lab panels should follow the frequency of Nivolumab treatment (q 2 weeks or q 4 weeks) and should occur simulataneously within the same visit

10.2 Shipping of Specimens

All samples must be labeled with the unique MSKCC CRDB participant study identification number and date of the specimen collection.

Frozen, banked PBMC samples are to be shipped on dry ice to MSK along with the appropriate Study Requisition Form to the address indicated on the form . Shipments should be made in batches every 3-6 months.

FFPE slides or blocks are to be shipped at ambient temperature to MSK along with the appropriate Study Requisition Form to the address indicated on the form . Shipments should be made in batches every 3-6 months.

Frozen purified DNA and RNA samples for sequencing are to be shipped on dry ice to UConn along with the appropriate Study Requisition Form to the address indicated on the form . Shipments should be made in batches every 2-4 weeks.

All participating sites will notify the MSK study coordinator when samples are shipped by completing and emailing the sample requisition form.

10.3 Future Unspecified Use of Biospecimens

The protocol includes an informed consent document and research authorization that meets statutory guidelines. Each participating site will have its own consent form meeting the requirements described in this section. The consent form will inform patients of the purpose of the bank, their rights in relation to it, and the safeguards in place to protect the confidentiality of their health information. The consent will state that some of the biospecimens will be saved to use for future research.

Type of future use
The consent specifically describes the types of future research that may be performed, including use of tissues to develop new drugs with cancer-associated molecular targets, development of cell lines, future use of cell lines to define cancer phenotype and (somatic) genotype, DNA sequence analysis of tumor compared to normal and identification of tumor-associated proteins as diagnostic or prognostic markers. It will be stated that researchers at MSK may either keep indefinitely or dispose of any leftover blood or tissues or other samples, including DNA that the samples contain. Blood and tissues will be stored with identifiers in secure tissue or fluid banks. It is stated that the samples could be lost or ruined because of mechanical failure, and that MSK cannot guarantee that samples will be stored indefinitely. The samples will be stored for as long as deemed useful for research purposes.

Consent for future use and re-contact
Patients are asked in a series of check boxes at the end of the consent if 1) they permit their biospecimen samples to be stored and used in future research to learn about or prevent cancer or side effects of treatment, or to develop new treatments; 2) if they permit their samples to be stored and used in future research to learn about, prevent, or treat diseases other than cancer; or 3) if they permit their samples, with personal identifiers protected, to be

used for research about inherited genetic factors, 4) if they permit their samples to be used for genetic analysis of the tumor and normal tissue to learn about the causes of cancer, 5) participants are asked if they agree to be contacted in the future as part of research studies for additional health information or to be asked to participate in future biospecimen research studies and 6) if they consent to be contacted to discuss research findings which may come from their sample. Finally, if not available (e.g. deceased), if they wish to have their designee designated on the consent to be contacted.

Participants will not be provided with specific results of research tests performed on their collected human biologic specimens.

Use of identifiable information for genetic studies

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service or Clinical Genetics Service at their site.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK patients, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: ocrgapirb@mskcc.org

For non-MSK patients being treated at one of the participating institutions, if the GAP determines the finding to be reportable to the participant and the participant has consented to be re-contacted, results will be returned to the Site Principal Investigator via the study team. Site policies on returning these research findings to the patient should be followed.

We anticipate that other research assays may be incorporated into this protocol as technology evolves.

Voluntariness of research participation

It is stated that taking part in this tissue and blood bank is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

Withdrawal
Participants may decide at a later date that they do not want identified blood and tissue samples to be stored in the tissue bank and /or used for future research. If participants decide to withdraw from the study, specimens that have not yet left the specimen archive will not be used in new studies and any remaining portions of samples that have not been used for research will be used only for clinical purposes or, if requested by the patient, destroyed. For specimens already shipped out from the archive, it may not be possible to locate the samples or stop already ongoing research. The withdrawal request will be documented in CRDB and the system updated accordingly. In addition, a note-to-file documenting the patient withdrew must be filed in his/her medical records.

Rights after death
The consent states that if the research participant dies or is unable to make his/her wishes known, all of their rights to decide about future uses of the blood or tissues will pass to the authorized representative of the estate. If there is no representative of the estate, the rights pass to the next of kin.

Risks of research participation
The greatest risk is release of information from health or research records in a way that violates privacy rights. MSK and any participating sites will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Costs/compensation
There is no cost to the participant to enroll in this research. Tissue or blood obtained in this research may be used to make a cell line, and these may be patented or licensed and thus may have significant commercial value. The participant is informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research.

Biospecimen Privacy
Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. The MSK IRB/PB will review all requests for research performed involving biospecimens ascertained through this protocol. Blood and tissue samples may be stored with a code linked to the patient's medical record. The results of any research using blood or tissues will not be placed in the medical record.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the

Research Authorization (HIPAA Authorization) that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

Use of banked samples (at MSK)
When samples are to be analyzed, the individual investigator needs to write an IRB biospecimen protocol. This protocol is fast-tracked through MSK Research Council review and is reviewed at the MSK IRB by the expedited review process. This protocol is only for research that will be done on biospecimens obtained under identified protocols and their informed consent and research authorization that include the institutional future use questions. The consent and research authorization for the use of the biospecimens will be waived as per 45 CFR 46.116(d) and 45 CFR 164.512(i)(2)(ii).

11.0 TOXICITIES/SIDE EFFECTS

Anticipated Toxicities for Ipilimumab and Nivolumab and detailed in the attached Investigators Brochures provided by BMS.

11.1 Definition of an Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient administered the study intervention, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, or drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented as part of the patient's medical history.

Adverse event reporting will be performed in accordance with institutional guidelines for reporting to each participating sites local IRB. Toxicities and laboratory abnormalities will be assessed according to CTCA 4.0. All toxicities that meet criteria of Grade 2 or higher, regardless of causal relationship to nivolumab and/or ipilimumab, will be reported to MSK. Grade 1 toxicities unrelated to study drug will not be required to be reported. Any toxicity related to study drug will be reported to MSK. All serious adverse events will be reported to both MSK and to BMS in accordance with guidelines outlined in section 17.2.1.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients are considered evaluable for the primary and secondary endpoints if adequate sequencing data is generated from pre-study biopsy material to determine mutation burden/neo-antigen score.

Responses will be assessed by RECIST 1.1.

Additional clinical endpoints will be evaluated in an exploratory manner.

Duration of Response (DOR) Duration of Response will be determined for each patient with time origin at the first occurrence of confirmed response (CR,PR) until the first occurrence of confirmed progression or date of death if the patient dies due to any causes before progression. Every effort will be made to follow patients for progression after they discontinue the study.

Progression-free Survival (PFS) Progression-free Survival will be determined for each patient with time origin at the start of the treatment (day 1) until the first occurrence of confirmed progression or date of death if the patient dies due to any causes before progression. If a patient does not progress and is still alive, they will be censored on the date of last follow-up. Every effort will be made to follow patients for progression after they discontinue the study.

Overall Survival (OS) Overall survival (OS) will be measured for each patient with time origin at the start of the treatment (day 1) until recorded date of death. If a patient is still alive, they will be censored on the date of last follow-up. Every effort will be made to follow patients for overall survival after they discontinue the study.

Patient Evaluation & Statistics

All patients who receive at least one dose of nivolumab will be evaluated for tumor response (ORR, DOR), including patients who (1) develop rapid symptomatic disease progression, or (2) drop out early due to death or treatment-related toxicities. All patients who received at least one dose of nivolumab will be included in the clinical efficacy analyses of PFS and OS. Kaplan- Meier methodology will be implemented to estimate the median OS and PFS.

Of note, atypical responses are well known to occur in patients treated with immune checkpoint blockade, including early radiographic progression due to immune infiltration followed by subsequent radiographic response and durable clinical benefit. Thus, patients who

have early radiographic progression but are felt to be clinically benefitting and convert to confirmed stable disease, partial response, or complete response will be considered progression-free and will be assgiend a best confirmed overall response of SD, PR, or CR.

13.0 CRITERIA FOR TREATMENT DISCONTINUATION OR REMOVAL FROMSTUDY

Treatment Discontinuation Criteria
Discontinuation criteria apply for all drug-related adverse events attributed to nivolumab, ipilimumab, or both.

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 adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, 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 liver function test (LFT) abnormality that meets the following criteria require 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 adverse event 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 and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and a 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 adverse events 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

Patients who discontinue treatment due to toxicity, as outlined above, will remain eligible for continued followup on study. Followup on study will be modified as described in Study Flowchart 1 and 2.

CRITERIA FOR REMOVAL FROM STUDY

Patients with confirmed disease progression will be removed from the study with limited exceptions outlined below.Progressive disease must be confirmed on a second imaging study at least 4 weeks later and should demonstrate at least 10% or greater additional increase in disease burden. If, based upon the treating physicians judgment, the patient is deriving clinical benefit despite disease progression,treatment beyond progression may be considered provided that (1) the decision is discussed with the MSK and or site PI, who agrees (2) in the opinion of the treating physician, no alternative therapy would offer greater benefit and (3) the treating physician discusses the risks and benefits of continuing on study with the patient, this conversation is documented in the patients' medical records, and the patient wishes to continue treatment.

Removal from study for patients symptomatic progression warranting alternative anti-cancer treatment should be considered in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased. These patients will be removed from treatment at the Investigator's discretion in accordance with standard practice.

A patient 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.

Patients who are unable or unwilling to comply with study treatment and care plan will be removed from treatment at the Investigator's discretion in accordance with standard practice.

Patient death.

14.0 BIOSTATISTICS

Statistical Plan for Evaluation of Primary and Secondary Endpoints

A total of 81 patients will be accrued to this study (10 melanoma patient and 71 bladder

patients).Only patients with bladder cancer will be evaluated for the primary and secondary objectives as decribed here. Melanoma and bladder patients will be evaluated for the exploratory endpoints described in the next section. The primary clinical objective is to determine the confirmed response rate defined per RECIST 1.1 to protocol therapy. Of note, atypical responses are well known to occur in patients treated with immune checkpoint blockade, including early radiographic progression due to immune infiltration followed by subsequent radiographic response and durable clinical benefit. Thus, patients who have early radiographic progression but are felt to be clinically benefitting and convert to confirmed stable disease, partial response, or complete response will be considered progression-free and will be assgiend a best confirmed overall response of SD, PR, or CR.

The primary correlative objective is to obtain information on mutational load and obtain preliminary prospective data on whether this factor is predictive of response to immunotherapy. Patient's mutational load will be assessed using tissue prior to treatment and the number of mutations will be calculated. We will perform a nonparametric receiver operator characteristic (ROC) curve analysis with mutational load as a continuous measure and estimate the area under the curve (AUC) to assess the detectability of responders. The cutoff point will be identified using Youden's index. It is estimated that approximately 85% of enrolled patients will be considered evaluable for both the clinical and research (WES, RNAseq) study endpoints, with an approximate 10% failure rate related to the biopsy, biopsy sample preparation and sequencing, and an approximate 5% failure rate for clinical reasons (i.e. patient replaced for clinical reasons and non-evaluable for response). Based upon these calculations, we estimate that we will have approximately 60 bladder patients and approximately 8 melanoma patients with both clinical and research (genomic) data for anlysis, consistent with the protocol statistical plan. With 60 bladder patients, 80% power and 5% significance level, we can detect a difference in AUC from: 0.5 to 0.7 if the response rate 50%; 0.5 to 0.71 if the response rate is 33%; and from .0.5 to 0.73 if the response rate is 25%.

All patients who receive at least one dose of nivolumab will be evaluated for the primary clinical endpoint defined as the proportion of patients who achieve a confirmed complete or partial response based on RECIST 1.1 criteria. Patients who develop rapid symptomatic disease progression or drop out early due to death will be treated as progressive disease. Patients who develop early toxicities that require treatment delay or discontinuation will continue to be evaluable for response on study.

Patients who receive at least 1 dose of nivolumab and have adequate biopsy material for whole exome sequencing and adequate sequencing data for determination of mutation burden will be considered evaluable for clinical and correlative objectives. Tumor mutation burden and neo-antigen score will be determined for each patient enrolled as described in section Appendix 3. We will perform the same analysis for patients according to their neo-antigens score (as described in Appendix 3). This analysis of the relationship between mutation burden and response rate will be performed for each tumor type independently.

It is anticipated that 4-5 patients per month will be accrued per cohort and accrual will be completed within two years.

Exploratory Endpoints

Patient Evaluation & Statistics for Clinical Endpoints

All patients who received at least one dose of nivolumab will be evaluated for clinical endpoints including tumor response (ORR, DOR, OS and PFS), rate of grade 3/4 toxicity, and survival. Patients who (1) develop rapid symptomatic disease progression, or (2) drop out early due to death will be treated as non responders. Patients who develop early toxicities that require treatment delay or discontinuation will continue to be evaluated for response on study. Kaplan-Meier methodology will be implemented to estimate the median survival time, median progression-free survival, and the PFS and OS rates. Overall survival will defined as the time from treatment start to death or last follow-up; progression-free survival will be defined as the time from treatment start to the date of progression/death or last follow-up.

Exploratory Tumor and Peripheral Blood Immune Markers

The following endpoints will be evaluated in an exploratory fashion as sample availability permits. Descriptive statistics and graphical measures will be employed. Details related to methods are described in Appendix 3.

1. **Compare tumor characteristic (mutation burden, neo-antigen score, PD-L1, TCR repertoire, immune infiltrate) between pre-treatment and on-treatment (optional) tumor biopsies**

We aim to collect ~ 20 matched tumor biopsies (pre-treatment/on treatment) (target 10 per tumor type), and the comparison will be primarily descriptive and hypothesis generating. Mean and median mutation burden will be quantified in both pre-treatment and on-treatment biopsies. The difference in mean and median between these timepoints will be compared usingnonparametric tests such as Wilcoxon signed rank test. Qualitative comparisons (i.e. types of mutations, neo-antigens) will be descriptive. Adaptive Biotechnologies and MedGenome will serve as collaborators for this TCR analysis.

2. **Evaluate tumor PD-L1 expression across range of mutation burden/predicted neo-antigens.**

PD-L1 expression will be evaluated in pre-treatment and on-treatment biopsies. PD-L1 expression on tumor cells will be graded as positive or negative, according to the most up to date standards for the assay in use. The tumor positivity of PD-L1 expression (on either tumor or immune cells) will be compared in the pre- and post-treatment biopsies using a Wilcoxon signed rank test. Comparisons of immune infiltrate and TCR repertoire will be descriptive. Summary statistics will be generated and differences between mutation burden or neo-antigen score as they relate to PD-L1 expression will be compared using the Wilcoxon rank sum test.

3. **Evaluate TCR repertoire across a range of mutation burdens/predicted neo-antigen scores.**

Tcell receptor frequencies in the repertoire per patient will be tabulated. Summary statistics will be generated and differences between mutation burden or neo-antigen score as they

relate to TCR repertoire will be compared using the Wilcoxon rank sum test. Adaptive Biotechnologies and MedGenome will serve as collaborators for this TCR analysis.

4. **Evaluate for the presence of predicted neo-antigen specific T cells in peripheral blood samples.**

Ex vivo and in vitro analysis of peripheral blood T cells will be employed to evaluate for the presence of predicted neo-antigen specific T cells as described in detail in appendix 3.

5. **Compare IMPACT assay to whole exome sequencing for the evaluation of patients according to mutation burden.**

The number of mutations quantified according to whole exome sequencing and according to IMPACT assay will be quantified and correlation analysis between whole exome analysis and IMPACT will be assessed. This will be exploratory. If a cutoff of high versus low mutation burden is determined from earlier analyses using the whole exome this will be used to guide the IMPACT preliminary analysis.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.1.1 Registration for Participating Sites

Central registration for this study will take place at MSK.

To complete registration and enroll a participant from another institution, the site must contact the MSK study coordinator to notify him/her of the participant registration.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form

- Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the MSK study coordinator will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing, the participant will be registered PENDING and the site will be responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the participating site is in good standing, the MSK study coordinator will send the completed registration documents to the MSK Protocol Participant Registration Office for participant enrollment as stated in section 15.1.

Once the participant is registered, the participant will be assigned a protocol participant number in the MSK Clinical Research Database (CRDB). This number will be relayed back to study staff at the registering participating site via e-mail and will serve as the enrollment confirmation. The number is unique to the participant and must be written on all data and correspondence for the participant.

15.2 Randomization

Not applicable

16.0 DATA MANAGEMENT ISSUES

A MSK Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the MSK CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure internet based system, Medidata Rave. Source documentation will be available to support the computerized patient record.

MSKCC will be the data coordinating center under the guidance of the Multicenter Protocol Executive Committee (MPEC). MSKCC will be responsible for reporting to BMS and/or governing agencies.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based system, Medidata Rave. Data entry guidelines have been generated for this study and site staff will receive database training prior to enrolling its first participant. The participating site PI is responsible for ensuring these forms are

completed accurately and in a timely manner. A Data and Source Documentation Submission Timeline is shown in section 16.0.3.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events of grades that meet study reporting requirements not previously submitted with SAE Reports
- Response designation
- Any other forms of source documentation required per protocol

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into Medidata Rave. Source documentation should be sent to MSK to the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSK according to chart below.

Data and Source Documentation Submission Timelines

Time point	Data	Source Documentation
Baseline	Within 24 hours of consent (see section 15.1.1)	Within 24 hours of consent (see section 15.1.1)
Study Visits	Within 14 days of the study visit	Within 14 days of the study visit
Serious Adverse Events	Within 3 days of event (see section 17.3); Updates to be submitted as available	Within 3 days of event (see section 17.3)

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSK will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSK Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt**.**

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Monitoring
Each data collection site including MSK will be monitored periodically by MSK. Monitoring visits will be conducted every 4-8 weeks, dependent upon the protocol and patient accrual and activity. The monitor and the participating site will identify a mutually agreeable time for each monitoring visit. At least 10 business days ahead of the visit, the monitor will send the site a notification letter that details the date and expectations of the visit. Monitoring may be conducted remotely or in-person. The monitor must be allowed access to all protocol regulatory and source documents to assess compliance with the protocol, federal regulations and GCPs. The monitor will assess all data for completeness of source documents and to confirm data being recorded in the eCRFs is accurate. If monitoring will be done remotely, sites must agree in advance to provide source documents as required. During onsite visits, the monitor will also inspect and review the facilities and investigational product storage area. The participating site will maintain accurate records of dispensing of study drugs for drug accountability. Drug accountability will be reviewed at monitoring visits. Study drug and bottles must be retained until the monitor performs drug accountability of the study drug(s).

The site Investigator(s) and/or an authorized member of the Investigator's staff should allow sufficient time during monitoring visits to discuss findings. The Investigator(s) or an authorized member of the Investigator's staff will make any necessary corrections during and between monitoring visits.

Auditing

Each participating site accruing participants to this protocol may be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participants' responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key study personnel at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain IRB approval for all amendments within 45 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the site IRB approval of the revised protocol documents is granted and submitted to MSK.

The following documents must be provided to MSK for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 17.2 and 17.5 of this protocol.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations

Deviations to the research protocol that involve an informed consent procedure change and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the MSK PI who will in turn seek approval from the MSK IRB/PB. Deviations to the research protocol that involve patient eligibility will not be permitted.

Retrospective Deviations

Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of official site correspondence, including approvals and acknowledgements. to MSK.

16.3.3 Regulatory Documentation Submission for Participating Sites

Participating sites should submit all aforementioned regulatory documentation to MSK via the Multicenter Office at the e-mail provided below. Submissions should include the provided Participating Site Submission Form as a cover page listing all enclosed documents.

Regulatory Contact:
Email: Multicntrproc@mskcc.org to the attention of 15-126 Document Submission

For questions regarding regulatory documentation submissions, please call 646-888-0924.

For protocol related questions, please contact your MSK Study Coordinator.

16.4 Document maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an onsite regulatory binder and sent to MSK as outlined within the protocol. The on-site regulatory binder will be reviewed by the MSK designated study monitor at monitoring visits. A regulatory binder for each site will also be maintained at MSK within the institution's Protocol Information Management System (PIMS).

After study closure, the participating sites will maintain all source documents, study related documents and eCRFs for 7 years.

16.5 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

The informed consent for this study will describe in detail to all potential study participants the risk/benefits, toxicities/side effects, alternatives/options for treatment, and potential financial costs/burdens. As the study will include whole exome sequencing of matched tumor and normal tissue samples, special considerations/additional risks related to maintaining patient privacy and protecting genomic data will be described in

the informed consent. The informed consent will also describe the voluntary nature of the study.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be

submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 SAE Reporting by MSKCC to BMS

Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing. Any SAEs that occur after the 100-day period and that are at least possibly related to protocol treatment must also be reported.

All SAEs must be collected that occur during the screening period. SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, pregnancies, and overdosing of study drug(s) must be reported to BMS by MSK **within 3 business days of MSK's determination of the event**. An SAE report should be completed for any event where doubt exists regarding its seriousness. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent by MSK **within 24 hours** to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries

according to local regulations (either as expedited and/or in aggregate reports).

17.3 SAE Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report Form to MSK within 3 calendar days of learning of the event.
- Participating sites should notify the MSK PI of any grade 5 event immediately.
- When a life-threatening event or death is unforeseen and indicates participants or others are at increased risk or harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

SAE contact information:
Email the 15-126 MSK Study Coordinators

AND

Email: Dr. Callahan at callaham@mskcc.org

Responsibilities of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2 and to the funding entity as described in 17.2.1.
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE from the MSK IRB/PB. The MSK PI is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

17.4 Safety Reports

MSK must submit external safety reports to the MSK IRB/PB according to institutional guidelines. All outside safety reports will be made available to the participating sites. Outside safety reports that are reportable to the MSK IRB/PB will be distributed to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB. Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

17.5 Unanticipated Problems

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); **and**
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section 7.0 of this addendum. All other UPs should be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 INFORMED CONSENT PROCEDURES FOR PARTICIPATING SITES

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to Good Clinical Practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1: Pharmacy Manual
Appendix 2: Algorithms for Management of Select Toxicities
Appendix 3: Laboratory Procedures
Appendix 4: Serious Adverse Event Form for Non-MSK Sites
Appendix 5: Shipping Manual