TITLE: Phase II study of Optimized Management of NIVOlumab based on Response in patients with advanced renal cell carcinoma (OMNIVORE study)

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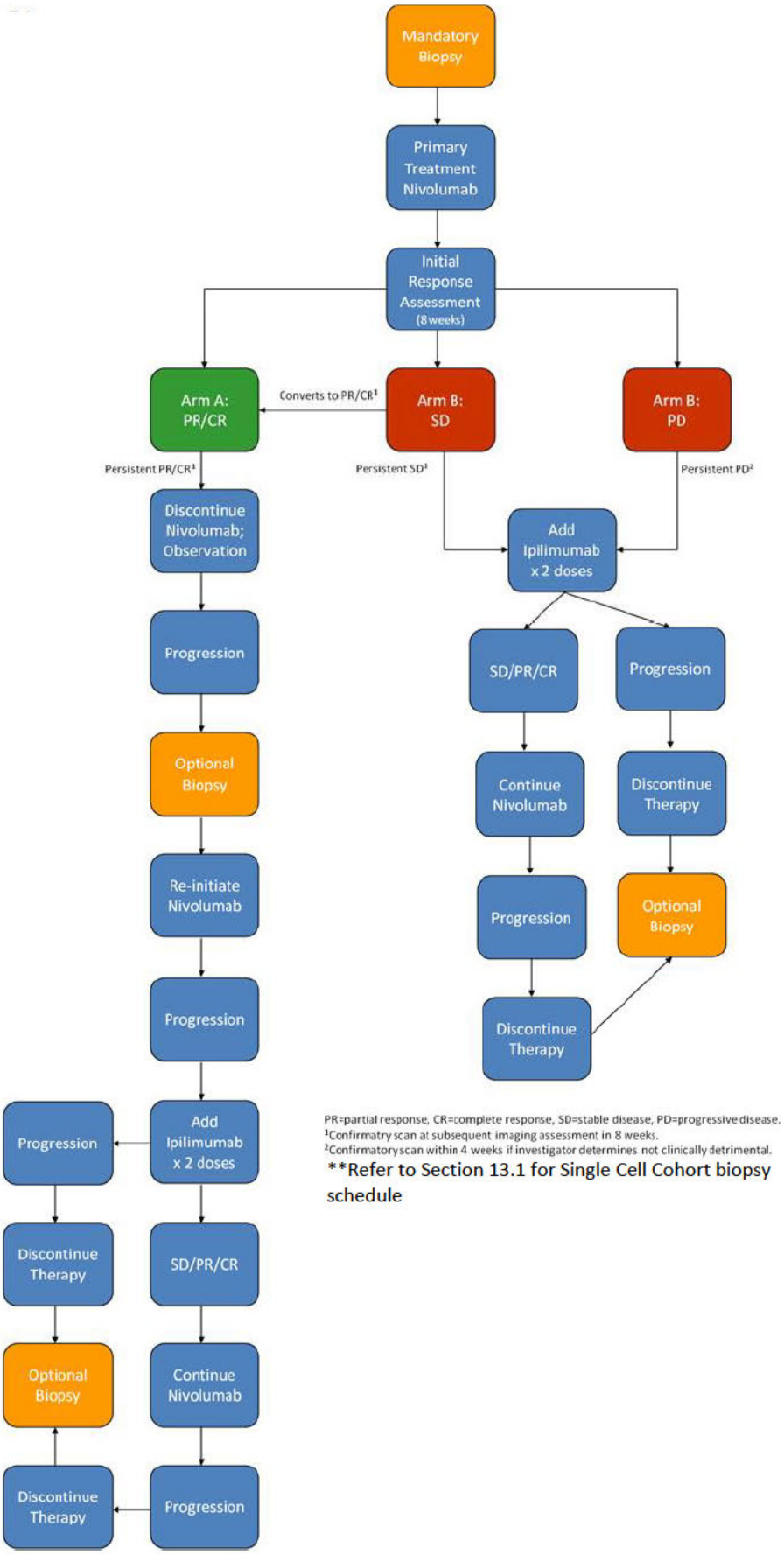
TABLE OF CONTENTS

1. SCHEMA



PR=partial response, CR=complete response, SD=stable disease, PD=progressive disease.
[1]Confirmatry scan at subsequent imaging assessment in 8 weeks.
[2]Confirmatory scan within 4 weeks if investigator determines not clinically detrimental.
**Refer to Section 13.1 for Single Cell Cohort biopsy schedule

2. BACKGROUND AND RATIONALE

2.1 Disease Background

RCC arises from the renal parenchyma and accounts for 90% of all kidney cancer[1]. In 2015, there were an estimated 61,500 new cases of kidney cancer in the United States and ≥ 14,000 deaths. RCC is a heterogeneous disease divided into two major classifications: clear-cell disease which accounts for 80% of all RCC cases and non-clear cell disease.

An increased understanding of the pathogenesis of RCC has changed the landscape of advanced disease management and has shifted the paradigm for front-line treatment. The previous use of cytokines, has largely been replaced by therapies that target vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), and most recently checkpoint inhibitors. Currently, nine agents have demonstrated efficacy in large phase III clinical trials in metastatic RCC: sunitinib, pazopanib, sorafenib, axitinib, bevacizumab (in combination with IFN-α), temsirolimus, everolimus, and most recently nivolumab and cabozantinib (Table 1).

Table 1. Randomized phase III trials of treatments in metastatic RCC.

Trial	Treatment	#	OS			PFS			ORR
			Median (months)	HR (95%CI)	P value	Median (months)	HR (95%CI)	P value	%
First-Line Setting									
Motzer al (2007; 2009)[2,3]	Sunitinib	375	26.4	0.82 (0.67-1.00)	0.051	11	0.54 (0.45-0.64)	<0.001	47%
	IFN-α	375	21.8			5			12%
Escudier et al (2007; 2010)[4,5]	Bevacizumab + IFN-α	327	23.3	0.86 (0.72-1.04)	0.1291	10.2	0.61 (0.51-0.73)	<0.0001	31%
	IFN-α	322	21.3			5.4			13%
Rini et al (200 2010)[6,7]	Bevacizumab + IFN-α	369	18.3	0.86 (0.73-1.01)	0.069	8.5	0.71 (0.61-0.83)	<0.0001	26%
	IFN-α	363	17.4			5.2			13%
Sternberg al (2010; 2013)[8,9]	Pazopanib	290	22.9	0.91 (0.71-1.16)	0.224	9.2	0.46 (0.34-0.62)	<0.0001	30%
	Placebo	145	20.5			4.2			3%
Hudes et al (2007)[10]	Temsirolimus	209	10.9	0.73 (0.58-0.92)	0.008	3.8	0.73 (0.58-0.92)	<0.001	8.6%
	Temsirolimus + IFN- α	210	8.4			3.7	0.96 (0.76-1.20)	0.70	8.1%
	IFN-α	207	7.3			1.9			4.8%

Motzer et al (2013, 2014)[11,12]	Sunitinib	553	29.1	0.92 (0.79-1.06)	0.24	9.5	1.05 (0.90-1.22)	NR	25%
	Pazopanib	557	28.3			8.4			31%
Second-Line Setting									
Escudier et al (2007, 2009)[13,14]	Sorafenib	451	17.8	0.88 (0.74-1.04)	0.146	5.5	0.44 (0.35-0.55)	<0.01	10%
	Placebo	452	15.2			2.8			2%
Motzer et al (2008, 2010)[15,16]	Everolimus	272	14.8	0.87 (0.65-1.15)	0.162	4.0	0.30 (0.22-0.40)	<0.001	1%
	Placebo	138	14.4			1.9			0%
Rini et al (2011, 2013)[17,18]	Axitinib	361	20.1	0.969 (0.800-1.174)	0.3744	6.7	0.655 (0.55-0.812)	<0.001	19%
	Sorafenib	362	19.2			4.7			9%
Motzer et al (2015)[19]	Nivolumab	406	25.0	0.73 (0.57-0.93)*	0.002	4.6	0.88 (0.75-1.03)	0.11	25%
	Everolimus	397	19.6			4.4			5%
Choueiri et al (2015)[20]	Cabozantinib	330	NR	0.67 (0.51-0.89)	0.005	7.4	0.58 (0.45-0.75)	<0.001	21%
	Everolimus	328	NR			3.8			5%

HR=hazard ratio, IFN-α=interferon-alpha, NR=not recorded, ORR=objective response rate, OS=overall survival, PFS=progression-free survival.
*98.5% confidence interval.

The efficacy of nivolumab was demonstrated in a phase III, open-label, randomized trial comparing nivolumab with everolimus in patients with metastatic RCC having receiving previous treatment.[21] Treatment with nivolumab resulted in an improved OS compared to everolimus (Table 1). From this study, objective responses were observed in 25% of patient treated with nivolumab: CR 1% and PR 24%. The median time to response was 3.5 months (range 1.4-24.8 months) in the 103 patients with a response to nivolumab. The median duration of response was 12.0 months (range 0-22.2 months) in responders. The rate of SD and PD as best response were 34% and 35%, respectively.

As demonstrated, individual patient responses to treatment are heterogeneous. A minor portion of patients experience an objective response. Given the heterogeneity of response to treatment, there is a critical need to tailor treatment recommendations to the individual needs of the patient. At the present, it is not clear if treatment with nivolumab can be discontinued in patients with an ORR and result in persistent disease response. Furthermore, in patients who do not experience a response to therapy, can further checkpoint inhibition with ipilimumab convert SD or PD to an objective response. Phase I data suggest that nivolumab combine with ipilimumab has demonstrated substantially greater clinical activity as measured by ORR then either agent alone. This question is currently being answered in a phase III, open label study of nivolumab combine with ipilimumab versus sunitinib in patients with previously untreated advanced RCC (CheckMate214). In this study, we propose to investigate a response-based approach to treatment with nivolumab in patients with metastatic RCC.

2.2 Nivolumab

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems[22, 23]. PD-1 delivers a negative signal by the recruitment of a protein tyrosine phosphatase SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region[24, 25]. PD-1 is primarily expressed on activated T cells, B cells and myeloid cells[26].

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN−γ release in the MLR.

Nivolumab monotherapy has been studied in subjects with RCC. In a phase 1 dose escalation followed by dose expansion study, the safety and clinical activity of nivolumab was investigated[27]. A total of 34 patients with previously treated RCC were enrolled between 2008 and 2012 and received nivolumab (1-10 mg/kg) in an outpatient setting once every 2 weeks for up to 96 weeks. Ten patients (29%) achieved an objective response by RECIST 1.0 with median response duration of 12.9 months. Nine additional patients (27%) demonstrated SD lasting > 24 weeks. Three of five patients who stopped treatment while in response continued to respond for ≥ 45 weeks. Median OS in all patients (71% with 2-5 prior lines of therapy) was 22.4 months. And the 1, 2, and 3 year survival rates were 71%, 48%, and 44%. Grade 3-4 treatment-related adverse events (AEs) occurred in 18% of patients and all were reversible.

In a phase II study, 168 patients with clear cell RCC who received at least one prior-anti-angiogenic therapy (70% received ≥2 prior systemic therapy regimens) were randomized to receive nivolumab 0.3 mg/kg (n=60), 2 mg/kg (n=54), and 10 mg/kg (n=54).21 Median PFS was 2.7 months, 4.0 months, and 4.2 months at 0.3, 2, and 10 mg/kg respectively. The median OS was 18.2 months, 25.5 months, and 24.7 months, respectively. The ORR ranged from 20-22% across dose levels.

Most of the 167 patients (n=122, 73%) experienced treatment-related AEs (any grade) and 19 patients (11%) experienced grade 3-4 treatment-related AEs. The incidence of treatment-related AEs of any grade was similar across the dose arms: 75%, 67%, and 78% in the 0.3, 2, and 10 mg/kg respectively. Grade 3-4 events occurred in 5%, 17%, and 15%, respectively. The most common any grade treatment-related AEs were fatigue, nausea, pruritis, rash, decreased appetite, diarrhea, dry mouth, arthralgia, dry skin, and hypersensitivity. Systemic corticosteroids were administered in 9 (15%), 10 (19%), and 18 (33%) patients in the 0.3, 2, and 10 mg/kg arms, respectively. Treatment-related AEs leading to discontinuation of study drug occurred in 7% (n=11), the most common reason being elevated serum aspartate aminotransferase (AST), occurring in two patients.

The efficacy of nivolumab in RCC was demonstrated in a randomized, open-label, phase III study of nivolumab compared to everolimus in patients with RCC who had received previously treatment.19 In this study, a total of 821 patients with advanced clear cell RCC were randomized 1:1 to received 3 mg/kg of nivolumab IV every 2 weeks of 10 mg of everolimus orally. The primary endpoint was OS.

The median OS was 25.0 months (95% CI 21.8 to NR) with nivolumab and 19.6 months (95% CI 17.6-23.1) with everolimus (HR 0.73, 95% CI 0.57-0.93, p=0.002). The ORR was 25% in the nivolumab arm and 5% in the everolimus arm (OR 5.98, 95% CI 3.68-9.72, p<0.001). PR were observed in 99 patients (24%) in the nivolumab group and in 20 patients (5%) in the everolimus group. CR were observed in 4 patients (1%) in the nivolumab group and 1 patient (<1%) in the everolimus group. The median time to response was 3.5 months (range 1.4-24.8 months) among the 103 patients with a response in the nivolumab group and 3.7 months (range 1.5-11.2 months) among the 22 patients with a response in the everolimus group. The median duration of response was 12 months (range 0-27.6 months) in the nivolumab group and 12 months (0-22.2 months) with everolimus. The median PFS was 4.6 months (95% CI 3.7-5.4) with nivolumab and 4.4 months (95% CI 3.7-5.5) with everolimus (HR 0.88, 95% CI 0.75-1.03, p=0.11).

Treatment-related AEs of any grade occurred in 319 of the 406 patients (79%) treated with nivolumab and in 349 of the 397 patients (88%) treated with everolimus. The most common treatment-related AEs among patients who received nivolumab were fatigue (134 patients, 33%), nausea (57 patients, 14%), and pruritus (57 patients, 14%); among patients who received everolimus, the most common events were fatigue (134 patients, 34%), stomatitis (117 patients, 29%), and anemia (94 patients, 24%). Grade 3 or 4 treatment-related AEs occurred in 76 of the 406 patients (19%) treated with nivolumab and in 145 of the 397 patients (37%) treated with everolimus; the most common grade 3 or grade 4 event was fatigue (10 patients, 2%) with nivolumab and anemia (31 patients, 8%) with everolimus. Treatment-related adverse events leading to treatment discontinuation occurred in 31 of the 406 patients (8%) treated with nivolumab and in 52 of the 397 patients (13%) treated with everolimus.

2.3 Ipilimumab

Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4-mediated signals are inhibitory and turn off T cell-dependent immune responses[28, 29].

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells (APCs), with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

Ipilimumab monotherapy for the treatment of metastatic RCC was studied in a phase 2 clinical trial. Two sequential cohorts were studied, each with a loading dose of 3 mg/kg followed by 3 doses of either 1 mg/kg (group 3-1; n = 21) or 3 mg/kg (group 3-3; n = 40). Subjects with stable disease or partial or complete response were allowed additional treatment. In group 3-1 (n = 21), one subject (5%) had a PR. In group 3-3 (n = 40), 5 subjects (12.5 %) had a PR. Among 14

treatment-naive subjects in group 3-3, 3 (21%) had a PR. The major toxicities were colitis (all grade 3-4; 14% in group 3-1, 33% in group 3-3) and hypophisitis (1 grade 3-4, 1 grade 1-2 in group 3-3; none in group 3-1). Most reported AEs were grade 1-2 (57% in group 3-1, 35% in group 3-3) or grade 3 (38% in group 3-1, 48 % in group 3-3). There were 6 subjects (15%) with grade 4 AEs in group 3-3. The most common treatment-related AEs in group 3-1 (total 81%) and group 3-3 (total 93%) were diarrhea (38% and 40%, respectively) and fatigue (33% and 38%, respectively). Most AEs were manageable with appropriate treatment, including high dose corticosteroids and hormone replacement.

2.4 Nivolumab and Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN−γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone[30].

A phase I study investigated the safety and activity of nivolumab and ipilimumab in RCC[31]. Subjects with metastatic RCC (favorable/intermediate Memorial Sloan Kettering Cancer Center (MSKCC) score; Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV every 3 weeks for 4 doses then nivolumab 3 mg/kg IV every 2 weeks until progression/toxicity. The primary objective was to assess safety/tolerability and the secondary objective was to assess antitumor activity. Subjects were randomized to N3 + I1 (n = 21) and N1 + I3 (n = 23). Most patients (n=34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). The confirmed ORR was 43% (N3 + I1) and 48% (N1 + I3). Duration of response was 4.1+ to 42.1+ weeks (7 of 9 responses ongoing) in N3 + I1, and 12.1+ to 35.1+ wks (9 of 11 responses ongoing) in N1 + I3. Best response of SD was seen in 5 (24%) patients (N3 + I1) and 8 (35%) pts (N1 + I3). Median PFS was 36.6 weeks (N3 + I1) and 38.3 weeks (N1 + I3). These data are still immature, with 11 of 21 events reported for N3 + I1 and 10 of 23 events reported for N1 + I3.

The safety of nivolumab combined with ipilimumab was assessed in the phase 1 study. Treatment-related AEs were seen in 39/44 patients (89%), including 16/21 (76.2%) in N3 + I1 and 23/23 (100%) in N1 + I3. Across the N3 + I1 and N1 + I3 arms, the most common (≥ 20%) treatment related AEs of any grade were fatigue (61%), diarrhea (32%), nausea (30%), rash (27%), pruritis (25%), ALT increased (23%), AST increased (20%), hypothyroidism (20%), and lipase increased (20%). Grade 3–4 related AEs occurred in 19 patients (29%), including 6/21 (29%) at N3 + I1 and 14/23 (61%) at N1 + I3. The most common (≥ 5%) drug-related grade 3-4 events were lipase increased (21%), ALT increased (14%), AST increased (7%), diarrhea (9%), fatigue (5%), amylase increased (5%), colitis (5%), lymphocyte count decreased (5%). No grade 3–4 pneumonitis was seen. No treatment-related deaths were reported.

Treatment-related AEs (including Grade 3-4), treatment-related AEs leading to discontinuation, and treatment-related SAEs all occurred more commonly in subjects in the N1 + I3 arm than in the N3 + I1 arm: treatment related AEs 76.2% N3 + N1 versus 100% N1 + I3; treatment related grade 3-4 AEs 28.6% versus 60.9%, treatment related AEs leading to discontinuation 9.5% versus 26.1%.

2.5 Rationale

Patients with metastatic RCC have multiple treatment options however the only one currently demonstrated to improve OS is nivolumab. Little information is known about whether treatment can safely be discontinued in patients who experience a response. Data from early drug trials of nivolumab suggest that some patients who discontinued therapy while demonstrating a response continue to derive benefit from therapy for a durable period of time. This study will plan to formally investigate this question. Nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg has demonstrated substantial clinical activity, as measured by ORR, while still exhibiting an acceptable safety profile. Given the promising data of the combination of nivolumab and ipilmumab, this study will investigate whether ipilimumab can be used to improve ORR for patients who experience SD or PD initially. In this study, we are evaluating the efficacy of nivolumab when given in combination with a total of 2 doses of ipilimumab every 3 weeks (± 3 days). The efficacy of 2 doses compared to 4 doses of ipilimumab when given in combination with nivolumab is unknown. Furthermore, the efficacy of re-treatment with nivolumab combined with ipilimumab is unknown. Studies exploring differing treatment schedules are lacking in RCC. The responses induced by immunotherapy are expected to be more durable than those induced by VEGF receptor therapy, and are therefore likely to translate into improvements OS, as seen with nivolumab alone.

2.6 Correlative Studies Background

PD-L1/PD-1 pathway activation in tumors, as determined by PD-L1 levels, may be an important predictive diagnostic for checkpoint inhibition. Published results suggest that expression of PD-L1 in tumors correlates with response to anti-PD-1 therapy[32]. This correlation was also observed with nivolumab in data from the phase II study of nivolumab alone. Tumor specimens (collected from baseline fresh tumor specimens) from patients meeting eligibility criteria will be tested for PD-L1 expression and other markers of immunogenicity and angiogenesis. In addition, PD-L1 status (as defined by expression of PD-L1 on tumor cells or TIMC) will be correlated with outcomes. Because the expression of PD-L1 on the surface of both tumor cells and TIMC can be a dynamic process and because PD-L1 expression on these cells may vary between primary and metastatic sites, mandatory fresh tumor specimens will be collected at baseline. Additionally, to investigate mechanisms of acquired resistance to therapy, we will obtain progression biopsies. For patients in Arm A who experience an initial CR/PR to nivolumab alone, we will obtain an optional biopsy at time of progression prior to re-initiation of nivolumab . From patients who demonstrate progression to nivolumab and ipilimumab we will obtain an optional tumor biopsy at progression on both agents.

Changes in biomarkers in the blood may provide evidence for the biological activity of nivolumab alone or in combination with ipilimumab in humans and may allow for the developed of a blood based biomarkers to help predict which patients may benefit from therapy. A secondary objective is to assess the immunomodulatory properties of nivolumab alone or in

combination with ipilimumab by evaluating baseline levels and changes in levels upon treatment of surrogate pharmacodynamic markers in the blood. In addition, we will correlate levels with the anti-tumor activity of the combination of these agents.

2.7 Study Design

This is a phase II study investigating a response-based approach to therapy with nivolumab and ipilimumab in subjects with advanced renal cell carcinoma (RCC). All subjects will initiate therapy with nivolumab. After 8 weeks (± 7 days), subjects will undergo the first response assessment, as well as additional assessments for the response confirmations if applicable, then be assigned to the study arms A and B. Confirmation scans for patients with CR/PR/SD will occur following an additional 8 weeks (± 7 days). For patients with PD, initial confirmation scans will be obtained at 4 weeks (± 7 days) at the discretion of the treating investigator if the patient is stable to wait for confirmatory imaging. Arm allocation will occur within the first 6 months of the study. For subjects to be allocated to Arm A, they need to have a confirmed CR/PR on two serial and consecutive imaging assessments within the first 6 months of the study while on nivolumab treatment alone. All other subjects who are not able to demonstrate a persistent confirmed CR/PR within the first 6 months of the study, will be allocated to Arm B.

Single Cell Sequencing Cohort: An additional subset of patients (n=25) will be enrolled to the study at DFCI and selected sites with capability for single cell molecular transcriptomic assessment. These patients will receive the same treatment at detailed above and will be allocated in Arm A and B as detailed above. All patients will undergo a mandatory baseline biopsy. Biopsy schedule by treatment arm is detailed below:

Arm A:
Mandatory biopsy at baseline
Optional biopsy at time of response following discontinuation of nivolumab
Mandatory biopsy at final treatment disconuation/off study

Arm B:
Mandatory biopsy at baseline
Mandatory biopsy at final treatment disconuation/off study

Arm A (persistent PR/CR) includes the following patient scenarios:

- Subjects who experience a partial response (PR) or complete response (CR) at 8 weeks (initial response assessment) from initiation of primary nivolumab therapy and who maintain a persistent PR or CR at the subsequent imaging assessment in 8 weeks (+/- 7 days) (i.e.,~16 weeks from initiation of nivolumab);

OR

- Subjects who experience stable disease (SD) at the initial response assessment at 8 weeks from initiation of primary nivolumab therapy, with the subsequent scan in 8 weeks (+/- 7 days) documenting CR/PR which is maintained at the next imaging assessment in 8 weeks (+/- 7 days) (i.e, ~24 weeks from initiation of nivolumab).

Patients who have SD on initial assessment followed by CR/PR on first confirmatory assessment which does not persist on the second confirmatory imaging assessment will be allocated to Arm B as CR/PR was not persistent and confirmed on consecutive imaging assessments.

Subjects with confirmed PR/CR (arm A) will discontinue nivolumab and be followed with serial imaging assessments every 8 weeks. If progressive disease (PD) develops, therapy with nivolumab will be resumed and will not be discontinued if a subsequent PR or CR were to occur. Subjects who experience subsequent PD following re-initiation of nivolumab, will be treated with nivolumab + ipilimumab every 3 weeks x 2 doses and will continue nivolumab. All patients will continue on treatment with nivolumab alone every 4 weeks which will begin 5 weeks ± 3 days after the last dose of nivolumab + ipilimumab. For subjects who experience a PD on nivolumab and ipilimumab, treatment will be discontinued.

If by 24 weeks, subjects have not demonstrated a persistent CR/PR confirmed on at least two serial scan assessments, then subjects will be allocated to Arm B at the 24 week time point.

Arm B (persistent PD/SD) includes the following patient scenarios:

- Subjects who experience PD at 8 weeks (initial response assessment) on primary nivolumab therapy which is then confirmed by a second scan within 4 weeks (+/- 7 days). The confirmatory scan is not required if the site investigator determines that this is clinically detrimental;
- Subjects who initially experience SD at 8 weeks (initial response assessment), which is confirmed with a second scan showing SD in 8 weeks (± 7 days)
- Subjects who have receive at least 3 doses of nivolumab and may have signs and/or symptoms concerning for early clinical progression with radiographic evidence of PD before 8 weeks
- Subjects who do not meet the criteria for allocation into Arm A given lack of persistent CR/PR confirmation on serial and consecutive imaging within the first 6 months of the study will be allocated to Arm B by the 6-month time point.

Subjects in Arm B will receive ipilimumab every three weeks x 2 doses in addition to nivolumab. Treatment with nivolumab alone every 4 weeks will begin 5 weeks ± 3 days after the last dose of nivolumab + ipilimumab. Subjects will be followed with serial imaging assessments every 8 weeks (except the first imaging assessment which will take place at 12 weeks since ipilimumab addition). If PD persists or develops, all treatments will be discontinued. If PR/CR/SD is observed subjects will continue nivolumab.

3. STUDY OBJECTIVES

3.1 Objectives

3.1.1 Primary Objectives

- Assess the proportion of subjects with persistent complete response (CR) or partial response (PR) at one year after

nivolumab discontinuation (Arm A)
- Assess the proportion of subjects with progressive disease (PD)/stable disease (SD) that convert to PR/CR at one year upon the addition of ipilimumab to nivolumab (Arm B)

3.1.2 Secondary Objectives

- Assess progression-free survival (PFS) and overall survival (OS) rates in Arm A and Arm B
- To assess the rate of re-initiation of nivolumab (salvage) therapy (arm A)
- Assess the immune-related ORR (irORR) in subjects in Arm A and B
- Assess safety and toxicity in study arms A and B
- Summarize PR/CR rate, PFS, and OS in the overall cohort and by each arm according to subgroups:
  - International mRCC Database Consortium (IMDC) risk groups.
  - Untreated versus previously treated subjects
  - Histologic subtype (clear cell versus non-clear cell renal cell carcinoma (RCC) subtypes; sarcomatoid components present versus absent)

3.1.3 Correlative/Exploratory Objectives

- Evaluate the relationship between tumor-infiltrating lymphocytes (TILs), programmed death-ligand 1 (PD-L1) tumor expression, and other tissue biomarkers with efficacy outcomes (proportion of PR/CR, PFS, OS)
- Evaluate the relationship between PD-L1 status in archival tissue and in fresh tumor specimens
- Evaluate mechanisms of response to nivolumab in fresh tumor specimens obtained at baseline in subjects with a durable response to treatment (≥1 year)
- Evaluate mechanisms of intrinsic and acquired resistance to nivolumab and ipilimumab treatments in fresh tumor specimens obtained at time of radiographic progression
- Assess molecular mechanisms of resistance to treatment via circulating free DNA (cfDNA) assessment and to correlate cfDNA molecular profile with metastasis biopsy molecular profile
- Assess molecular mechanisms of resistance to treatment via circulating tumor cell (CTC) assessment
- Correlate CTC molecular profile with metastasis biopsy molecular profile

- Assess mechanisms of response and resistance to treatment via single cell molecular assessment (transcriptome assessment)
- Correlate single cell molecular profile with metastasis biopsy molecular profile

4 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Age ≥ 18 years at the time of consent.

2. ECOG Performance Status of ≤ 2 within 28 days prior to registration.
3. Unresectable advanced or metastatic RCC to include both clear cell and non-clear histologies.

   Patients who have suspected metastatic RCC, which has not yet been pathologically proven, may be enrolled if they plan to undergo a cytoreductive nephrectomy, metastectomy, or biopsy. Fresh tissue from one of these procedures can be used for the clinical trial requirements (eligibility #) as well as serve as pathologic confirmation of RCC. The pathologic confirmation must be documented prior to C1D1.

   Single Cell Sequencing Cohort only: Histology must have predominant clear cell component.

4. Availability at the study site of formalin-fixed, paraffin-embedded (FFPE) archival tumor specimens, when available, and willingness of the subject to undergo mandatory fresh tumor biopsy prior to treatment initiation. If a target lesion is biopsied at screening, this lesion must be followed as non-target lesion after the biopsy unless it is the patient's only target lesion. If there is only one target lesion, it should be followed as a target lesion regardless.
   a. The archival specimen must contain adequate viable tumor tissue.
   b. The specimen may consist of a tissue block (preferred and should contain the highest grade of tumor) or at least 30 unstained serial sections. Fine-needle aspiration/ biopsy, brushings, cell pellet from pleural effusion, bone lesion, bone marrow aspirate/biopsy are not acceptable.

Previously untreated or treated subjects with no limit on prior lines of systemic therapies are allowed. Patient may have received prior adjuvant therapy.

Single Cell Sequencing Cohort only: Can either have had no prior systemic therapy (treatment naïve) for RCC, prior IFN-α or IL-2, or a maximum of 1 prior VEGF targeted therapy (VEGFR TKI-based regimen or bevacizumab) for RCC. Agents given in combination in the first line would count as 1 regimen (e.g,. Lenvatinib +

Everolimus).

5. Measurable disease as defined by Response Evaluation Criteria In Solid Tumors RECIST 1.1 within 28 days prior to registration.

6. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to first study treatment.

System	Laboratory Value
Hematological	
White blood cell (WBC)	≥ 2500 cells/μL
Absolute Neutrophil Count (ANC)	≥ 1500 cells/μL
Platelet count (plt)	≥ 100,000/ μL
Hemoglobin (Hgb)	≥ 9 g/dL (transfusions allowed)
Absolute lymphocyte count	≥ 500 cells/μL
Renal	
Serum creatinine OR Calculated creatinine clearance[1]	≤ 1.5 x ULN ≥ 40 mL/min
Hepatic and Other	
Bilirubin[3]	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)[2]	≤ 2.5 × ULN
Alanine aminotransferase (ALT)[2]	≤ 2.5 × ULN
Alkaline Phosphatase[2]	≤ 2.5 × ULN
Albumin	> 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN (unless on prophylactic or therapeutic dosing with low molecular weight heparin, or oral anticoagulants (eg. coumadin, rivaroxaban)

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance (See SPM)
[2] Subjects with documented liver metastases should have AST and ALT ≤ 5 x ULN. Subjects with documented liver or bone metastases should have alkaline phosphatase ≤ 5 x ULN
[3] Subjects with known Gilbert's disease should have a serum bilirubin ≤ 3 x ULN.

7. Females of childbearing potential must have a negative serum pregnancy test within 28 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

8. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 150 days after treatment discontinuation for females and 210 days after treatment discontinuation for males. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

9. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

4.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Prior use of systemic checkpoint inhibitors for the management of metastatic RCC is excluded. Prior IFN-α or IL-2 is allowed.

2. **Single Cell Sequencing Cohort only**: Non-clear cell histology.

3. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitors) within 2 weeks of enrollment or receipt of any anti-cancer therapy (including investigational therapy, monoclonal antibodies) within 4 weeks of enrollment.

4. Treatment with systemic immunosuppressive medications including but not limited to:
   prednisone, dexamethasone, cyclosporin, azathioprine, methotrexate, thalidomide, anti-tumor necrosis factor (TNF) agents within 2 weeks of first study dose.
   - Subjects who have received acute, low-dose systemic immunosuppressant medications may be enrolled (such as steroids for acute nausea or cancer-related pain ≤ 10 mg prednisone) may be enrolled sooner than 2 weeks of first study dose.
   - Subjects with adrenal insufficiency on physiologic replacement doses of steroids may be enrolled (≤ 10 mg prednisone).
   - The use of inhaled, topical, ocular or intra-articular corticosteroids and mineralocorticoids are allowed.

5. Treatment with a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor (e.g. denosumab) within 2 weeks of first study dose.

6. Radiotherapy for RCC within 14 days of first study treatment with the exception of a single fraction of radiation administered for palliation of symptoms.

7. Known active metastases to the brain, spinal cord or leptomeninges unless adequately treated with radiotherapy, radiosurgery, or surgery and stable for at least 4 weeks of first study treatment as documented by magnetic resonance imaging (MRI) or computerized tomography (CT) imaging and having no ongoing requirement for steroids.

8. Malignancies other than RCC within 5 years of first study treatment with the exception of those with negligible risk of metastases or death and/or treated with expected curative outcome (included but not limited to carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ of the breast, non-muscle invasive urothelial carcinoma).

9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein.

10. Known hypersensitivity to any component of the nivolumab or ipilimumab product.

11. Any active or recent history (within 6 months of first study dose) of autoimmune disease or syndrome that requires systemic corticosteroids (>10 mg daily prednisone equivalent) or immunosuppressive medications including but not limited to: myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegner's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Subjects with vitiligo, controlled type I diabetes mellitus, hypo- or hyperthyroid disease, or surgical adrenal insufficiency requiring hormone replacement therapy are permitted to enroll.

12. Any condition requiring treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the first dose of study drug. Inhaled, topical, ocular or intra-articular steroids and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

13. Uncontrolled adrenal insufficiency.

14. History of idiopathic pulmonary fibrosis, organized pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening imaging CT of the chest. History of radiation pneumonitis in the radiation field is permitted.

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

16. Known active or chronic hepatitis B infection (defined as having a positive hepatitis B surface antigen (HBsAg) test at screening). Subject with past or resolved hepatitis B infection (defined as having a negative HBsAg test and positive antibody to hepatitis B core antigen test) are eligible. Hepatitis B viral DNA must be obtained in subjects with positive hepatitis B core antibody prior to first treatment start.

17. Active hepatitis C infection. Subjects positive hepatitis C antibody test are eligible if PCR is negative for hepatitis C viral DNA.

18. Severe infections within 4 weeks of first study treatment including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

19. Receipt of therapeutic oral or IV antibiotics within 2 weeks of first study treatment. Subjects receiving routine antibiotic prophylaxis (for dental extractions/procedures) are eligible.

20. Significant cardiovascular disease such as New York Heart Association (NYHA) class III or greater, myocardial infarction within the previous 3 months, unstable arrhythmias,

unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 45% must be on a stable regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist when appropriate.

21. Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on screening EKG > 500 msec.

22. History of abdominal or tracheoesophageal fistula or GI perforation within 6 months of first study treatment.

23. Clinical signs or symptoms of GI obstruction or requirement of routine parenteral nutrition.

24. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.

25. Serious, non-healing or dehiscing wound or active ulcer.

26. Major surgical procedure within 4 weeks of first study treatment.

27. Presence of any toxicities attributed to prior anti-cancer therapy that are not resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0) or baseline before administration of study drug.

28. Prior allogenic stem cell or solid organ transplant.

29. Administration of a live, attenuated vaccine within 4 weeks for first study treatment.

4.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5. SUBJECT REGISTRATION

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants will undergo a mandatory fresh tumor biopsy prior to starting protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the DFCI by the Project Manager. All sites should call the Project Manager to verify treatment availability.

Following registration, participants should begin protocol therapy within two weeks (14 days). Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

5.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and emailed/faxed to the Project Manager:

- Informed consent
- HIPAA authorization form (if not included in consent form).
- Medical History
- Diagnosis and staging assessment
- Physical Examination including review of medications (over-the-counter or prescribed) and side effects the subject is experiencing
- Vital signs (including temperature, heart rate, blood pressure, weight, height and oxygen saturation) and ECOG performance status
- ECG
- Laboratory Testing
- Documentation of at least one prior anti-cancer therapy
- Eligibility Checklist

The research nurse or data manager at the participating site will then e-mail the Project Manager to verify eligibility. To complete the registration process, the Project Manager will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The Project Manager will fax or e-mail the participant study number, and if applicable the dose

treatment level, to the participating site. The Project Manager will also call the research nurse or data manager at the participating site and verbally confirm registration.

6. TREATMENT PLAN

After informed consent has been obtained in writing, the subject will then undergo screening procedures and will enter the trial after successful screening. The subject must be willing to undergo a MANDATORY fresh tumor biopsy prior to treatment following successful screening and registration unless the site investigator deems the procedure medically unsafe.

Subjects who have signs and/or symptoms concerning for early clinical progression can undergo imaging before the initial 8 week imaging time point. In this scenario, if there is evidence of radiographic progression as per RECIST version 1.1, subjects will be allocated immediately to Arm B as long as they have received at least 2 doses of nivolumab (two doses of 480mg IV q 4 wks). Subjects who received fewer than 2 doses of nivolumab (480mg dosing) with early progression can either discontinue from study or may continue on to receive at least 2 doses of nivolumab before reassessing response at treating investigator's discretion. The per protocol 8 week scans should still be done on schedule even if earlier scans are done and compared to baseline for initial response assessment which should then be confirmed at the 16 week time point per protocol.

Primary Treatment with Nivolumab

Eligible subjects will be enrolled and will receive primary treatment with nivolumab 480 mg IV (D1) for 2 cycles. Each Cycle = 28 days. After 2 cycles (8 weeks +/- 7 days), all subjects will have initial disease assessment scans.

Arm A: CR or PR Response after Primary Treatment with Nivolumab:

- For subjects allocated to Arm A, nivolumab will be discontinued and subjects will be followed with serial imaging assessments every 8 weeks (Observation).
- If PD develops, therapy with nivolumab 480 mg IV every 4 weeks will be resumed. At this time, subjects will be asked to undergo an optional fresh tumor biopsy. Subjects will have disease assessment scans every 8 weeks (+/- 7 days). Nivolumab will continue until PD is documented.
- Subjects who experience subsequent PD following re-initiation of nivolumab will have ipilimumab 1 mg/kg IV every 3 weeks x 2 doses added. During this time, nivolumab 3 mg/kg IV will be administered every 3 weeks to coincide with ipilimumab 1 mg/kg x 2 doses. Treatment with nivolumab alone 480 mg IV every 4 weeks will begin 5 weeks ± 3 days after the last dose of nivolumab + ipilimumab. **NOTE:** When ipilimumab is added, the first radiology imaging from the time that combination therapy with nivolumab and ipilimumab is initiated will be obtained after 3 cycles (12 weeks ± 7 days) instead of 2 cycles (8 weeks). Subsequent imaging assessments after this first imaging assessment will occur every 2 cycles (8 weeks +/- 7 days).
- Subjects with CR/PR/SD after nivolumab plus ipilimumab will continue nivolumab alone starting 5 weeks +/- 3 days after the last dose of combination therapy with nivolumab and ipilimumab. When given alone, nivolumab will be given at 480 mg IV

every 4 weeks. If disease assessment scans after 3 cycles (12 weeks) from the time of initiation of combination therapy with nivolumab and ipilimumab show CR/PR/SD, subjects will continue nivolumab alone until PD is documented. Subsequent imaging assessments after this first imaging assessment will occur every 2 cycles (8 weeks ± 7 days).

- For subjects who experience a PD on nivolumab and ipilimumab, treatment will be discontinued.

Arm B: SD/PD Response after Primary Treatment Nivolumab:

- For subjects allocated to Arm B, ipilimumab 1 mg/kg IV every 3 weeks x 2 doses will be added. During this time, nivolumab 3 mg/kg IV will be administered every 3 weeks to coincide with ipilimumab dosing x 2 doses and then nivolumab will be continued at 480 mg IV every 4 weeks thereafter. Treatment with nivolumab alone every 4 weeks will begin 5 weeks ± 3 days after the last dose of nivolumab + ipilimumab at the start of Cycle 3/Day 1 following primary treatment with nivolumab. Subjects will be followed with serial imaging assessments every 8 week (+/- 7 days) and will continue nivolumab. If PD develops, treatment will be discontinued.
  NOTE: When ipilimumab is added, the first radiology imaging from the time that combination therapy with nivolumab and ipilimumab is initiated will be obtained after 3 cycles (12 weeks ± 7 days) instead of 2 cycles (8 weeks +/- 7 days). Subsequent imaging assessments after this first imaging assessment will occur every 2 cycles (8 weeks +/- 7 days).

- In certain cases if a patient is recovering from a recent hospitalization for a study irAE or comorbidity (unrelated to study intervention) at the time of transition to Arm B but has confirmed persistent stable disease on Initial treatment or is felt to be receiving clinical benefit, then the patient may be allowed to stay on Initial treatment with nivolumab alone. This must be confirmed with the sponsor-investigator. If ipilimumab is to be added it should be done at the next cycle (after 2 more doses of nivolumab). If prior irAE or non-study drug co-morbidity precludes addition of ipilimumab for safety concerns, the patient may continue on nivolumab monotherapy if thought to be achieving clinical benefit. This must be confirmed with the sponsor-investigator.

For either arm:

- Subjects will continue on therapy until radiographic progression on study therapy or withdrawal for some other reason as detailed in section 6.7. Subjects will be asked to undergo an OPTIONAL fresh tumor biopsy at the time of progression. Subjects will be permitted to continue treatment beyond progression as long as they meet the following criteria: (1) Site investigator-assessed clinical benefit AND (2) Subject is tolerating study drug.
- If brain metastases are identified on brain imaging, patients may continue on study therapy if:
  - All brain lesion(s) are amenable to focal therapy (e.g. stereotactic body

radiation therapy (SBRT) or metastectomy)
- They meet other criteria to continue on study therapy
- If the only site of progression is intracranial, the patient may continue on nivolumab monotherapy without transitioning to adding ipiliumumab at investigator discretion

6.1 Drug Administration

Table 1A Nivolumab Monotherapy Administration

Regimen Description					
Agent*	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nivolumab	None	480 mg flat dose	IV	Every 4 weeks (± 3 days)	4 weeks (28 days)

*Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Table 1B Nivolumab and Ipilimumab Administration

Regimen Description					
Agent*	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nivolumab	None	3 mg/kg	IV **before** ipilimumab	When administered concurrently **with** ipilimumab will be administered every 3 weeks** (± 3 days)	4 weeks (28 days)
Ipilimumab	None	1 mg/kg	IV **after** nivolumab	Every 3 weeks for a total of 2 maximum doses based on response (± 3 days)	

*Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.
Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.
**Nivolumab will be administered first followed by ipilimumab with a minimum of 30 minutes from the end of nivolumab infusion to beginning of ipilimumab infusion.

Nivolumab is to be administered as an approximately 30-minute IV infusion when given as a flat dose of 480 mg. When nivolumab is given concurrently with ipilimumab at 3 mg/kg it will be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

The dosing calculations should be based on the body weight from the initiation of treatment with nivolumab. If the subject's weight on the day of dosing differs by > 5% from the weight used to calculate the dose, the dose should be recalculated based on the current day of treatment weight. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Antiemetic premedications should not be routinely administered prior to dosing of drugs.

6.2 Pre-Treatment Criteria

Prior to every cycle 1 day 1: Initial treatment, day 1 Nivolumab plus Ipilimumab
Ipilimumab and day 1 of resuming nivo post discontinuation after response

6.2.1 Cycle 1, Day 1

Cycle 1, day 1 the following parameters must be met:

- Absolute Neutrophil Count (ANC) ≥1500 cells/ μL
- Platelet count ≥100,000/ μL
- Hemoglobin (Hgb) ≥9g/dl (transfusions allowed)
- Serum creatinine ≤ 1.5 x ULN OR Calculated creatinine clearance[1] ≥ 40 mL/min
- Bilirubin ≤1.5 x upper limit of normal (ULN)[2]
- Aspartate aminotransferase (AST)[3] ≤2.5 x ULN
- Alanine aminotransferase (ALT)[3] ≤2.5 x ULN

1. Cockcroft-Gault formula will be used to calculate creatinine clearance
2. Subjects with known Gilbert's disease should have a serum bilirubin ≤ 3 x ULN.
3. Subjects with documented liver metastases should have AST and ALT ≤ 5 x ULN. Subjects with documented liver or bone metastases should have alkaline phosphatase ≤ 5 x ULN

For patients that had fresh tissue collected at baseline (via biopsy or surgery) with no prior pathology review, the final pathology from baseline procedures must be reviewed and documented in the patient's medical records prior to initiating therapy (finalization of a pathology report is sufficient).

6.3 Concomitant Medications

6.3.1 Allowed Concomitant Medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject after 7 days preceding the screening evaluation and prior to the end of treatment visit. All concomitant medications administered within 14 days preceding Cycle 1 Day 1 and throughout the study until the treatment termination visit will be collected on

study- specific electronic Case-Report Forms (eCRFs). The reason(s) for treatment and dates of treatment should be reported to the site investigator and recorded as instructed on the study- specific eCRFs.

Subjects who experience treatment related infusion reactions should be managed as per guidelines in Section 6.4.1.

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids for treatment of non-irAEs are permitted but a dose that exceeds 10 mg/day prednisone equivalents must be discussed with the sponsor-investigator. At eligibility, subjects must be on ≤ 10 mg/day prednisone equivalent. Use of steroids exceeding prednisone 10 mg/day equivalent to treat irAEs is permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study. Mineralocorticoids for orthostatic hypotension or adrenal cortical insufficiency are acceptable. Use of osteoclast targeted therapy (including bisphosphonates and denosumab) is permitted and these agent are allowed to be newly initiated for patients while on study.

Influenza vaccination should be given during influenza season only (approximately October to March). Subjects must not receive live attenuated influenza vaccine within 4 weeks prior to Cycle 1 Day 1 or at any time during the study but may receive inactivated influenza vaccines. Subjects who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular-weight heparin at a stable dose level or oral anticoagulants (eg.warfain, rivaroxaban)) should continue their use. Males and females of reproductive potential should use highly effective means of contraception. The use of denosumab is allowed on study once treatment has been initiated.

All concomitant medications should be reported to the site investigator and recorded on the appropriate eCRF.

6.3.2 Prohibited Concomitant Medications

Instructions for subjects regarding concomitant therapies can be found in Appendix B.

- Any concomitant therapy intended for the treatment of cancer, whether health authority−approved or experimental, is prohibited. This includes but is not limited to the following:
    - Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, i-nvestigational agents, or herbal therapy. Radiotherapy may be considered for pain palliation if subjects are deriving benefit (such as treatment of known bony metastases, see eligibility).
        - In the event that the investigator chooses to wait to add ipilimumab until after radiation completion, patient may continue on single agent nivolumab in the meantime. Restaging scans will occur 12 weeks (+/- 7 days) AFTER ipilimumab starts.

- Subjects experiencing a mixed response requiring local therapy (such as surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Subjects who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the sponsor-investigator.

- Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

- Initiation or increased dose of granulocyte colony-stimulating factors (such as granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

- Concomitant immunostimulatory agents, including but not limited to IFN- α or IL-2, are not permitted during the entire study. These agents, in combination with nivolumab and/or ipilimumab, could potentially increase the risk for autoimmune conditions.

- Immunosuppressive medications (except to treated drug-related AE), including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide, are not permitted. These agents could potentially alter the activity and the safety of nivolumab and/or ipilimumab. Systemic corticosteroids (>10 mg daily prednisone equivalent) and anti-TNF-α agents may attenuate potential beneficial immunologic effects of treatment with nivolumab and/or ipilimumab but may be administered for the treatment of non irAEs only after consultation with the sponsor-investigator. If feasible, alternatives to these agents should be considered. In addition, all subjects (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of nivolumab and/or ipilimumab. Use of systemic corticosteroids (>10 mg daily prednisone equivalent) and anti-TNF- α is permitted for management of irAEs as detailed in Appendix C.

- Elective major surgery should be delayed whenever possible. No data are available to define a safe interval. Re-initiation of nivolumab and/or ipilimumab following surgery requires documented approval from the sponsor-investigator.

6.4 Supportive Care

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate. Subjects who require therapeutic anticoagulation with low molecular weight heparin (e.g., enoxaparin and tinzaparin), coumadin or other oral anticoagulants at study entry will be eligible for enrollment. In addition, subjects requiring therapeutic anticoagulation with these agents during study participation will be allowed to remain on study therapy.

6.4.1 Treatment of Nivolumab or Ipilimumab-Related Infusions Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (v4)
guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

Grade 1 Symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

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

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

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

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

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine

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

6.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (unless otherwise specified in section 6.7)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Subject decides to withdraw from the protocol therapy
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the site investigator
- Female subject becomes pregnant
- Protocol therapy is interrupted for > 6 weeks (unless otherwise specified in 6.3).

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the DF/HCC website at http://www.dfhcc.harvard.edu/research/clinical-research-support/document-library-forms-sops- etc/.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, [redacted]

6.6 Duration of Follow Up

Subjects will have safety follow up visits at D30 following the last dose of study drug. Subjects who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the site investigator as stable, new anticancer treatment is initiated,

the subject is lost to follow-up, the subject withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE. If not seen in clinic, subjects will be called on day 100 (+/-3) following the last dose of study drug for assessment of adverse events.

After progression/treatment discontinuation, subjects will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after end of treatment visit. Follow-up will be via phone calls and through review of medical records.

6.7 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue treatment beyond site investigator assessed progression after the administration of ipilimumab for rescue as detailed in the study schema and continued nivolumab as long as they meet the following criteria:

- Site investigator-assessed clinical benefit
  AND
- Subject is tolerating study drug(s).

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond progression on nivolumab after addition of ipilimumab should be discussed with the sponsor-investigator and documented in the study records.

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

New lesions are considered measurable at the time of progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm) on followup imaging.

6.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must

be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6.9 Replacement

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been assigned to treatment or administered at least one dose of the study drug. Subjects who have dropped out but have not received at least one dose of treatment will be replaced. Subjects who have not received at least one dose of treatment will not be included in data analysis and thus will not require data entry.

7. DOSING DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation.

There will be no dose reductions or dose escalations for either nivolumab or ipilimumab on this study, however, dose delays will be permitted as detailed below for each agent. The descriptions and grading scales found in the revised NCI CTCAE v4 will be utilized for dose delays.

7.1 Dose Delays for Nivolumab with or without Ipilimumab

Nivolumab with or without ipilimumab administration should be delayed for the following:

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

7.2 Criteria to Resume Treatment with Nivolumab with or without Ipilimumab

Nivolumab and/or ipilimumab should be administered as soon as the subject meets criteria to resume treatment. If a dose has been missed for combination therapy, the subject should not wait until the next scheduled dosing date but can restart when clinically safe as long as it has been at least 3 weeks from last ipilimumab. If a dose is held or missed for single agent nivolumab, the subject should resume treatment at the next scheduled dosing date. Efforts should be made to administer as many doses as possible, if a subject cannot be treated on a particular day the cycle should either be skipped or frame shifted to a point when the patient is able to be treated. All efforts should be made to refrain from skipping doses of Ipilimumab. If a subject has been holding for an extended period of time or clarifying questions are needed in regards to resuming treatment please reach out to the Principal Investigator

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- 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 (Section 7.3) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 7.3. If irAEs require management with systemic steroids, dosing may resume once patient is tolerating prednisone 10 mg/day equivalent or lower.

For the period in which ipilimumab is administered with nivolumab, treatment must be resumed on the same day. If a subject is unable to resume both nivolumab and ipilimumab within 6 weeks of dose interruption, permanent discontinuation is required.

7.3 Criteria to Discontinue Treatment with Nivolumab with or without Ipilimumab

Treatment with nivolumab with or without ipilimumab should be permanently discontinued for any of 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 toxicity, hypersensitivity reactions, and infusion reactions:

  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - 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:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the PI for Grade 4 amylase or lipase abnormalities.
  - 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 unless the sponsor-investigator is consulted and agrees with the rationale for resuming therapy after a delay > 6 weeks. Note that 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 site investigator, presents a substantial clinical risk to the subject with continued nivolumab with or without ipilimumab dosing.

7.4 Management Algorithms for Immune-Mediated Adverse Events

Appendix C provides general management algorithm for immune-mediated AEs to provide guidance to the site investigator and may be supplemented by discussions with the sponsor- investigator. The guidance applies to all immuno-oncology agents and regimens.

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

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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

8. STUDY CALENDARS & EVALUATIONS

CALENDAR FOR ALL SUBJECTS PRIMARY TREATMENT		Initial Primary Treatment		Continued Primary Treatment During Period to Confirm Response[14]	While on Primary Treatment
Study Evaluation **Cycle = 28 days**	Screening	Nivolumab ALONE Cycle 1		Nivolumab ALONE Cycle 2 +	Nivolumab ALONE Every 2 cycles
	-28 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days	Every 2 cycles (8 weeks +/- 7 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History	X				
Diagnosis and Staging	X				
Physical Exam	X	X	X	X	
Vital signs and ECOG Performance Status[1]	X	X	X	X	
ECG[2]	X				
MUGA or ECHO[2]	X				
AEs & concomitant medications	X	X	X	X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)[3]	X	X	X	X	
Comprehensive Metabolic Profile (CMP)[3]	X	X	X	X	
PT/INR and aPTT	X				
Thyroid Function (TSH, free T4)[4]	X				X
Pregnancy Test (serum) (WOCBP)[5]	X				
Viral Serologies[6]	X				
DISEASE ASSESSMENT					
CT of chest[7]	X				X
CT or MRI of abdomen and pelvis[7]	X				X
MRI or CT Brain[7]	X				
TREATMENT EXPOSURE					
Nivolumab[8]		X		X	
SPECIMEN COLLECTION					
Archival Tumor Tissue[9]	X				
Tumor Biopsy[10]	X				
Research Blood Sample- Germline DNA[11]		X			
Research Blood Sample- Biomarkers[12]		X			X

CALENDAR FOR ALL SUBJECTS PRIMARY TREATMENT		Initial Primary Treatment		Continued Primary Treatment During Period to Confirm Response[14]	While on Primary Treatment
Study Evaluation Cycle = 28 days	Screening	Nivolumab ALONE Cycle 1		Nivolumab ALONE Cycle 2 +	Nivolumab ALONE Every 2 cycles
	-28 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days	Every 2 cycles (8 weeks +/- 7 days)
Research Blood Sample- cfDNA and CTCs[13]	X	X			X

Key to Footnotes

1: Vital signs to include blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, body weight (kg) and height (cm). Height at SCREENING ONLY.

2: If the initial QTcF is found to be > 500 msec, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard. For Single Cell Sequencing Cohort ECHO will not be required at screening.

3: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential. Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and LDH (baseline LDH only). C1D1 laboratory assessments do not need to re-meet eligibility criteria.

4: TSH and free T4 will be done at screening and every 2 cycles (8 weeks ± 7 days).

5: For women of childbearing potential (WOCBP): urine or serum βhCG. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. WOCBP should be counseled regarding the importance of contraception from the time of screening until 180 days after last dose of study drug(s). If a subject communicates that pregnancy is possible, a serum βhCG should be performed per site investigator's discretion.

6: Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, antibodies against hepatitis B core antigen), and HCV serology (anti-HCV) will be performed. HBV DNA test is required for subjects who have known positive serology for anti HBc. HCV RNA test is required for subjects who have known positive serology for anti HCV.

7: Radiology Imaging at screening to include: Diagnostic CT chest and CT or MRI of the abdomen and pelvis and MRI of the brain. If a subject is not able to obtain an MRI, CT imaging with contrast is acceptable. If a subject is not able to receive contrast, CT head without contrast is acceptable. Radiology Imaging during Primary Treatment: Initial scans will be done after 2 cycles (8 weeks +/- 7 days) of nivolumab. Subjects with PR/CR/SD will have confirmatory scans 8 weeks later (+/- 7 days). Confirmatory scans for subjects with PD are not mandatory but may be attained 4 weeks later if clinically feasible (+/- 7 days). Subjects who have two serial consecutive imaging assessments (8 weeks +/- 7 days apart) which demonstrate CR/PR within the first 6 months of study will be allocated to Arm A. All other subjects who do not meet this criteria will enter Arm B by the 6 month time point. Subjects have who signs and/or symptoms concerning for early clinical progression can undergo imaging before 8 weeks (+/- 7 days). In this scenario, if there is evidence of radiographic progression, subjects may be allocated to Arm B immediately, assuming they have received at least 3 doses of nivolumab. For Single Cell Sequencing Cohort MRI or CT of the Brain will not be collected at screening.

8: Primary Treatment: Nivolumab will be administered on Day 1 (+/- 3 days) of each 28-day cycle for 2 cycles. After 2 cycles, disease assessment will occur. Nivolumab alone will continue until disease status documented with confirmatory scans (See Footnote 7) or site investigator

confirmation of PD and inability to wait for confirmatory scan.

9: MANDATORY if available: Archival tissue will be requested and received prior to Cycle 1 Day 1. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue block is preferred. Alternatively, a minimum of 30 unstained, charged, paraffin coated slides will suffice. Fine-needle aspiration, brushings, cell pellet from pleural effusion, bone marrow aspirate/biopsy are not acceptable. Please see the laboratory manual for additional collection, labeling and shipping information.

10: MANDATORY: Pre-treatment biopsy. Given that fresh tumor tissue is required for correlative assessments, archival tissue cannot take the place of the pre-treatment biopsy. The pre-treatment biopsy will take place following confirmation of eligibility, after registration and prior to Cycle 1 Day 1. In the case that a patient will be undergoing a cytoreductive nephrectomy, or metastatectomy, or biopsy within 12 months of enrolling on the study with no intervening systemic therapy from the time of surgery to study enrollment, fresh tissue obtained from the surgical specimen may be used to replace the mandatory baseline fresh tumor biopsy.

11: MANDATORY: Blood for germline DNA analysis collected once between screening to prior to treatment Cycle 1 Day 1

12: MANDATORY: Blood samples for biomarkers will be collected (1) once between screening to prior to treatment C1D1 then (2) every 2 cycles (± 7 days) prior to treatment and corresponding to all imaging assessment time points and (3) at time of EOT visit. Additionally, blood samples for biomarkers will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.

13: MANDATORY: Blood samples for cfDNA and CTCs will be collected at screening and prior to C1D1 treatment, every 2 cycles (± 7 days) prior to treatment and corresponding to all imaging assessment time points, and at time of EOT visit. Additionally, blood samples for cfDNA and CTCs will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.

14: Nivolumab will continue to be administered on D1 of each 28-day cycle. Once confirmatory scans are complete subjects will either be followed per Arm A or Arm B calendar. Subjects that show SD/PD with confirmatory scans after Primary Treatment with nivolumab will be assigned to Arm B. Subjects with SD after initial scans with Primary Treatment with nivolumab and CR/PR with confirmatory scans will have additional scans 8 weeks later (± 7 days) to confirm CR/PR. If CR/PR is confirmed, these subjects will be assigned to Arm A, go into observation and be followed as described in the calendar titled "Arm A: CALENDAR FOR SUBJECTS WITH CR/PR AFTER PRIMARY TREATMENT." Subjects that show CR/PR with confirmatory scans after Primary Treatment with nivolumab will be assigned to Arm A.

ARM A: CALENDAR FOR SUBJECTS WITH CR/PR AFTER PRIMARY TREATMENT	CR/PR after Primary Treatment[4] ± 3 days	PD after Observation[5] ± 3 days	PD after Re-initiation of nivolumab[6] ± 3 days			CR/PR/SD after nivolumab PLUS ipilimumab[7] ± 3 days	Every 2 cycles (±7 days)[2,3]	End of Treatment Visit[8] ± 7 days	Long Term Follow Up[9] ± 14 days
Study Evaluation Cycle = 28 days	Observation Cycle 1 +	Re-initiation of Nivolumab	Nivolumab PLUS Ipilimumab			Continued Nivolumab	During Observation and On Treatment	Off Study Treatment; On Study Follow-Up	
	Day 1 ± 3 days	Day 1 ± 3 days	Cycle 1/Day 1 ± 3 days	Cycle 1/Day 22 ± 3 days	Cycle 2/Day 15 +/- 3 days	Day 1 of Cycle 3 onward +/- 3 days	Every 2 cycles (+/- 7 days)	Day 30	Every 6 months
REQUIRED ASSESSMENTS									
Physical Exam	X	X	X	X	X	X		X	
Vital signs and ECOG Performance Status[1]	X	X	X	X	X	X		X	
AEs & concomitant medications	X	X	X	X	X	X		X	X
LABORATORY ASSESSMENTS									
Complete Blood Cell Count with diff (CBC)[2]	X	X	X	X	X	X		X	
Comprehensive Metabolic Profile (CMP)[2]	X		X	X	X	X		X	
Thyroid Function (TSH and free T4)[2]							X	X	
DISEASE ASSESSMENT									
CT of chest[3]							X[3]		
CT or MRI of abdomen and pelvis[3]							X[3]		
TREATMENT EXPOSURE									
Nivolumab		X	X	X		X			
Ipilimumab			X	X					
SPECIMEN COLLECTION									
Tumor Biopsy[10]	X	X						X	
Research Blood Sample- Biomarkers[11]	X	X					X	X	
Research Blood Sample- cfDNA and CTCs[12]	X	X					X	X	
FOLLOW-UP									
Survival Status, Subsequent Therapy									X

Key to Footnotes:
1: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, body weight (kg) and height (cm). Height at SCREENING ONLY.
2: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential. Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, AST, ALT, alkaline phosphatase, and total bilirubin. C1D1 laboratory assessments do not need to re-meet eligibility criteria. TSH and free T4 will be done every two cycles (8 weeks ± 7 days), except when ipilimumab is added, TSH and free T4 will be obtained after 3 cycles (12 weeks ± 7 days) instead of 2 cycles (8 weeks) to align with scans.
3: Diagnostic CT chest and CT or MRI of the abdomen and pelvis should be obtained every 2 cycles (± 7 days). **NOTE:** When ipilimumab is added, the first set of post-ipilimumab imaging will be obtained after 3 cycles (~12 weeks ± 7 days) instead of 2 cycles. After the initial set of scans after ipiliumumab initiation, the scan timing will revert back to every 2 cycles (+/- 7 days). If dosing is delayed, imaging should follow guidelines of cycles over absolute weeks.
4: **OBSERVATION:** Subjects with a CR/PR (Arm A) after Primary Treatment with nivolumab will have nivolumab discontinued and go onto Observation. Radiology imaging will be done every 2 cycles (8 weeks ± 7 days) as described in bullet 3. Subjects will continue observation until PD. During the observation period subjects will be seen in clinic once per cycles (28 days +/- 3 days).
For subjects who have shown persistent CR/PR while on observation, in clinic study visits can be extended to every 8 weeks. A nurse, NP/PA, or physician will call subjects in between visits for assessment of symptoms (at least every 4 weeks). This must be approved by sponsor-investigator prior to modifying subjects visit schedule.
5: **RE-INITIATION OF NIVOLUMAB:** Subjects that experience PD during observation will re-initiate nivolumab. Radiology imaging will be done every 2 cycles (8 weeks +/- 7 days) as described in bullet 3. Subjects will continue nivolumab until PD.
6: **ADDITION OF IPILIMUMAB**: Subjects that show PD after re-initiation of nivolumab will have ipilimumab added for 2 doses ONLY. During this time, nivolumab will be given every 3 weeks to match ipilimumab administration. Disease assessment scans will occur after completion of 3 cycles (12 weeks ± 7 days) from the time ipilimumab is added to nivolumab. Nivolumab ALONE will be continued starting 5 weeks +/- 3 days after last dose of nivolumab PLUS ipilimumab at the start of cycle 3/day 1 from when ipilimumab is added to nivolumab.
7: **CONTINUATION OF NIVOLUMAB**: Subjects with CR/PR/SD after initial scans following the addition of ipilimumab to nivolumab will continue nivolumab ALONE until PD. During this time nivolumab will be given every 4 weeks and disease assessment scans will occur every 2 cycles (8 weeks +/- 7 days). Subjects will be permitted to continue treatment beyond site investigator assessed progression as long as they meet the following criteria: (1) Site investigator-assessed clinical benefit AND (2) Subject is tolerating study drug.
8: End of treatment (EOT) visit will occur 30 days (± 7 days) after last dose of study drug. Subjects will come off study treatment if they have PD as described in bullet #6 or for other reasons such as toxicity or subject choice. Subjects who (1) had study drugs delayed or modified due to toxicity or other factors and (2) were then discontinued from study treatment can use a study visit as EOT visit. Subjects who have an ongoing study treatment-related AE upon discontinuation from the study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the site investigator as stable, new anticancer treatment is initiated, the subject is lost to follow-up, the subject withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE. If not seen in clinic, subjects will be called on day100 following the last dose of study drug for assessment of adverse events.
9: Long term follow-up for survival and initiation of a new anti-cancer treatment will occur every 6 months (± 14 days) until death or 2 years after EOT visit whichever comes first. This follow up may be via phone calls and through review of medical records.
10: An OPTIONAL tumor biopsy at time of progression will be requested from subjects unless the procedure is deemed medically unsafe or not feasible.

ARM A subjects will have biopsies (1) following progression off nivolumab prior to reinitiation of nivolumab (ideally prior to restart but within 10 days of re-starting nivolumab is permitted if scheduling issues and clinical need to start sooner than biopsy can be obtained), (2) at progression following treatment with both nivolumab and ipilimumab. For patients enrolled on ARM A in the Single Cell Sequencing Cohort a mandatory biopsy will be performed at baseline, an optional biopsy at the time of response following discontinuation of nivolumab and a mandatory biopsy at time of permannent treatment discontinuation/off study if deemed safe and feasible. Biopsies should be performed per institutional standards and/or operator preference. Blood samples should be drawn within 2 weeks of the biopsy to document an acceptable coagulation profile (INR $\leq$ 1.5, PTT $\leq$ 60, platelets > 50,000). Aspirin and NSAIDS should be discontinued 5 days prior to the biopsy. Please see the laboratory manual for additional collection, labeling and shipping information.
11: MANDATORY: Blood samples for Biomarkers will be collected every 2 cycles (± 7 days) prior to treatment, corresponding to all imaging assessment time points and at time of EOT visit. Additionally, blood samples for biomarkers will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.
12: MANDATORY: Blood samples for cfDNA and CTCs will be collected every 2 cycles (± 7 days) prior to treatment, corresponding to all imaging assessment time points and at time of EOT visit. Additionally, blood samples for cfDNA and CTCs will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.

ARM B: CALENDAR FOR SUBJECTS WITH SD/PD AFTER PRIMARY TREATMENT	SD/PD after Primary Treatment[4] ± 3 days			SD/PR/CR after nivolumab PLUS ipilimumab[5] ± 3 days	Every 2 cycles (± 7 days)[2,3]	End of Treatment Visit[6, 7] ± 7 days	Long Term Follow Up[8] ± 14 days
Study Evaluation Cycle = 28 days	Nivolumab PLUS Ipilimumab			Nivolumab ALONE Cycles 3 +	While on treatment	Off Study Treatment; On Study Follow-up	
	C1D1	C1D22	C2D15	Day 1 of Cycle 3 onward +/- 3 days	Every 2 cycles (+/- 7 days)	Day 30	Every 6 months
REQUIRED ASSESSMENTS							
Physical Exam	X	X	X	X		X	
Vital signs and ECOG Performance Status[1]	X	X	X	X		X	
AEs & concomitant medications	X	X	X	X		X	X
LABORATORY ASSESSMENTS							
Complete Blood Cell Count with diff (CBC)[2]	X	X	X	X		X	
Comprehensive Metabolic Profile (CMP)[2]	X	X	X	X		X	
Thyroid Function (TSH and free T4)[2]					X	X	
DISEASE ASSESSMENT							
CT of chest[3]					X[3]		
CT or MRI of abdomen and pelvis[3]					X[3]		
TREATMENT EXPOSURE							
Nivolumab	X	X		X			
Ipilimumab	X	X					
SPECIMEN COLLECTION							
Tumor Biopsy[9]						X	
Research Blood Sample- Biomarkers[10]					X	X	
Research Blood Sample- cfDNA and CTCs[11]					X	X	
FOLLOW-UP							
Survival Status, Subsequent Therapy							X

Key to Footnotes

1: Vital signs to include upright blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, body weight (kg) and height (cm). Height at SCREENING ONLY.

2: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential. Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, AST, ALT, alkaline phosphatase, and total bilirubin. C1D1 laboratory assessments do not need to re-meet eligibility criteria. TSH and free T4 will be done every two cycles (8 weeks ± 7 days), except when ipilimumab is added, TSH and free T4 will be obtained after 3 cycles (12 weeks ± 7 days) instead of 2 cycles (8 weeks) to align with scan visits

3: Diagnostic CT chest and CT or MRI of the abdomen and pelvis should be obtained every 2 cycles (- 7 days). **NOTE:** When ipilimumab is added, imaging will be obtained after 3 cycles (~12 weeks ± 7 days) instead of 2 cycles. If dosing is delayed, imaging should follow guidelines of cycles over absolute weeks.

4: **ADDITION OF IPILIMUMAB**: Subjects that show SD/PD with confirmatory scans after Primary Treatment (Arm B) will have ipilimumab added for 2 doses ONLY. During this time, nivolumab will be given every 3 weeks to match ipilimumab administration. Disease assessment scans will occur after completion of 3 cycles from the addition of ipilimumab to nivolumab. Nivolumab ALONE will be continued starting 5 weeks +/- 3 days after last dose of nivolumab PLUS ipilimumab at the start of cycle 3/day 1 from when ipilimumab is added to nivolumab.

5: **CR/PR/SD AFTER ADDITION OF IPILIMUMAB:** Subjects will continue nivolumab ALONE until PD. During this time nivolumab will be given every 4 weeks and disease assessment scans will occur every 2 cycles (8 weeks +/- 7 days).

6: **PD AFTER ADDITION OF IPILIMUMAB:** Subjects that experience PD after nivolumab PLUS ipilimumab will be taken off study treatment and continue follow up per protocol. Confirmatory scans for subjects with PD are not mandatory but may be attained 4 weeks later if clinically feasible. Subjects will be permitted to continue treatment beyond site investigator assessed progression as long as they meet the following criteria: (1) Site investigator-assessed clinical benefit AND (2) Subject is tolerating study drug.

7: End of treatment (EOT) visit will occur 30 days (± 7 days) after last dose of study drug. Subjects will come off study treatment if they have PD as described in bullet #6 or for other reasons such as toxicity or subject choice. Subjects who (1) had study drugs delayed or modified due to toxicity or other factors and (2) were then discontinued from study treatment can use a study visit as EOT visit. Subjects who have an ongoing study treatment-related AE upon discontinuation from the study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the site investigator as stable, new anticancer treatment is initiated, the subject is lost to follow-up, the subject withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE. If not seen in clinic, subjects will be called on day 100 (+/- 3) following the last dose of study drug for assessment of adverse events.

8: Long term follow-up for survival and initiation of a new anti-cancer treatment will occur every 6 months (± 14 days) until death or 2 years after EOT visit whichever comes first. This follow up may be via phone calls and through review of medical records.

9: An OPTIONAL tumor biopsy at time of progression will be requested from subjects unless the procedure is deemed medically unsafe or not feasible. For patients enrolled on the Single Cell Sequencing Cohort a mandatory biopsy will be performed at the time of treatment discontinuation/off study following treatment with nivolumab and ipilimumab if deemed safe and feasible. Arm B (1) following progression on treatment with BOTH nivolumab and ipilimumab. Biopsies should be performed per institutional standards and/or operator preference. Blood samples should be drawn within 2 weeks of the biopsy to document an acceptable coagulation profile (INR $\leq$ 1.5, PTT $\leq$ 60, platelets > 50,000). Aspirin and NSAIDS should be discontinued 5 days prior to the biopsy. Please see the laboratory manual for additional collection, labeling and shipping information.

10: MANDATORY: Blood samples for Biomarkers will be collected every 2 cycles (± 7 days) prior to treatment, corresponding to all imaging assessment time points and at time of EOT visit. Additionally, blood samples for biomarkers will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.

11: MANDATORY: Blood samples for cfDNA and CTCs will be collected every 2 cycles (± 7 days) prior to treatment, corresponding to all imaging assessment time points and at time of EOT visit. Additionally, blood samples for cfDNA and CTCs will be collected at confirmatory imaging assessment time points. If EOT collection is within 2 weeks of prior collection, research samples do not need to be collected. For patients enrolled on the Single Cell Sequencing Cohort, whole blood for CTC collection and whole blood for plasma/PBMC isolation will not be collected.

8.1 Duration of Follow Up

Subjects who have an ongoing study treatment-related AE upon end of treatment visit will be followed until the event has resolved to baseline grade, the event is assessed by the site investigator as stable, new anticancer treatment is initiated, the subject is lost to follow-up, the subject withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE. After progression/treatment discontinuation, subjects will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after treatment discontinuation. Follow-up will be via phone calls and through review of medical records.

9. BIOSPECIMEN STUDIES AND PROCEDURES

Correlative studies will be exploratory in nature. In this study, we will evaluate the immunomodulatory properties of nivolumab in combination with ipilimumab and correlate findings with outcomes. In addition, we will evaluate tumor tissue and TIMC for expression of PD-L1 in mandatory baseline biopsies and optional progression biopsies and correlate with outcomes. Lastly, we will evaluate mechanisms of resistance to therapy in optional progression biopsy specimens. Please see the Laboratory Manual for collection, processing, labeling and shipping instructions.

Whole blood for germline DNA and cfDNA plasma samples will be analyzed by investigators at collaborating institutions, such as the Broad Institute, for all patients enrolled on this trial. From these samples, the data will be submitted to the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP) and other public databases. Samples and data will be de-identified.

9.1 Blood for Germline DNA

- This sample will be drawn once prior to C1D1 treatment
- Five (5) mL of blood will be drawn into purple top vacutainers with EDTA. DO NOT use heparin as anticoagulant, since the polymer will tightly bind downstream PCR enzyme during sequencing.

9.2 Blood for Research Analysis

9.2.1 Biomarker Analysis

Blood will be collected for flow cytometry studies to analyze peripheral blood mononuclear cells. Additionally, plasma will be collected to analyze soluble biomarkers to include cyotkines/chemokines and angiogenic/growth factors. This analysis will require 30 mL of blood in green or purple top tubes at each time point. These samples are to be collected prior to treatment C1D1, every 2 cycles corresponding with radiology imaging. If off treatment collection is within 2 weeks of prior collection, research samples do not need to be collected.

9.2.2 cfDNA Plasma

Plasma will be collected for genomic analysis of circulating free DNA (cfDNA). cfDNA assessments will require 10 mL of blood in an EDTA tube at each time point. These samples are to be collected prior to treatment C1D1, every 2 cycles corresponding with radiology imaging. If off treatment collection is within 2 weeks of prior collection, research samples do not need to be collected.

The cfDNA from each time point will be subjected to low pass whole genome sequencing to assess DNA quality, tumor purity (i.e. the approximate percentage of DNA isolated from peripheral blood originating from tumor rather than normal cells), and copy number profile of tumor DNA. For subjects with cfDNA of adequate quality and purity, we will also perform whole exome sequencing from cfDNA isolated at baseline, at best tumor response, and at progression.

9.2.3 CTC Analysis

CTC analysis will require 20mL of blood in EDTA tubes at each time point. These samples are to be collected during screening, prior to treatment C1D1, every 2 cycles, corresponding with radiology imaging. If off treatment collection is within 2 weeks of prior collection, research samples do not need to be collected.

9.3 Tissue Studies

Tissue will be collected to assess the immunomodulatory properties of nivolumab in combination with ipilimumab as determined immunohistochemistry assessment of immunologic parameters including, but not limited to, T cell subset markers (CD4, CD8, FoxP3, LAG3), cytokines/chemokines (IFN, TNF), immune regulation (PD-L2, CTLA-4), and tumor infiltrating lymphocytes (TILs). Additionally, mutation profiling of molecular mechanisms of response and resistance will be analyzed via whole exome sequencing and RNA sequencing.

Mutational profiling of molecular mechanisms of response and resistance will be analyzed via whole exome or whole genome sequencing and via RNA-sequencing. If fresh tissue is available, the specimen will be collected, as stated in this protocol and according to institutional guidelines, and put on ice to be transported to the processing laboratory. A portion of fresh tissue will be dissociated into a single cell suspension and frozen for future studies, including single cell transcriptome studies and cell line creation.

9.3.1 Archival tumor specimens

Archival tissue is MANDATORY if available. The archival specimen must contain adequate viable tumor tissue and be overall representative of the whole tumor (i.e. containing predominant and highest Fuhrman grade areas). Formalin-fixed paraffin-embedded tumor tissue blocks are preferred and should contain tumor areas that measure at least 1 cm square in aggregate.
Alternatively, a minimum of 30 unstained 4-micron-thick sections (on charged slides) can be provided. The unstained slides should be coated with paraffin. Surgical specimens are preferred with order of preference being 1) nephrectomy specimens and 2) metastatectomy specimens. If surgical specimens are not available, core-needle biopsy specimens are acceptable. Fine-needle aspiration, brushings, cell pellet from pleural effusion, bone marrow aspirate/biopsy are not acceptable.

9.3.2 Fresh Tumor Specimens

MANDATORY tumor biopsies will be performed on all subjects prior to treatment, and OPTIONAL tumor biopsies will be performed on subjects at the time of disease progression and for patients in arm A at time of disease progression after discontinuation of nivolumab.

For patients enrolled on the Single Cell Sequencing Cohort the biopsy schedule will be as follows:

Arm A:
Mandatory biopsy at baseline
Optional biopsy at time of response following discontinuation of nivolumab
Mandatory biopsy at final treatment discontinuation/off study

Arm B:
Mandatory biopsy at baseline
Mandatory biopsy at final treatment discontinuation/off study

Progression biopsies are strongly recommended in patients who demonstrate a response to therapy and subsequently progress. Biopsies will be obtained in a manner that minimizes risk and will be taken only if there is no intervening condition (e.g., thrombocytopenia or neutropenia) that, in the opinion of the site investigator, increases the likelihood of procedural complications to an unacceptable level.

Biopsies should be performed per institutional standards and/or operator preference. Blood samples will be drawn within 2 weeks of the biopsy to document an acceptable coagulation profile (INR $\leq$ 1.5, PTT $\leq$ 60, platelets > 50,000). Aspirin and NSAIDS should be discontinued 5 days prior to the biopsy.

Preferred biopsy sites include: lymph nodes, peripheral based liver lesions, exophytic soft tissue components associated with bone lesions, subcutaneous nodules, pleural-based lesions, and kidney lesions.

In the case that a patient will be undergoing a cytoreductive nephrectomy, metastatectomy, or biopsy within 12 months of enrolling on the study with no intervening systemic therapy from the time of surgery to study enrollment, fresh tissue obtained from the surgical specimen may be used to replace the mandatory baseline fresh tumor biopsy.

9.4 Radiology Imaging Studies

Images of all radiologic assessments at baseline, on study, and at treatment discontinuation with corresponding imaging reports for non-DFCI patients need to be placed on a CD and sent to the DFCI for eventual central review of exploratory imaging response assessment by irRC. Images and reports should be sent on all patients once they discontinue study treatment. Please ensure that patient data is de-identified and patient study ID is referenced on all materials as detailed in the lab manual. Reference the Laboratory Manual for additional information.

9.5 Storage of Biospecimens

Samples will be processed for correlative studies and remaining specimens will be stored for future use to include assessment of biological and molecular predictive and prognostic biomarkers.

9.6 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time

of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

10. CRITERIA FOR DISEASE EVALUATION

Subjects should be re-evaluated for response every 2 cycles. Response and progression will be evaluated in this study using the new international criteria proposed by the RECIST guideline (version 1.1).[33] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1 Definitions

Evaluable for Target Disease response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). **NOTE:** Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

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

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

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

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal

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

10.3 Response Criteria

10.3.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). For subjects who demonstrate PD at the first on-treatment imaging assessment, subjects will be allowed to remain on study until confirmatory imaging at the next imaging assessment at the discretion of the treating investigator if it appears that the subjects is clinically benefiting from treatment.

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

If a target lesion is biopsied at screening, this lesion must be followed as non-target lesion after the biopsy unless it is the patient's only target lesion. If there is only one target lesion, it should be followed as a target lesion regardless.

10.3.2 Evaluation of Non-Target Lesions

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal*

progression of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. For subjects who demonstrate PD at the first on-treatment imaging assessment, subjects will be allowed to remain on study until confirmatory imaging at the next imaging assessment at the discretion of the treating investigator if it appears that the subjects is clinically benefiting from treatment.

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

For patients who continue on treatment past progression (past the confirmatory scans), see section 6.7 for details on what constitutes subsequent progression and discontinuation rules.

10.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).
However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.3.4 Evaluation of Best Overall Response

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

Table 2: For Subjects with Measurable Disease (*i.e.*, Target Disease)

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

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	no prior SD, PR or CR

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

Table 3. For Subjects with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

10.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Subjects without events reported are censored at the last disease evaluation).

Duration of overall CR: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Subjects without events reported are censored at the last disease evaluation.

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

10.5 Immune-Related Response Criteria (irRC)

The sum of the products of the two largest perpendicular diameters of lesions (SPD; 5 lesions per organ, up to 10 visceral lesions) at tumor assessment using the immune related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions (up to 5 new lesions per organ: 10 new visceral lesions).[34] Each net Percentage

Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

10.5.1 Definition of Index Lesions Response Using irRC

irComplete Response (irCR): Complete disappearance of all target lesions in two consecutive observations not less than 4 weeks apart. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.

- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable lesions in two consecutive observations not less than 4 weeks apart. (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by > 25% when compared to SPD at nadir.
- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- irProgressive Disease (irPD): At least 25% increase in the percentage change in tumor burden (i.e., taking SPD of all target lesions and any new lesions) when compared to SPD at nadir, in two consecutive observations at least 4 weeks apart, in the absence of rapid clinical deterioration.

10.5.2 Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Non-index lesion(s) are not considered in the definition of PR; this term does not apply.
- irStable Disease (irSD): Does not meet the criteria for irCR or irPD.
- irProgressive Disease (irPD): Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the target lesions increases by the required amount).

10.5.3 Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

10.5.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- Immune-Related Complete Response (irCR): Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-Related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD

baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
Immune-Related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.

- Immune-Related Progressive Disease (irPD): It is recommended to confirm PD by serial imaging. Any of the following will constitute progressive disease:
    - At least 25% increase in the SPD of all target lesions over nadir SPD calculated for the index lesions, in two consecutive observations at least 4 wk apart, if clinically permissible*.
    - At least a 25% increase in the SPD of all index lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the target lesions, in two consecutive observations at least 4 wk apart, if clinically permissible*.

Table 4. Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent Change in Tumor Burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR*
Partial Response	Any	Any	Any	≥-50%	irPR*
				<-50% to <+25%	irSD*
				>+25%	irPD*
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD*
				>+25%	irPD*
Progressive Disease	Any	Any	Any	≥+25%	irPD*

* In two consecutive observations at least 4 weeks apart, if clinically permissible*

10.5.5 Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered. irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than

4 weeks after the criteria for response are first met.

10.6 Response Review

Tumors will be assessed for response and progression by RECIST version 1.1 by central radiology review.

11. DRUG INFORMATION

11.1 Nivolumab

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Bristol-Myers Squibb (BMS) will supply nivolumab. Ordering of nivolumab will take place through BMS. Each participating institution will receive its own supply of drug.

11.1.1 Pharmacokinetics (PK)

Nivolumab as a single agent: A pooled analysis dataset from a comprehensive population pharmacokinetics analysis dataset consisting of covariate data from 3203 patients with melanoma (n = 875), RCC (n = 695), non-small cell lung cancer (n = 896), squamous cell carcinoma of the head and neck (n = 172), classical Hodgkin's Lymphoma (n = 256), and urothelial carcinoma (n = 308) was used to simulate exposures from nivolumab clinical trials. Using a previously established population pharmacokinetics model across multiple tumor types, nivolumab exposure was predicted for 480 mg every 4 weeks and 3 mg/kg every 2 weeks dose schedules.

The time-averaged concentration over the first 28 days for nivolumab 480 mg every 4 weeks was 27% higher compared to nivolumab 3 mg/kg every 2 weeks. The time-averaged concentration at steady-state was similar between these two dosing schedules.

To analyze exposure-response safety, a pooled safety dataset from nivolumab clinical trials containing 2560 patients with melanoma (n = 481), RCC (n= 604), squamous non-small cell lung cancer (n = 293), non-squamous non-small cell lung cancer (n = 354), squamous cell carcinoma of the head and neck (n = 172), classical Hodgkin's Lymphoma (n = 253), and urothelial carcinoma (n = 308), who received nivolumab 1 to 10 mg/kg every 2 weeks or 0.3 to 10 mg/kg every 3 weeks were used. Logistic regression models were used to describe the relationships between nivolumab exposure and the risk of AEs (AEs leading to discontinuation or death, AEs > Grade 3, immune mediated AEs > Grade 2). Cavgd28 was the designated exposure measure for exposure-response safety analysis. Exposure (Cmax) produced by nivolumab 480 mg every 4 weeks was lower than that produced by 10 mg/kg every 2 weeks, which has been shown to have a favorable safety and tolerability profile. The predicted risk of experiencing AEs leading to discontinuation or death was similar between the 480 mg every 4 weeks and 3 mg/kg every 2 weeks dosing schedules across the tumor types.

To analyze exposure-response efficacy, individual datasets from nivolumab clinical trials of patients with melanoma (n = 364), RCC (n = 604), squamous non-small cell lung cancer (n = 293), and non-squamous non-small cell lung cancer (n = 354), who received nivolumab 1 to10 mg/kg every 2 weeks or 0.3 to 10 mg/kg every 3 weeks were used. OS was assessed by Cox Proportional Hazards and objective response by logistic regression. The predicted OS for the 480 mg every 4 week dose was similar to the 3 mg/kg every 2 week dose in the four indications. In predicted probabilities of achieving response, there were no differences between the 480 mg every 4 week dose and 3 mg/kg every 2 week dose, consistent with previously established flat exposure-efficacy relationships.

Nivolumab in combination with ipilimumab: The geometric mean (%CV) CL, Vss, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies.
There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

Specific Populations: Based on a population PK analysis, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in subjects with mild (eGFR 60 to 89 mL/min/1.73 m2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m 2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m 2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between subjects with renal impairment and subjects with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in subjects with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin < 1-1.5 x ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between subjects with mild hepatic impairment and subjects with normal hepatic function. Nivolumab has not been studied in subjects with moderate (total bilirubin > 1.5-3 x ULN and any AST) or severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

11.1.2 Preparation

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale yellow liquid that may contain light (few) particles. Nivolumab injection for IV infusion is supplied in single-use vials. Each mL of Nivolumab solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

Injection: 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Withdraw the required volume of nivolumab and transfer into an intravenous container. Dilute nivolumab with either 0.9% Sodium Chloride solution or 5% Dextrose solution to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of nivolumab.

11.1.3 Storage and Stability

The product does not contain a preservative. Store nivolumab under refrigeration at 2°C to 8°C (36°F-46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake.

After preparation of infusion, store the nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

11.1.4 Administration

Administer the infusion over approximately30-minutes through an IV line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion. When administered in combination with ipilimumab, infuse nivolumab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

11.1.5 Handling and Disposal

Accountability for investigational product is the responsibility of the investigator. The research pharmacy will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to BMS. Destruction will be documented in the Drug Accountability Record Form.

11.1.6 Compatibility

No incompatibilities between the nivolumab and ipilimumab have been observed. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose

solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution.

11.1.7 Adverse Events

Based on data from phase II and III studies in RCC, nivolumab monotherapy has an acceptable safety profile. Based on data from phase III study of nivolumab versus everolimus in RCC, treatment-related AEs of any grade occurred in 319 of the 406 subjects (79%) treated with nivolumab. The most common treatment-related AEs among subjects who received nivolumab were fatigue (134 subjects, 33%), nausea (57 subjects, 14%), and pruritus (57 subjects, 14%).
Grade 3 or 4 treatment-related AEs occurred in 76 of the 406 subjects (19%) treated with nivolumab. The most common grade 3 or grade 4 event was fatigue (10 subjects, 2%) with nivolumab. Treatment-related AEs leading to treatment discontinuation occurred in 31 of the 406 subjects (8%) treated with nivolumab. No deaths from study-drug toxic effects were reported in the nivolumab group. Please refer to the most current IB and package insert for a comprehensive list of AEs.

11.2 Ipilimumab

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4. Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

Bristol-Myers Squibb (BMS) will supply ipilimumab. Ordering of ipilimumab will take place through BMS.

11.2.1 Pharmacokinetics (PK):

Ipilimumab as a single agent: The pharmacokinetics of ipilimumab was studied in 499 subjects with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (Cmax), trough concentration (Cmin), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab

administered every 3 weeks, ipilimumab clearance was found to be time invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population PK analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab Cmin achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Nivolumab in combination with ipilimumab: The geometric mean (%CV) CL, Vss, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies.
There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

Specific Populations: Cross-study analyses were performed on data from subjects with a variety of conditions, including 420 subjects with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab PKs were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of Ipilimumab is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti- ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of subjects in non-Caucasian ethnic groups.
Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in subjects with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in subjects with various degrees of hepatic impairment.

11.2.2 Preparation

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to- white, amorphous ipilimumab particulates. It is supplied in single-use vials of 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine penta acetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7. 200 mg/40 mL (5 mg/mL). Do not shake product.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale yellow color), or there is foreign particulate matter other than translucent-to white, amorphous particles.

Preparation of Solution:

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of ipilimumab.

11.2.3 Storage and Stability

Store ipilimumab under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials from light.

11.2.4 Administration

Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.

Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 0.5% Dextrose Injection, USP after each dose.

Administer diluted solution approximately 30 miuntes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

11.2.5 Handling and Disposal

Accountability for investigational product is the responsibility of the investigator. The research pharmacy will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to BMS. Destruction will be documented in the Drug Accountability Record Form.

11.2.6 Compatibility

No incompatibilities between the nivolumab and ipilimumab have been observed. When both study drugs are to be administered on the same day, separate infusion bags and filters must be

used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose

solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5%

Dextrose solution.

Table 5. Summary of Safety with Nivolumab in Combination with Ipilimumab in RCC.

	IPI1 + Nivo3 N = 21 n (%)		IPI3 + Nivo1 N = 23 n (%)		Total IPI + Nivo N = 44 n (%)	
Category Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
AEs	20 (95.2)	14 (66.7)	23 (100.0)	14 (60.9)	43 (97.7)	28 (63.6)
Drug-related AEs	16 (76.2)	6 (28.6)	23 (100.0)	14 (60.9)	39 (88.6)	20 (45.5)
Drug-related AEs in ≥ 20% of Subjects						
Fatigue	11 (52.4)	0	16 (69.6)	2 (8.7)	27 (61.4)	2 (4.5)
Rash	8 (38.1)	0	4 (17.4)	0	12 (27.3)	0
Diarrhoea	6 (28.6)	1 (4.8)	8 (34.8)	3 (13.0)	14 (31.8)	4 (9.1)
Pruritus	6 (28.6)	0	5 (21.7)	0	11 (25.0)	0
Nausea	4 (19.0)	0	9 (39.1)	0	13 (29.5)	0
Hypothyroidism	3 (14.3)	0	6 (26.1)	0	9 (20.5)	0
Lipase Increased	3 (14.3)	3 (14.3)	6 (26.1)	6 (26.1)	9 (20.5)	9 (20.5)
Decreased Appetite	2 (9.5)	0	6 (26.1)	0	8 (18.2)	0
Vomiting	2 (9.5)	0	6 (26.1)	0	8 (18.2)	0
ALT Increased	1 (4.8)	0	9 (39.1)	6 (26.1)	10 (22.7)	6 (13.6)
Dysgeusia	1 (4.8)	0	5 (21.7)	0	6 (13.6)	0
Weight Decreased	1 (4.8)	0	5 (21.7)	0	6 (13.6)	0
AST Increased	0	0	9 (39.1)	3 (13.0)	9 (20.5)	3 (6.8)
SAEs	9 (42.9)	6 (28.6)	12 (52.2)	9 (39.1)	21 (47.7)	15 (34.1)
Drug-related SAEs in ≥ 5% of Subjects						
Diarrhoea	1 (4.8)	1 (4.8)	2 (8.7)	2 (8.7)	3 (6.8)	3 (6.8)
ALT Increased	0	0	3 (13.0)	3 (13.0)	3 (6.8)	3 (6.8)
AST Increased	0	0	2 (8.7)	2 (8.7)	2 (4.5)	2 (4.5)
AEs Leading to Discontinuation	2 (9.5)	2 (9.5)	6 (26.1)	4 (17.4)	8 (18.2)	6 (13.6)
Drug-related AEs Leading to Discontinuation in ≥ 5% of Subjects						
ALT Increased	0	0	2 (8.7)	1 (4.3)	2 (4.5)	1 (2.3)
Lipase Increased	1 (4.8)	1 (4.8)	2 (8.7)	2 (8.7)	3 (6.8)	3 (6.8)
Deaths	0		3 (13.0)		3 (6.8)	

Source: Preliminary data for CA209016, database lock date 21-Mar-2014

Abbreviations: IPI = ipilimumab; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; Nivo = nivolumab; Nivo1 = nivolumab 1 mg/kg; Nivo3 = nivolumab 3 mg/kg.

12. ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 12.1) and the characteristics of an observed AE (Section 12.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

12.1 Adverse Event List for Nivolumab

Based on data from the Phase I study, nivolumab in combination with ipilimumab has an acceptable safety profile in RCC. In summary, AEs were reported in 97.7% of subjects treated with nivolumab in combination with ipilimumab. The most frequently reported drug-related AEs in subjects treated with 3-mg/kg nivolumab + 1-mg/kg ipilimumab included fatigue (11 subjects, 52.4%), rash (8 subjects, 38.1%), diarrhea (6 subjects, 28.6%), and pruritus (6 subjects, 28.6%); the majority were Grade 1-2. The most frequently reported drug-related AEs in subjects treated with 1-mg/kg nivolumab + 3-mg/kg ipilimumab included fatigue (16 subjects, 69.6%); nausea, ALT increased, AST increased (9 subjects each, 39.1%); and diarrhea (8 subjects, 34.8%). The majority were Grade 1-2. The majority of deaths were due to disease progression. No drug-related deaths have been reported to date. See Table 5. Please refer to the most current IB for a comprehensive list of AEs.

12.2 Adverse Event Characteristics

AE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web sitehttp://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

12.3 DF/HCC and BMS Expedited Adverse Event Reporting

Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. All SAEs that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety using the MedWatch Form 3500A, which can be accessed at http://www.accessdata.fda.gov/scripts/medwatch/. The BMS protocol ID number must be included on the MedWatch Form. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: [redacted]

SAE Facsimile Number: [redacted]

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

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

The Sponsor will reconcile the clinical database SAE cases transmitted from BMS Global Pharmacovigilance (GPV&E) on an quarterly basis. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to [redacted]. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

12.3.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

12.3.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

12.3.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

12.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

12.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

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

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

12.7 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify [redacted] of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form (provided upon request from BMS).

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

13. STATISTICAL METHODS

13.1 Study Design

The study uses a single arm phase II design. Originally the study planned to enroll a total of 58 subjects into the two treatment Arms A and B. The design details are stated in Section 2.7.

Single Cell Sequencing Cohort: The study was amended to enroll an additional cohort of 25 patients to allow for single cell molecular transcriptomic assessment. These additional 25 patients will undergo the following biopsy schedule:

Arm A:
Mandatory biopsy at baseline
Optional biopsy at time of response following discontinuation of nivolumab
Mandatory biopsy at final treatment disconuation/off study

Arm B:
Mandatory biopsy at baseline
Mandatory biopsy at final treatment disconuation/off study

The cohort addition increases the overall enrollment to 83 subjects in the trial.

No stratification factors are used in enrolling subjects.

13.2 Endpoints

13.2.1 Definition of Primary Endpoint

- The number and proportion of subjects remaining on PR or CR at 1 year since nivolumab discontinuation (Arm A) and the number and proportion of subjects achieving PR or CR upon the addition of ipilimumab to nivolumab (Arm B).

- The response status of PR or CR will be assessed according to RECIST criteria v1.1.

13.2.2 Definition of Secondary Endpoints

- Progression-free survival (PFS): defined as the time from nivolumab discontinuation (Arm A) or from ipilimumab initiation (Arm B) until documented progression by

RESIST criteria or death from any cause, censored at date last known progression-free for those who are alive and have not progressed.

- Overall Survival (OS): defined as the time from nivolumab discontinuation (Arm A) or from ipilimumab initiation (Arm B) until death from any cause, censored at date last known alive or at the time of last assessment of follow-up.

- Salvage therapy-free interval: defined as time from nivolumab discontinuation (arm A) to the receipt of re-starting nivolumab.

- Immune related objective response rate defined according to immune-related Responses Criteria (irRC) and detailed in section 10.5.
- Safety and tolerability according to NCI CTCAE v4.

13.2.3 Definition of Correlative Endpoints

Marker assessments:

- Tumor expression for PD-L1 expression in baseline (prior to primary nivolumab) biopsy tissue, and progression biopsy specimens will be analyzed in all evaluable samples.

- WES, RNAseq, and IHC assessment of immunologic parameters including Tumor-infiltrating lymphocytes (TILs), T cell markers (CD4, CD8, FoxP3, LAG3), cytokines/chemokines (IFN, TNF), immune regulation (PD-L1, PD-L2, CTLA-4) will be evaluated in fresh tumor specimens obtained prior to initial nivolumab in order to assess the mechanisms of responses to nivolumab, with the focus on subjects with a durable response (confirmed PR/CR) to the nivolumab assessed during the 1st year since the discontinuation of the primary nivolumab start (Arm A)

- Mechanisms of intrinsic and acquired resistance to nivolumab (alone, Arm A) and with ipilimumab (Arm B) in fresh tumor specimens obtained at time of radiographic progression by WES, RNAseq, and IHC assessment of immunologic parameters including T cell subset markers (CD4, CD8, FoxP3, LAG3), cytokines/chemokines (IFN, TNF), immune regulation (PD-L1, PD-L2, CTLA-4), and TILs

- cfDNA and CTC evaluated as baseline, on treatment, and at progression.
- Single cell molecular profile according to baseline and metastasis biopsy specimens

13.3 Sample Size and Accrual

Arm A: It's estimated that 23 subjects of confirmed PR or CR responses after initial nivolumab monotherapy will be enrolled (about 29% of total 80 subjects, accounting for 4% lost to follow-up from the overall enrollment of N=83). There is no prior data for this treatment strategy and the main purpose is to generate hypothesis and the assumptions were considered to be clinically meaningful from investigators perspectives. We assume that 1-year remission (continued CR/PR) rate of 10% is not acceptable and a true PR or CR rate of 35% or higher will be considered acceptable for the treatment strategy of nivolumab discontinuation. A single-arm design is employed with 23 eligible subjects entered. If 5 or more of the 23 subjects continue CR or PR at 1 year off nivolumab (observed rate of 22%), we will conclude that the treatment strategy warrants further study. The probability of concluding that the treatment strategy

effective is 7% if the true PR or CR rate is 10% and is >94% if the true PR or CR rate is 35% or higher.

Arm B: Approximately 57 subjects with PD or confirmed SD after initial nivolumab monotherapy will be available for the analysis. From historical data, the rates of PR/CR are 25%, SD 40%, PD 35% in patients treated with nivolumab. We assume that a PR/CR rate of 20% would be considered promising in this population who do not respond to nivolumab alone. The study uses Simon's optimal two-stage design (Simon Controlled Clinical Trials 1989) to allow for early termination if evidence suggests that the addition of ipilimumab is inactive. 20 subjects will be enrolled in the first stage. If 1 or fewer PR/CR are observed, the enrollment of ipilimumab addition will be stopped. If 2 or more PR/CR are observed, then an additional 37 subjects will be enrolled for a total of 57 evaluable patients. The regimen will be declared worthy of further study if 6 or more PR/CR are observed. These decision rules result in 73% probability of stopping early (at the end of first stage) if the regimen is inactive. The design yields a 92% probability (statistical power) of declaring the regimen active given a true PR/CR rate of 20% or 4.7% probability (targeted type I error rate of 0.05) of declaring the regimen active given a true PR/CR rate of 5% or less.

A total accrual goal is 83 subjects. Subjects will continue study therapies till disease progressions, withdraw or adverse events. Additional 2-year follow-up after the end of treatments (EOT) is planned. The primary study analysis is expected to be at 2 years; 6 months for accrual, and 18 months from enrollment for last subject.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	24	+	55	=	79
Ethnic Category: Total of all subjects	26	+	57	=	83
Racial Category					
American Indian or Alaskan Native	2	+	3	=	5
Asian	2	+	5	=	7
Black or African American	2	+	6	=	8

Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	20	+	39	=	59
Racial Category: Total of all subjects	26	+	53	=	83

13.4 Analysis Datasets

Population	Definition
Enrolled	All subjects who meet the eligibility criteria and are registered onto the study.
Evaluable/Analysis	All subjects who receive at least one dose of trial drug or die before any evaluation.
Safety	All subjects with at least one dose of nivolumab or ipilimumab contribute data to the safety analysis.

Population	Definition
Treated	This will comprise all subjects who have been exposed to the planned course of treatment to any extent.

13.5 Assessment of Safety

Adverse event reports are to be submitted within 28 days of each clinic visit. All relevant adverse events will be reviewed by the DSMC for up to 4 times each year or more frequently if requested by the DSMC.

Arm A: As part of the early safety monitoring to make sure that discontinuation of nivolumab is not detrimental for subjects with initial confirmed PR/CR, futility assessments will be implemented after 9 (~39%) of the 23 subjects have image assessment (8 +/- 7 days) since discontinuing nivolumab: an estimate of PD rate with a two-sided binomial CI will be constructed. If 5 or more of the first 9 subjects experience PD (i.e, to have a lower bound of the CI $\geq$ 25%), then the enrollment of arm A may be suspended. The following table gives the operating characteristics of the early futility stopping; if the true unknown probability of PD rate is 60% or higher, the probability of observing 5 or more subjects with PD will be greater than 48% at the time of the first subsequent image assessment after discontinuing nivolumab.

13.6 Operating Characteristics of Early Futility Stopping

True-unknown PD rate (%)	Probability of observing 5 or more PD among 9 subjects
30	0.03
40	0.1
50	0.25
60	0.48
70	0.73

For subjects who re-start nivolumab due disease progression, given there is no prior data for this treatment strategy, and the expected number of subjects to re-start nivolumab maybe small, the study team will monitor the non-response rate carefully. Similar futility analysis may take place at the subsequent image assessment to assess the risk of subjects no longer respond to nivolumab and decide if the strategy is not safe for subjects. The exact criteria will be determined as deemed clinically relevant.

Arm B: The safety review will be concurrent with the first efficacy review of PR/CR that is specified by the Simon two-stage design. Review of these safety data will be conducted by the study team and an independent DFCI Data and Safety Monitoring Committee (DSMC). Based on the review, the DSMC may advise that the study regimen be suspended for additional review. After this initial safety assessment, toxicity and adverse event data will be evaluated as part of the recurrent trial review by the DSMC.

13.7 Efficacy Analysis

13.7.1 Primary Efficacy Analysis

Tumor assessment will be performed every 8 weeks. At the time of each restaging, subjects will be classified as achieving complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or non-evaluable for response according to RECIST (Version 1.1) criteria.

Arm A: The proportion of subjects with sustained/continued PR or CR during the 1 year since the nivolumab discontinuation will be presented with a two-sided 90% CI using exact binominal method. Based on a sample size of 23 subjects, the confidence interval will be no wider than 0.37. For a targeted 35% PR or CR rate, the estimated PR or CR rate precision (width of two sided 90%CI) would be 0.35.

Arm B: The proportion of subjects with PR or CR during the 1-year from the date of first dose of ipilimumab will be presented with a two-sided 90% confidence interval calculated using the method of Atkinson and Brown, corresponding to the two-stage design.

13.7.2 Secondary Analysis

PFS and OS: The progression-free survival (PFS), and overall survival (OS) will each be summarized using the product-limit method of Kaplan-Meier. Median times for each endpoint will be presented with two-sided 90% confidence intervals estimated using log(-log(survival)) methodology. Kaplan-Meier estimates of PFS at 6 or 12 months may also be presented with two-sided 90% confidence intervals.

Salvage Therapy-Free Interval: The proportion of subjects re-start nivolumab since nivolumab discontinuation (arm A) during 1-year will be estimated with two-sided 90% confidence intervals. In addition, the reasons for re-starting nivolumab (Arm A) will be tabulated.

Subset analysis of study endpoints will be explored according to IMDC* risk group (favorable, intermediate, versus poor risk); prior systemic treatment for RCC (yes versus no); first line versus second line targeted therapy; histology (clear cell versus non-clear cell RCC subtypes; sarcomatoid components present versus absent)

*IMDC risk factors include ECOG < 1, time from original diagnosis to treatment less than one year, hemoglobin less than the lower limit of normal, and serum calcium, neutrophil count, or platelet count greater than the upper limit of normal

Immune Related Objective Response Rate: The proportion of subjects with immune ORR will be presented with two-sided 90% confidence interval estimated using exact binomial methods.

Safety and Tolerability: All adverse events recorded during the trial will be summarized for the safety population. The incidence of events that are new or worsening from the time of first dose of treatment will be summarized according to system organ class and/or preferred term, severity (based on CTCAE version 4), type of adverse event, and relation to study treatment.

The worst grade will be used if any toxicity event is reported multiple times on the same participant. All adverse events resulting in discontinuation, and/or dosing interruption, and/or treatment delay will also be summarized.

Given the potential multiple treatment sequences, the incidence of events (grade 3+) will be summarized according to treatment arms as well as the type of therapies they are on at the time of events.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, and type of adverse event.

13.7.3 Exploratory Efficacy Analyses

All expected samples (n=80 presuming approximately 5% unevaluable rate) will be used for the exploratory analysis. The sample size justifications are based on assessing the association of TILs and response status.

Tumor Infiltrating Lymphocytes (TILs): The relationship between tumor-infiltrating lymphocytes (TILs) and study outcomes will be explored according to pre-nivolumab TIL percentages (use the mandatory biopsy specimen). It is hypothesized that higher levels of lymphocytic infiltration will be associated with better outcomes.

Arm A: With an expected samples of N=23, TILs will be descriptively summarized according to response status assessed during the first year after nivolumab discontinuation. An estimated difference of TIL score between the response groups will be summarized with 90% conference interval.

Arm B: To examine responses according to levels of TILs, the expected samples of N=57 will be divided retrospectively according to response status (response (PR/CR) or non-response (assessed via serial image assessments after ipilimumab addition to nivolumab). Pre-treatment percentages of stromal infiltrating lymphocytes will be summarized descriptively for the two response groups and compared using Wilcoxon rank-sum tests. Assume a targeted PR/CR rate of 20% (our primary study alternative hypothesis), if there are 11 responses (20% of 57 subjects) and 46 non-responses, a Wilcoxon rank-sum test with a two-sided, 10% type I error will have 93% power to detect a difference in pre-treatment TILs that is 1.06 times the common standard deviation.

Kaplan-Meier estimates will be used to visualize the relationship between the PFS or OS and median of the distribution of intratumoral or stromal percentages (TILs) or disease phenotype defined by TILs (≥ 50% versus TILs < 50%) in pre-treatment/baseline samples TILs. Medians of the time-to-event endpoints will be calculated with two-sided 90% CIs according to the disease phenotype groups.

Changes in TILs between pre-treatment and disease progression/treatment discontinuation will be calculated (post-pre) for patient with available biopsy samples at both timepoints and summarized descriptively.

PD-L1 Expression:

The association between pre-treatment PD-L1 expression and outcomes will be explored. The PD-L1 expression will be evaluated by IHC in both tumor cell membrane and tumor-infiltrating mononuclear cells (TIMC). It is hypothesized that higher expression levels of PD-L1 will be associated with poor outcomes, due to the fact that up-regulation of PD-L1 may allow cancers to evade the immune system.

To examine responses according to PD-L1 expression, the evaluable samples will be divided retrospectively according to study objective response or non-response. Pre-nivolumab treatment PD-L1 expression will be summarized descriptively for the two response groups.

For the samples from arm A: with the expected small sample (n=23), the analysis will be descriptive. Specifically, the proportion of patients remaining on PR or CR at 1 year since nivolumab according to pre-treatment PD-L1 positivity (PD-L1>5%) will be summarized with two-sided 90% exact, binomial confidence intervals.

For the samples from arm B: in order to assess the association of PD-L1 positivity (PD-L1+) with objective response (i.e., achieving PR or CR upon the addition of ipilimumab to nivolumab), based on a targeted ORR of 20% for this portion of study, which corresponds to have groups of non-responders (n=46) vs responders (n=11) respectively, and assuming an overall expected PD-L1+ of 50%-60% in TIMC, the following table provides the statistical power using a fisher's test to detect the PD-L1+ difference between the two response groups, with a one-side type I error of 0.05. Note, only large differences in % of PD-L1 positivity (51% in non- responder vs. 4% in responders) could be detected with at least 80% power.

Non-responders (N=46)	Responders (N=11)	
% PD-L1 + in TIMC	% PD-L1 + in TIMC	Statistical Power (Fisher's exact test)
50	5	91
60	11	91
70	17	93

In addition, the proportion of patients with objective response i.e., achieving PR or CR upon the addition of ipilimumab to nivolumab according to pre-treatment PD-L1+ will be summarized with two-sided 90% exact, binomial confidence intervals. Visualization of the relationship between baseline PD-L1 expression and the distributions of PFS or OS will employ Kaplan-Meier estimates stratified by PD-L1+. Medians of the time-to-event endpoints of PFS and OS may be shown with two-sided 90% confidence intervals.

Single Cell Sequencing:

The 25 paired samples collected at DFCI and selected sites will undergo the molecular profiles (transcriptome) assessments. The molecular profiles will be descriptively summarized for the paired samples. The exploratory analysis to assess the correlations of single cell molecular profiles with the clinical outcome may be performed.

14. DATA REPORTING/REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 12 (Adverse Events).

14.1 Data Reporting

14.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

14.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

14.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix D.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14.4 Data Quality Oversight Activities

Validation of data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into InForm. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by the sponsor/investigator or its designee.

14.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Management

The Dana-Farber Cancer Clinical Trials Office will provide Project Management and Monitoring services for this trial. Data will be collected through the web based clinical research platform, InForm, a system compliant with Good Clinical Practices and Federal Rules and Regulations created by the Clinical Trials Research Informatics Office (CTRIO). All data will be collected and entered into InForm by study site personnel from participating institutions.

Before trial completion, it is permissable to report data on a subset of patients regarding safety, specific cohorts that complete accrual and mature earlier than the overall trial, or results from cohorts that were added mainly for correlatives purposes such as the single cell sequencing cohort.

15.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in InForm and correlative results will be captured in spreadsheets or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in InForm, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator.

15.3 Record Retention

To enable evaluations and/or audits from Health Authorities, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract. No records will be destroyed until the sponsor/investigator confirms destruction is permitted.

15.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, BMS, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential.

16. PUBLICATION PLAN

The data will be collected by the investigators and analyzed by the co-principal investigators and the statistical team at DFCI. It is anticipated that the results will be made public within 12 months of the end of data collection. A report is planned to be published in a peer-reviewed journal, however initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. [redacted] in consultation with [redacted]. [redacted] as well as outside investigators will decide on the authorship orders for abstracts and manuscripts from the trial.

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18. APPENDICES

A. Performance Status Criteria

B. Information on Possible Drug Interactions

C. Management Algorithms for Immune-Mediated Adverse Events

D. Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

19. APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

20. APPENDIX B: INFORMATION ON POSSIBLE DRUGINTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Nivolumab and ipilimumab interact with many drugs that affect your immune system. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. These are the things that you and they need to know:

Nivolumab and ipilimumab interact with many drugs that affect your immune system.

- These specifically include corticosteroid agents and other medications that can affect the immune system.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is:

_____ and he or she can be contacted at

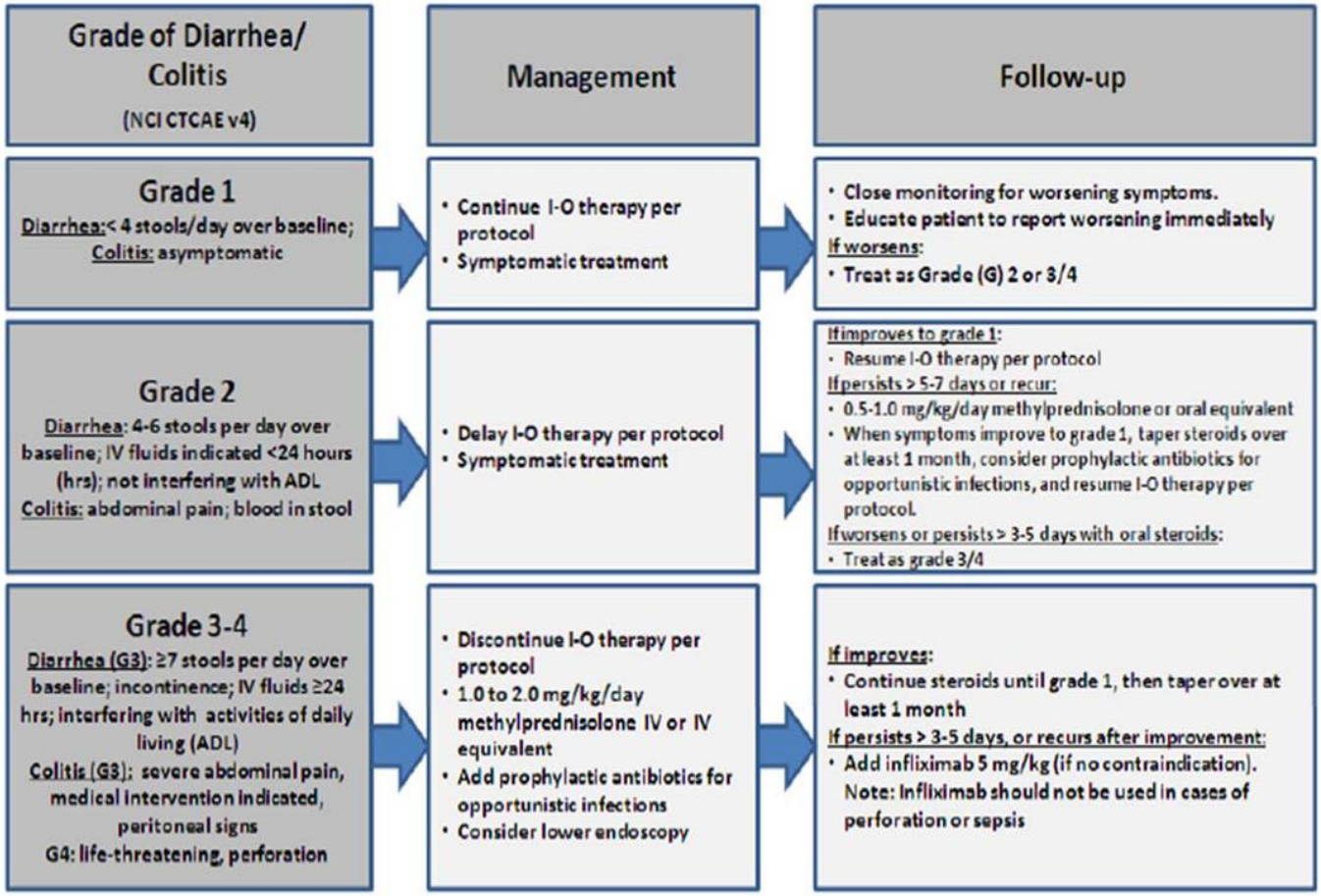
_____

21. APPENDIX C: MANAGEMENT ALGORITHMS FOR IMMUNE-MEDIATED ADVERSE EVENTS

Recommended Management of Immune-mediated AEs. Will not be considered deviations/violations if not followed exactly.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

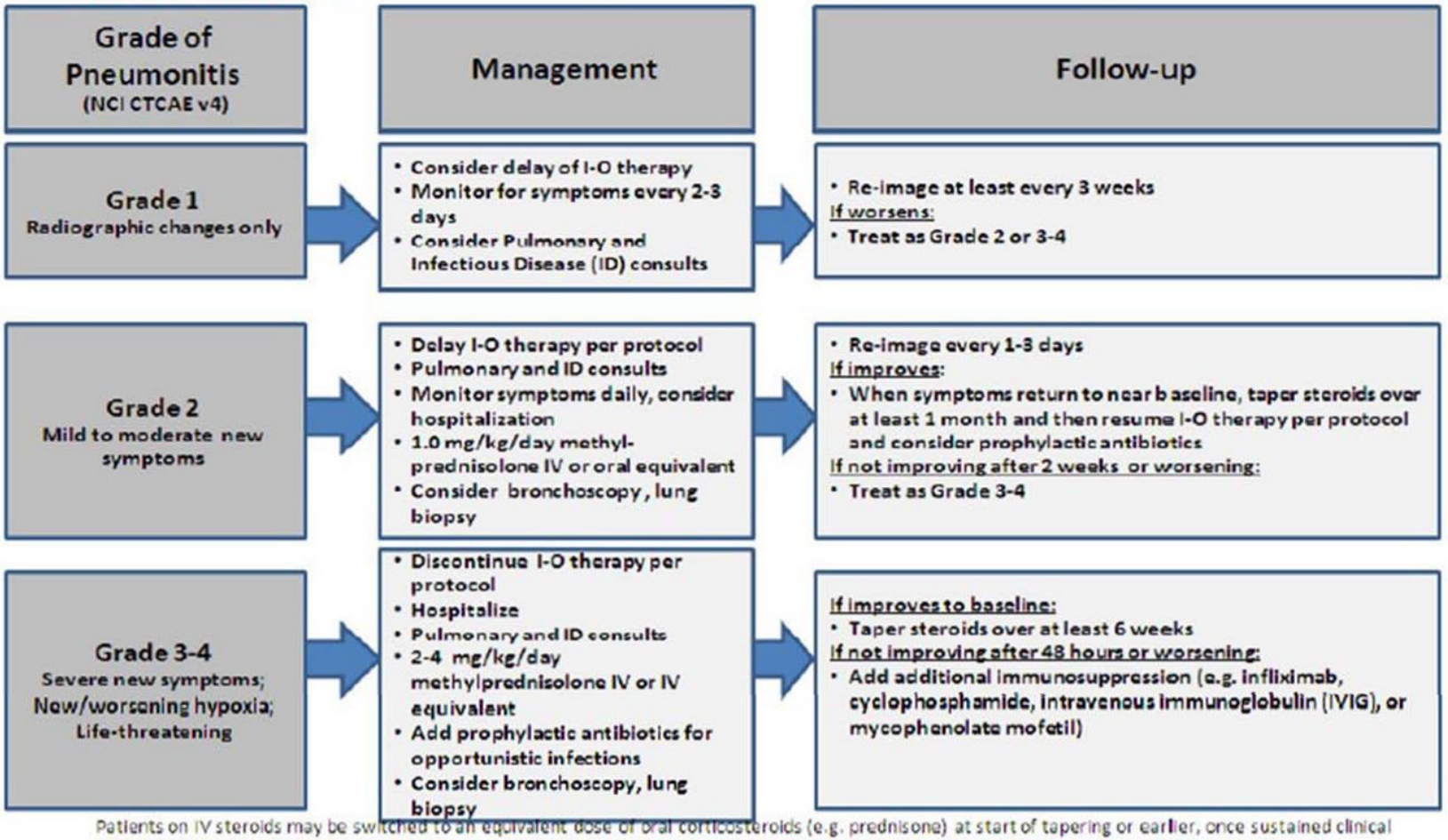
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u>: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Pulmonary Adverse Event Management Algorithm

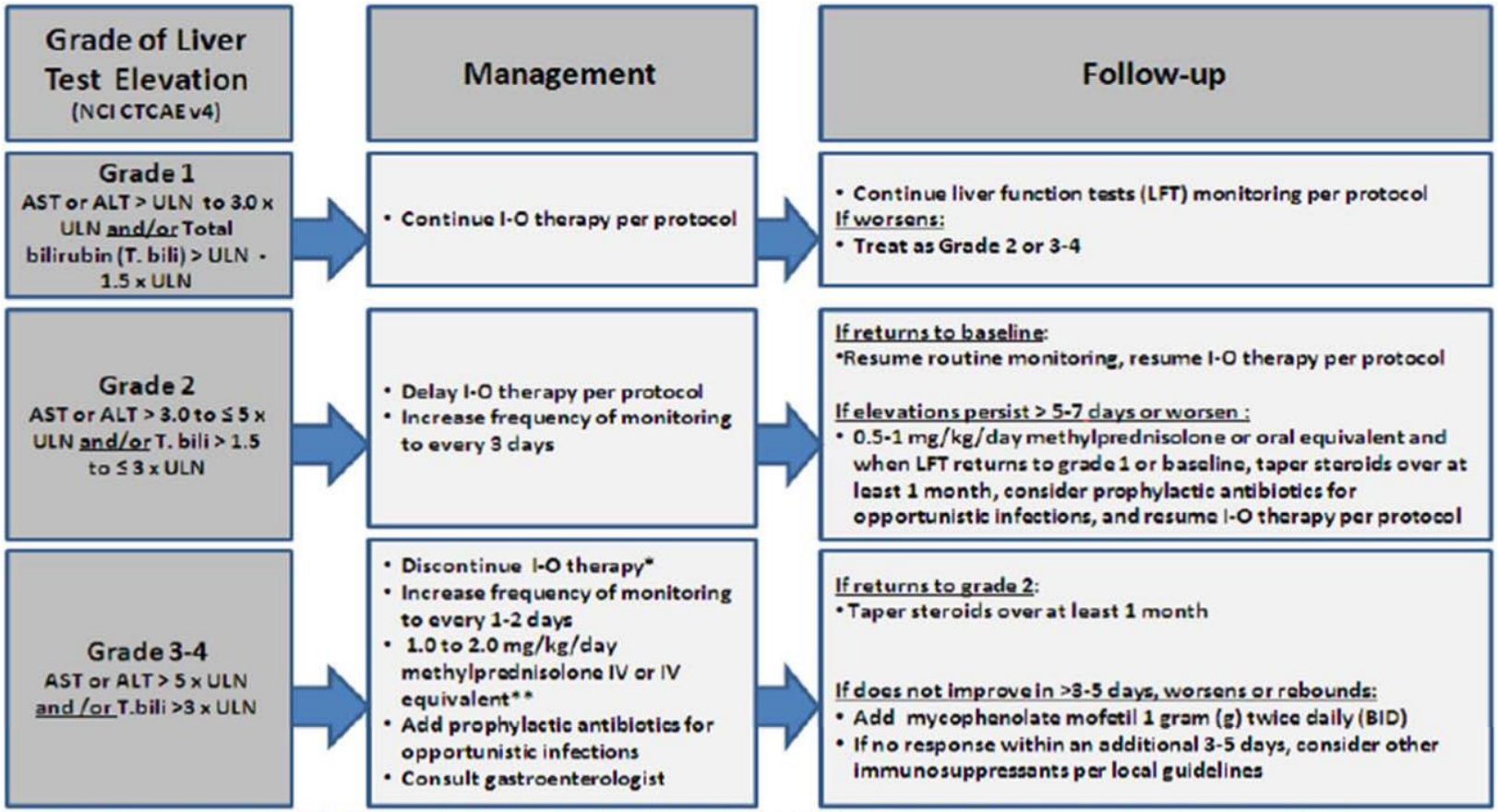
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



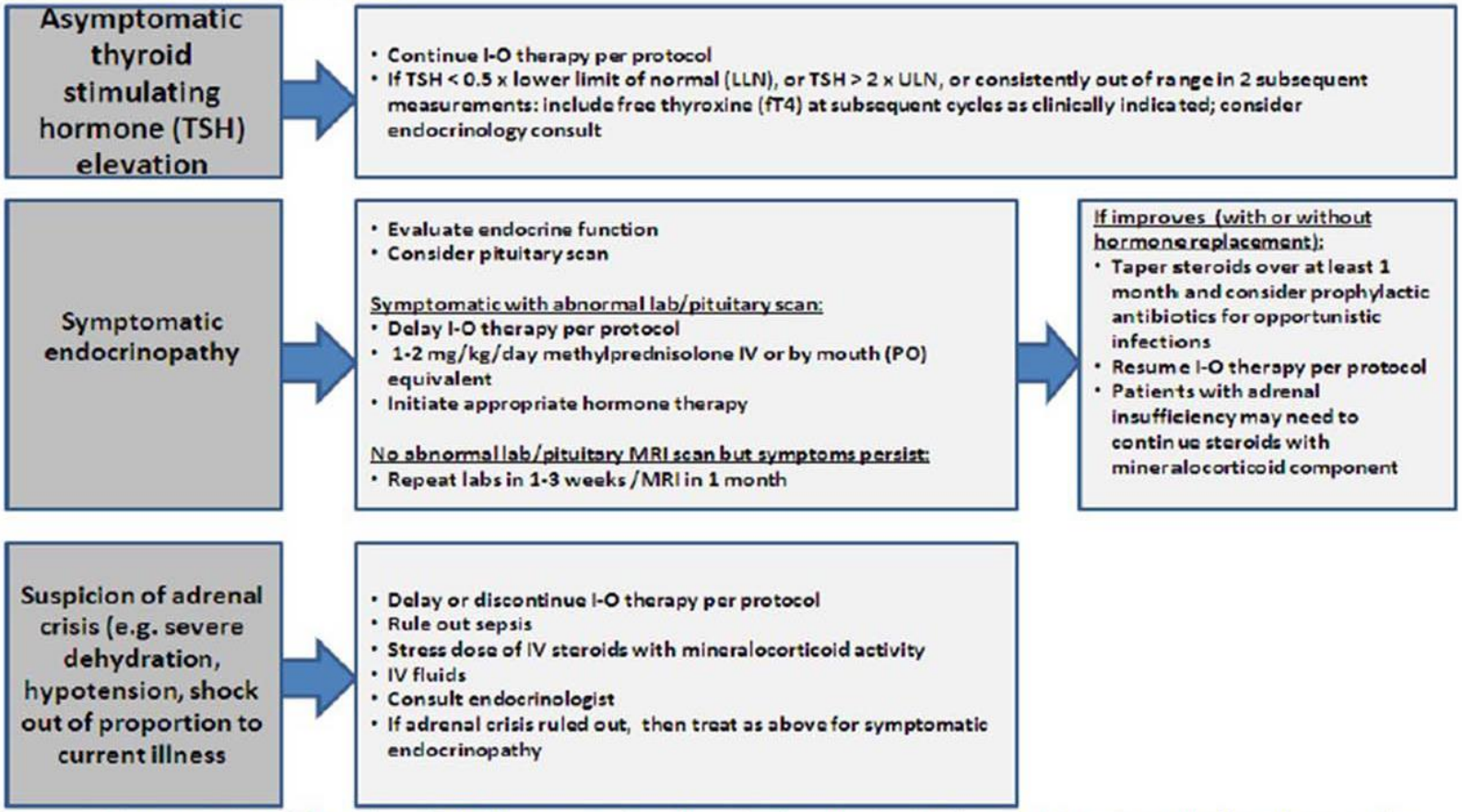
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

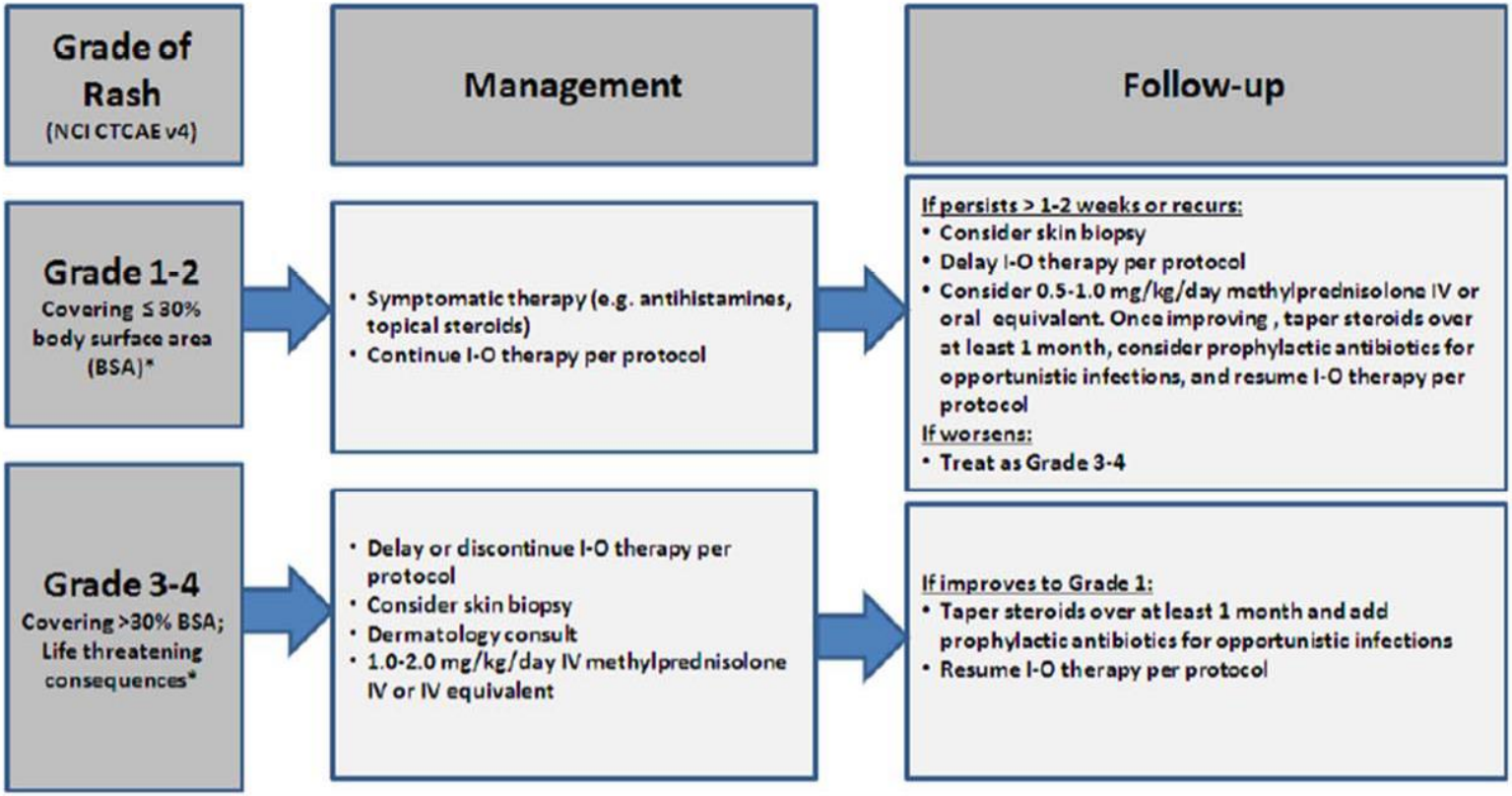
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

22. APPENDIX D: DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLANTABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, OHRP, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, [redacted] will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Require all DFCI and Participating Institution Institutional Review Boards' (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor and as approved by BMS.
- Identify and qualify Participating Institutions and obtain accrual projections prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Maintain FDA correspondence, as applicable.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal Wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Review registration materials for eligibility and register participants from Participating Institutions
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per institutional requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.

- Submit Serious Adverse Event (SAE) reports to IRB per local requirements and to the Coordinating Center, in accordance with protocol requirements.
- Submit protocol deviations and violations to IRB per local requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with DFCI ODQ auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the use and disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned unique subject number (as described below)

be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

- Informed consent must be obtained from subjects before they can be screened. A patient will be considered "in screening" when he/she has signed the IRB approved Informed Consent Form.
- Each patient screened must be documented on the Potential Patient/Pre-Screening Log or equivalent site form/software. The Potential Patient Log/Pre-Screening Log is to aid in fulfilling the ICH requirement of maintaining a confidential list of patient names. It should be stored in the site study files.
- Eligibility Criteria Worksheet is provided as a tool for registration.
- Once the investigator verifies the patient is eligible, the lead site (DFCI) will formally register the patient in the DF/HCC Clinical Trial Management System (CTMS) and enter the On Study Date. The sequence number used at screening will remain the same for the remainder of the study to identify the enrolled patient.
  - Subjects must be registered prior to starting protocol therapy and begin therapy within five business days of the lead site (DFCI) entering the On Study Date into the DF/HCC Clinical Trial Management System (CTMS).

Participant Registration and Randomization
All subjects must be registered by the lead site (DFCI) through the DF/HCC Clinical Trial Management System (CTMS) in accordance with section 5 of the protocol. A subject is considered registered when an "On Study" date is entered into OnCore.

- To register a participant, the following documents should be completed by the Participating Institution and maintained in the Participating Institutions' records:
  - Signed informed consent document
  - HIPAA authorization form (if separate from the informed consent document)
  - Other appropriate forms (See Section 5 of the Protocol)

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Registration can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy

Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, Coordinating Center requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique sequence number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this sequence number to identify the subject.

Protocol Deviations, Exceptions, and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol deviations occurring at their

site. The DF/HCC Sponsor will also be responsible for ensuring that all protocol deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported to the DF/HCC Sponsor within 1 business days of becoming aware of the event.

Additional safety assessments and toxicity monitoring is outlined in the protocol.

Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 12.

Participating Institutions must report the SAEs to the Coordinating Center according to the protocol.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the protocol requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

Guidelines for Processing IND Safety Reports
The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management
Data will be handled and recorded in accordance with Section 15 of the protocol.

Data Forms Review
Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG
For the Nivolumumab and Ipilimumab, the site will order drug from Bristol-Myers Squibb (BMS). Drug will be supplied in boxes. Outside sites will receive their own supply of drug.

- Once site has IRB approval, the Coordinating Center will send initial drug request Form to Bristol-Myers Squibb (BMS) for shipment.
- Initial orders will be on site no later than three weeks from request date.
- Resupply orders will be on site no later than one week from request date.
- Fill out Bristol-Myers Squibb (BMS) Drug Request Form and email as needed (NO AUTOMATIC REFILLS)

The ordering of investigational agent is specified in the protocol Section 11.1.

5. MONITORING: QUALITY CONTROL
The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance
The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

DFCI will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences.

Remote Monitoring
Data will be monitored remotely throughout the study both manually and electronically. Data will be assessed for completeness and correctness by DFCI monitoring staff. A Missing Forms Report (MFR) will be run on a regular basis, and queries will be issued based on the results to site personnel. Site personnel will make all corrections and/or notations as appropriate.

On-Site Monitoring will occur per section 14.4 of the protocol.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, and DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.