TITLE: Phase II study of Nivolumab/Ipilimumab plus Cabozantinib in patients with unresectable advanced melanoma

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PROTOCOL

TITLE:	Phase II study of Nivolumab/Ipilimumab plus Cabozantinib in patients with unresectable advanced melanoma
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TEST PRODUCTS:	Nivolumab Ipilimumab Cabozantinib
INDICATION:	Advanced melanoma
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1.0 SYNOPSIS

TITLE	Phase II study of Nivolumab/Ipilimumab plus Cabozantinib in patients with unresectable advanced melanoma
SHORT TITLE	Nivolumab/Ipilimumab plus Cabozantinib in Advanced Melanoma
PHASE	II
OBJECTIVES	*Primary objective:* 1. To determine progression free survival (PFS) for nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma *Secondary objectives:* 1. To determine the response rate of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma 2. To determine the overall survival (OS) of patients with unresectable advanced melanoma treated with nivolumab/ipilimumab plus cabozantinib 3. To determine the safety profile of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma *Exploratory objectives:* 1. To determine associations between baseline tumor mutational burden (TMB), angiogenesis pathways, and immunophenotyping with clinical activity of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma 2. To determine associations between baseline mutations in genes regulating anti-tumor immunity with tumor immunophenotype and clinical activity of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma 3. To assess on treatment biopsy for evidence of increased immune infiltration, vascularization, and MHC expression to nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma
STUDY DESIGN	In this phase II advanced melanoma study, all patients will receive treatment with nivolumab/ipilimumab plus cabozantinib for a 12 week induction period followed by nivolumab plus cabozantinib maintanence to complete up to 2 years of therapy unless disease

	progression, dose limiting toxicity, provider/patient decision or patient withdrawal of consent occurs. The primary endpoint is the one year PFS rate. Patients will have staging scans at baseline and every 12 weeks during the first 2 years on study. Safety evaluations including labs, EKG and history and physical will occur at each visit. Baseline tumor sample is required and on treatment biopsy will be optional of superficial tumor in the skin, subcutaneous tissue or lymph node that is palpable.
KEY ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. All patients must have unresectable stage IIIb-IIId or IV melanoma by AJCC 8th edition. (Note: Patients with uveal melanoma are excluded from this study.) 2. Age ≥ 18 and ECOG Performance Status of 0 or 1. 3. Measurable disease by RECIST 1.1 4. Baseline tumor specimen available. (Note: unless waiver is granted) 5. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. 6. Adequate organ and marrow function. 7. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document. 8. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment. 9. Female subjects of childbearing potential must not be pregnant at screening. **Exclusion Criteria** 1. Prior treatment with anti-PD-1/PD-L1 therapy, anti-CTLA-4 therapy or cabozantinib. Prior adjuvant anti-PD-1 and/or anti-CTLA-4 therapy is allowed if relapse is greater than 6 months from last dose. 2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment. 3. Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 4 weeks before first dose of study treatment. 4. Radiation therapy for bone metastasis or brain metastasis within 2 weeks, any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment.

	5. Known brain metastases that are ≥10mm or cranial epidural disease unless adequately treated with radiosurgery and/or surgery (including radiosurgery). Eligible subjects must be neurologically asymptomatic and without corticosteroid requirement. Dexamethasone ≤ 2mg daily (or equivalent) will be allowed if discontinuation of corticosteroids is not feasible due to post-radiation effects and patient is asymptomatic. Patients with active, asymptomatic brain metastases that are <10mm and no corticosteroid requirement will be allowed without radiosurgery or surgery. 6. History of active autoimmune disorder requiring immunosuppressive agents. Patients with autoimmune disorders considered low risk, such as vitiligo and thyroiditis, will be allowed. 7. Concomitant anticoagulation with coumarin agents (eg, warfarin), direct thrombin inhibitors (e.g., dabigatran), betrixaban, or platelet inhibitors (eg, clopidogrel). Allowed anticoagulants are the following: a. Prophylactic use of Low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH) are permitted. b. Anticoagulation with therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. 8. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment. 9. The subject has uncontrolled, significant intercurrent or recent illness. 10. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. 11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment. 12. Pregnant or lactating females. 13. Inability to swallow tablets. 14. Previously identified allergy or hypersensitivity to components of the study treatment formulations. 15. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or

	localized, low grade tumors deemed cured and not treated with systemic therapy. 16. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
STATISTICAL CONSIDERATIONS	The primary endpoint for the study is 1 year landmark PFS rate. The historical control with nivo/ipi from the Checkmate 067 study is a 1 year PFS rate of ~50% [1]. The target for this study is 75% (improvement by 25%), which is deemed a clinically meaning improvement. This will require a sample size of 23 for a one sided alpha of 0.05 and the power of 0.80. A simon two stage approach will be utilized. The study will be stopped if there 7 or few subjects out of 14 subjects progression free at 1 year. If the study meets criteria for continuation to the second stage, an additional 9 subjects will be enrolled. In the final analysis, the null hypothesis will be rejected (i.e., accept the alternative hypothesis of improved efficacy with nivolumab/ipilimumab plus cabozantinib) if 16 subjects or more are progression free at 1 year of the 23 total subjects. Assuming a dropout rate of 15% during the time of study, up to 27 subjects will be enrolled.
TOTAL NUMBER OF SUBJECTS	27 enrolled subjects (23 subjects required for primary endpoint analysis)
ESTIMATED ENROLLMENT PERIOD	Estimated 18 months
ESTIMATED STUDY DURATION	Estimated 42 months (2 years beyond last patient enrolled)

2.0 INTRODUCTION

Combination immune checkpoint blockade with nivolumab and ipilimumab demonstrated objective responses in 58% of patients with advanced unresectable melanoma in the Checkmate 067 study [1]. While responses and progression free survival (PFS) are superior with nivolumab/ipilimumab over monotherapy, not all patients have long-term benefit. Twenty four percent of patients had progressive disease as their best response and over 30% of patients progressed after initial disease control. At one year, the PFS rate was 49%. In addition, several patient subgroups had less clinical benefit as demonstrated by shorter progression free survival in patients with PD-L1 low tumors, high LDH levels, M1c disease, or greater than 3 disease sites. Other studies have also shown that patients with low interferon gamma gene expression scores or low baseline tumor immune infiltrate are less likely to have a response to standard anti-PD-1 based therapy [2]. Therefore, further immunotherapy strategies are needed.

Targeting vascular signaling in the tumor microenvironment, along with other oncogenic pathways, can enhance the anti-tumor activity of immune checkpoint therapies. A phase 1 study ipilimumab in combination with the anti-VEGF antibody bevacizumab in patients with advanced melanoma demonstrated an increased response rate and longer median overall survival compared to historical data [3]. On-treatment tumor biopsies revealed activated vessel endothelium with extensive CD8+ and macrophage cell infiltration. Similarly, clinical trials of combination therapy with the VEGFR inhibitor axitinib plus pembrolizumab and bevacizumab plus atezolizumab have demonstrated markedly increased anti-tumor activity in patients with advanced renal cell carcinoma [4, 5]. In addition to increased immune cell infiltration, targeting VEGF/R can enhance T-cell priming and dendritic cell maturation, as well as increased MHC class antigen presentation on tumor cells, which can lead to greater anti-tumor immune responses [6-8].

Cabozantinib, an inhibitor of c-MET, VEGFR2, and other receptor tyrosine kinases (RTKs) may be able to further augment immune responses in combination with nivolumab plus ipilimumab. In a phase II study of cabozantinib 55% of patients with advanced melanoma demonstrated tumor regression in the first 12 weeks [9]. Our team performed biomarker analyses on baseline tumor samples from this study [Gibney GT, unpublished data]. Patients with tumor regression and stable disease had greater tumor mutational burden (TMB) than those with disease progression. The high TMB status has been associated with greater neoantigen exposure and clinical activity with immunotherapies [2], suggesting cabozantinib also functions as an immune agent in addition to its direct anti-tumor and anti-angiogenic activities. Other studies with cabozantinib have also demonstrated immune modulatory effects by decreasing Treg populations in the tumor microenvironment and by increasing cytotoxic lymphocyte and decreasing immunosuppressive myeloid cell levels in the peripheral blood [10, 11]. A phase I study of nivolumab/ipilimumab plus cabozantinib in a range of genitourinary malignancies demonstrated clinical activity and an acceptable safety profile with only 11% of patients discontinuing therapy due to toxicity [12].

We propose a single arm phase II study of nivolumab/ipilimumab plus cabozantinib in patients with advanced melanoma, along with correlative studies to assess biologic/immune activity and predictive biomarkers.

Hypotheses:

1) Nivolumab/ipilimumab plus cabozantinib will demonstrate greater clinical activity compared to either nivolumab/ipilimumab or cabozantinib alone (historical data) in patients with unresectable advanced melanoma.
2) Nivolumab/ipilimumab plus cabozantinib will demonstrate clinical activity in patients with low tumor PD-L1 and interferon (IFN) gamma gene expression profile (GEP) scores, particularly those who have high TMB.

3.0 BACKGROUND INFORMATION

3.1 Anti-PD-1 monotherapy in advanced melanoma

Nivolumab (BMS-936558; anti-PD-1 monoclonal antibody) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promote immune responses and antigen-specific T cell responses to both foreign and self antigens. PD-1 receptor blockade by nivolumab is an effective approach for immunotherapy of a variety of solid tumors. Results from a Phase 1/2 study (CA209-003) indicated that nivolumab was active in multiple tumor types including advanced melanoma, non-small cell lung carcinoma (NSCLC) and renal cell carcinoma (RCC) [13]. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). Among 106 subjects with advanced melanoma who received nivolumab and were evaluable for response, the preliminary objective response rates (ORR) were 6/17 (35%), 5/18 (28%), 11/34 (32%), 7/17 (41%), and 4/20 (20%) for melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively [14]. Duration of response range from 3.6 to 11.2, 1.8 to 9.2, 1.9 to 24.9, 9.2 to 22.4, and 17.0 to 25.7 months in the melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Stable disease ≥24 weeks occurred in an additional 1/18 (6%), 4/34 (12%), 1/17(6%) melanoma subjects at 0.3, 1, and 3 mg/kg, respectively. Finally, the PFS-24 week was 41%, 33%, 48%, 55%, and 30% in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.

In a Phase 3 trial (CheckMate 066), nivolumab monotherapy demonstrated an improvement in overall survival (OS) versus dacarbazine in treatment-naïve patients with BRAF wild-type tumors [15]. Follow-up of patients in this study has shown 2-year OS rates of 58% with nivolumab and 27% with dacarbazine. Frontline nivolumab monotherapy has also been studied in the CheckMate 067, which included both BRAF wild-type and mutant melanoma [1]. The objective response rate was 44% with 3 year PFS and OS rates of 32% and 52% respectively.

Pembrolizumab (MK-3475) is a selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The variable region sequences of a mouse antihuman PD-1 antibody were attached into a human IgG immunoglobulin with a stabilizing S228P Fc alteration, where the IgG4 subtype does not engage Fc receptors or activate complement, therefore avoiding cytotoxic effects of the antibody when it binds to the T cells that are intended to activate. Results from a Phase 1 study (KEYNOTE 001) demonstrated that pembrolizumab is active in patients with advanced melanoma [16]. In the overall population, the objective response rate was 33%, with

74% of responses ongoing at the time of data cut. For treatment naïve patients, the objective response rate was 45% and 12 month PFS rate was 54%.

Similarly, the randomized KEYNOTE 006 study confirmed the efficacy of pembrolizumab in advanced melanoma patients, demonstrating superiority over ipilimumab [17]. In the treatment naïve population, the objective response rate was 47% by immune-related response criteria (irRC) and the 12-, 24-, and 36-month PFS rates were ~45%, 34%, and 31%, respectively.

Overall, anti-PD-1 monotherapy with pembrolizumab and nivolumab have been well tolerated. The most common adverse events include fatigue, pruritus, rash, diarrhea, nausea, and arthralgias [1, 16]. Most are low grade events that do not require treatment interruption or discontinuation. Severe treatment related adverse events have been reported in up to 21% of patients treated with anti-PD-1 monotherapy [1]. The more common severe adverse events occurring in 1-4% of patients include fatigue, rash, diarrhea/colitis, and elevated transaminase levels/hepatitis. Refer to Table 3-1. Adverse events with anti-PD-1 and anti-CTLA-4 therapies are usually immune mediated events and specific treatment algorithms for management have been published [18].

Table 3-1. Treatment related adverse events (occurring in more than 5% of patients) on CheckMate 067.

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

3.2. Ipilimumab monotherapy in advanced melanoma

Ipilimumab is a fully humanized IgG1 monoclonal antibody (mAb) binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for patients with metastatic melanoma (Yervoy® Prescribing Information, 2018) and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine [19, 20].

In melanoma, the completed Phase 3 study MDX010-20 demonstrated a clinically meaningful and statistically significant survival benefit with ipilimumab in pre-treated advanced melanoma [19]. The study compared the OS of ipilimumab plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS (P = 0.0004 and 0.0026, respectively). The 1-year survival for the two ipilimumab-containing groups, respectively, was 44% and 46% respectively, compared to 25% for the gp100 control group. The 2-year survival was 22%, 24% and 14% respectively. The median survival was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively.

Ipilimumab has been shown to produce prolonged survival in over 20% of patients based on long-term follow up on a composite analysis of 12 clinical studies with ipilimumab in advanced melanoma [21]. In this series, 1,257 patients were pretreated and 604 were previously untreated for metastatic disease. The dose of ipilimumab was 3 mg/kg for 965 patients and 10 mg/kg for 706 patients. The median overall survival for the whole patient population was 11.4 months. Most importantly, the survival curve reached a plateau of 22% at 3 years, which extended to 10 years, and it was independent of the dose.

Both the KEYNOTE 006 and CheckMate 067 studies have demonstrated superior efficacy with anti-PD1 therapy (pembrolizumab and nivolumab) over ipilimumab [1, 17]. Hazard ratios for PFS and OS in treatment naïve patients with anti-PD-1 versus ipilimumab were reported to be 0.54-0.55 and 0.65- 0.73, respectively (all statistically significant with $P<0.05$). Based on this data, ipilimumab is now considered a second/third line agent or used in combination with anti-PD-1 therapy (see Nivolumab/Ipilimumab section 3.3).

Most common adverse reactions (≥5%) with ipilimumab as a single agent are fatigue, diarrhea, pruritus, rash, and colitis [YERVOY package insert, 2018]. These usually are immune-related toxicities based on the mechanism of action for anti-CTLA-4 therapy. Refer to package insert for further information on adverse reactions. Severe grade 3-4 adverse events (treatment related) have been reported in 23-28% patients receiving ipilimumab at 3mg/kg [1, 19]. See Table 3-1.

3.3 Nivolumab plus Ipilimumab

Combination therapy has emerged as an effective treatment option for advanced melanoma. The efficacy data further support the combination of nivolumab plus ipilimumab as first-line treatment option for patients with advanced melanoma, regardless of BRAF mutation status, based on the results of the CheckMate 069 and 067 studies [1, 22]. The combination of these immune checkpoint inhibitors was approved for the treatment of unresectable or metastatic melanoma in the USA in January 2016 and in the European Union in May 2016.

In a Phase 2 trial of treatment-naïve patients with BRAF wild-type melanoma (CheckMate 069), 142 patients with previously untreated advanced melanoma were randomized in a 2:1 ratio to either receive both ipilimumab (3mg/kg) and nivolumab (1mg/kg) every 3 weeks followed by nivolumab (3mg/kg), or ipilimumab (3mg/kg) and placebo every 3 weeks followed by placebo every 2 weeks [22]. The combination of nivolumab and ipilimumab demonstrated a statistically significant improvement in ORR and longer PFS compared with ipilimumab alone with an ORR

of 61% (44/72) in patients treated with the combination versus 11% (4/37) in ipilimumab monotherapy. Complete responses were reported in 22% (16/72) in the combination group, and no patients in the ipilimumab monotherapy group. With a minimum follow-up period of 11 months, median PFS and median duration of response were not reached in the combination group, compared with mPFS of 4.4 months with ipilimumab monotherapy.

In CheckMate 067 study, 945 patients with previously untreated advanced or metastatic melanoma were randomized in a 1:1:1 ratio to receive nivolumab monotherapy, nivolumab (1mg/kg) and ipilimumab (3mg/kg) combination therapy, or ipilimumab monotherapy [1]. The study was primarily powered to demonstrate efficacy differences between nivolumab versus ipilimumab and nivolumab/ipilimumab versus ipilimumab. The observed ORRs were 43.7% in nivolumab monotherapy, 57.6% in the combination group, and 19% in ipilimumab monotherapy. Nivolumab/ipilimumab as well as nivolumab monotherapy demonstrated superior PFS and OS compared to ipilimumab monotherapy. The 12 month PFS rate was 42% and 49% in the nivolumab monotherapy and nivolumab/ipilimumab combination groups, respectively. Longer follow up showed the 3 year PFS rates were 32% and 39%, respectively. Similarly, the overall survival at 3 years was numerically higher with nivolumab/ipilimumab versus nivolumab alone (58% versus 52%).

While response rates are greater with nivolumab/ipilimumab combination therapy, the serious adverse event rates are also greater compared to monotherapies. In the CheckMate 067 study, 59% of patients experienced a grade 3-4 treatment related adverse event with nivolumab/ipilimumab (see Table 3-1) [1]. The more concerning grade 3-4 events included diarrhea/colitis and increased transaminase levels/hepatitis, seen in up to 9% of patients each. To address this issue, alternative dosing for anti-PD-1/anti-CTLA-4 combination therapy in advanced melanoma has been investigated. The randomized, double blinded phase 3b/4 CheckMate 511 study compared the standard nivolumab 1mg/kg plus ipilimumab 3mg/kg (nivo1/ipi3) dose levels to the inverse nivolumab 3mg/kg plus ipilimumab 1mg/kg (nivo3/ipi1) dose levels in patients with advanced melanoma [23]. Patients in both arms then continued on with maintenance nivolumab 480mg every 4 weeks if tolerating with disease control. The primary endpoint of safety showed a significant reduction in treatment related grade 3-4 adverse events with nivo3/ipi1 versus nivo1/ipi3 (34% versus 48%, P=0.0059). Efficacy was similar in both group but still early in follow up. The 12 month PFS rate was 46-47% between the two groups. A separate study (KEYNOTE 029) supports the use of lower dose ipilimumab in combination with anti-PD-1 therapy [24]. In this study of 110 patients with advanced melanoma treated with pembrolizumab 2mg/kg plus ipilimumab 1mg/kg, the treatment related grade 3-4 adverse event rate was 45% (immune-related grade 3-4 was 27%).

3.4 Cabozantinib

Cabozantinib (also known at XL184) is an oral tyrosine kinase inhibitor that targets VEGFR2, c-MET, AXL, and other RTKs with half maximal inhibitory concentration (IC50) in the low nanomolar range [25]. Clinical activity with cabozantinib has been demonstrated in a range of tumor types, including advanced hepatocellular carcinoma, renal cell carcinoma and medullary thyroid cancer where the drug is now FDA approved [26-30]. The predicted terminal half life of cabozantinib at the approved dose of 60mg daily in RCC patients was 99hrs [Investigator's

Brochure version 14]. Of note, different pharmacokinetics was observed in medullary thyroid cancer patients. Cabozantinib is also highly protein bound in human plasma (≥ 99.7%).

Cabozantinib has previously been studied in melanoma patients as cohort in a larger phase 2 randomized discontinuation trial (RDT) [9]. A total of 77 patients with advanced melanoma (62% cutaneous melanoma) were treated with cabozantinib at 100mg daily for a 12 week lead in period. Patients with stable disease after 12 weeks were randomized to either continue on cabozantinib or discontinue and evaluate for progression free survival (those patients with partial or complete responses would stay on drug). At week 12, the ORR was 5%; however 55% of patients with evaluable disease demonstrated some tumor regression (refer to Figure 3-1). Of the 26 patients with stable disease and randomized to stay on treatment or discontinue, the median PFS was 4.1 months versus 2.8 months (HR 0.59, P=0.284). The median overall survival of the entire cohort was 9.4 months.

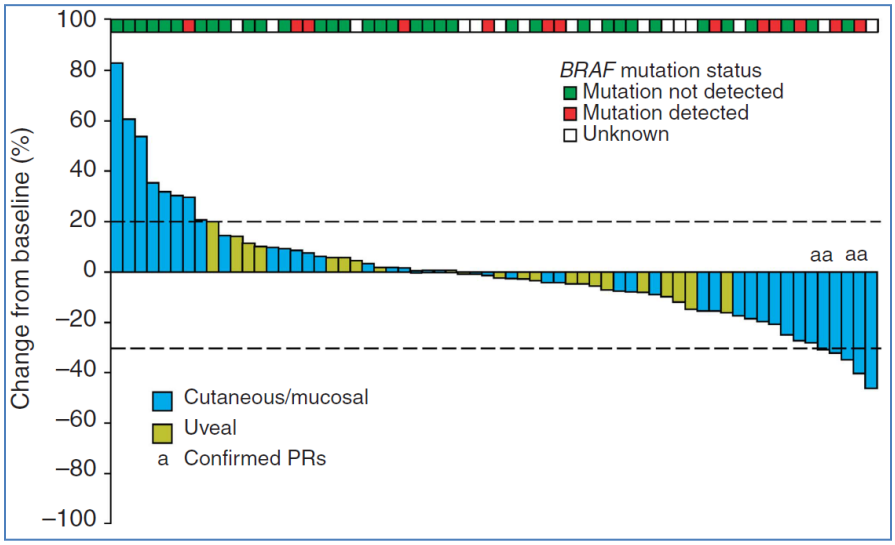


Figure 3-1. Best change in tumor response (RECIST) at week 12 from baseline on the Phase 2 RDT of cabozantinib in patients with advanced melanoma. N=64 for evaluable patients.

The most common adverse events (≥ 25%) reported for cabozantinib are diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation (Cabozantinib package insert, 2018). At the continuous 60mg daily dosing of cabozantinib in patients with advanced RCC, the treatment emergent grade 3-4 adverse event rate was 68% [27]. Dose reductions occurred in 60% of patients and drug discontinuation due to adverse event occurred in 9% of patients. In the phase 2 RDT of cabozantinib (100mg daily) in patients with advanced melanoma, safety data was reported on the 12 week lead in period [9]. During this window, dose reduction occurred in 29% of patients and drug discontinuation due to adverse event occurred in 8% of patients. The most common treatment emergent grade 3-4 events were fatigue (14%), hypertension (10%), and abdominal pain (8%) (see Table 3-2).

Table 3-2. Most frequently reported adverse events during the lead in stage regardless of causality on the phase II RDT of cabozantinib in patients with advanced melanoma.

	All grades (*N* = 77)	Grade ⩾3[a] (*N* = 77)
AE[b]	*n* (%)	*n* (%)
Fatigue	46 (60)	11 (14)
Diarrhoea	44 (57)	2 (3)
Nausea	39 (51)	1 (1)
Decreased appetite	35 (45)	0 (0)
Abdominal pain	24 (31)	6 (8)
Vomiting	23 (30)	2 (3)
Hypertension	22 (29)	8 (10)
Constipation	20 (26)	3 (4)
Dysgeusia	20 (26)	0 (0)
Hand-foot syndrome	19 (25)	4 (5)
Stomatitis	19 (25)	0 (0)
Aspartate aminotransferase increased	17 (22)	2 (3)
Dry mouth	17 (22)	0 (0)
Dysphonia	17 (22)	0 (0)
Rash	16 (21)	0 (0)
Weight decreased	16 (21)	0 (0)
Dyspnoea	13 (17)	3 (4)
Mucosal inflammation	13 (17)	0 (0)
Alanine aminotransferase increased	12 (16)	2 (3)
Hypomagnesaemia	12 (16)	0 (0)
Asthenia	11 (14)	4 (5)
Abdominal pain upper	11 (14)	1 (1)
Dizziness	11 (14)	1 (1)
Oral pain	11 (14)	1 (1)
Urinary tract infection	11 (14)	0 (0)
Back pain	10 (13)	4 (5)
Hypokalaemia	10 (13)	4 (5)
Pain in extremity	10 (13)	3 (4)
Dry skin	10 (13)	0 (0)

3.5 Nivolumab/Ipilimumab plus Cabozanitinib

The triple combination of nivolumab/ipilimumab plus cabozantinib has been evaluated in a metastatic urothelial cancer and other genitourinary malignancies (non-clear cell RCC) [12]. In this phase 1 study, nivolumab/ipilimumab plus cabozantinib was studied in part 2, after nivolumab plus cabozantinib was cleared. Primary endpoint was to define maximum tolerated dose and the recommended phase 2 dose. Three dose levels of the triple combination were planned: cohort 5 – cabozantinib 40mg PO daily + nivo1/ipi1, cohort 6 - cabozantinib 40mg PO daily + nivo3/ipi1, and cohort 7 – cabozantinib 60mg PO daily + nivo3/ipi1. Data was presented on 18 subjects with a median follow up of 12.8 months. All grade adverse events were seen in 16/18 subjects (89%) and grade 3-4 adverse events were seen in 13/18 subjects (72%) (this was similar to the adverse event data for nivolumab/cabozantinib). Treatment related adverse events leading to drug discontinuation occurred in 2/18 (11.1%) during the maintenance phase with

nivolumab plus cabozantinib (colitis and hepatitis). Dose holds for nivolumab and cabozantinib occurred in 7/18 (39%) and 12/18 (67%) of subjects, respectively. Cabozantinib was dose reduced in 6/18 (33%) of subjects. Treatment related grade 3-4 adverse events occurring in 2 or more patients included fatigue, hypertension, lymphopenia, hypophosphatemia, hyponatremia, elevated ALT level, and elevated lipase level. Only 1 case each of grade 3-4 immune colitis and hepatitis were reported. Refer to tables 3-3 and 3-4 for adverse event summaries for the triple combinations. Of the 18 subjects treated with nivolumab/ipilimumab plus cabozantinib, 4 (22%) demonstrated an objective response, which included patients with advanced/metastatic penile cancer (n=1), sarcomatoid RCC (n=1), and urothelial carcinoma of the bladder (n=2). The recommended phase 2 dose was cabozantinib 40mg PO daily plus nivolumab 3mg/kg and ipilimumab 1mg/kg.

Table 3-3. Select clinical treatment related adverse events: any grade ≥ 20% of patients and any irAE from the phase 1 study of Cabozantinib plus Nivolumab/Ipilimumab.

Event	Cabozantinib-Nivolumab-ipilimumab (n=18) #	
n (%)	Any Grade	G3-G4
Fatigue	15 (83)	2 (11)
Nausea or vomiting	12 (67)	-
Diarrhea	15 (83)	1(5)
Skin disorders (pruritus or dry skin or rash)	14 (78)	-
Anorexia	10 (55)	1(5)
Oral Mucositis or sore throat	8 (44)	1(5)
Hoarseness	8 (44)	-
Arthralgia and myalgia	8 (44)	-
Palmar-plantar erythrodysesthesia	4 (22)	-
Weight loss	7 (39)	-
Abdominal pain	3 (17)	-
Hypertension	3 (17)	3 (17)
Thromboembolic events	1(5)	1(5)
Infection (pyelonephritis)	-	-
irAE		
Colitis	1 (5) *	1 (5)*
Aseptic meningitis	-	-
Hypogonadism	-	-
Pneumonitis	2 (11)*	-
Hepatitis	1 (5) *	1 (5)*

Table 3-4. Laboratory abnormalities: any grade ≥ 20% of patients and any irAE from the phase 1 study of Cabozantinib plus Nivolumab/Ipilimumab.

Events	Cabozantinib-nivolumab-ipilimumab (n=18)	
n (%)	Any Grade	G3-G4
Hematology		
Anemia	9(50)	-
Neutrophil count decreased	3(17)	-
Lymphocyte count decreased	7(39)	3(17)
Platelet Count decreased	7(39)	-
Electrolytes		
Hypophosphatemia	11(61)	4(22)
Hypomagnesemia	6(33)	-
Hyponatremia	6(33)	2(11)
Hypocalcemia	7(39)	1(5)
Hypokalemia	5(28)	-
Renal		
Proteinuria	6(33)	-
Hepatic		
ALT increased	10(61)	2(11)
AST increased	8(44)	1(5)
Hypoalbuminemia	5(28)	-
Pancreatic		
Amylase increased	4(22)	1(5)
Lipase increased	8(44)	4(22)
Endocrine		
Hypothyroidism	8(44)	-
Hyperthyroidism	2(11)	-

4.0 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
To determine PFS for nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To determine the 1 year PFS rate for nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma using imRECIST
Secondary Objectives	**Secondary Endpoints**
To determine the response rate of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To determine the ORR by imRECIST of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma
To determine the OS of patients with unresectable advanced melanoma treated with nivolumab/ipilimumab plus cabozantinib	To determine the median and 3 year OS rate of patients with unresectable advanced melanoma treated with nivolumab/ipilimumab plus cabozantinib
To determine the safety profile of nivolumab/ipilimumab plus cabozantinib in	To determine the rate of all grade and grade 3-5 adverse events (treatment emergent and treatment related)

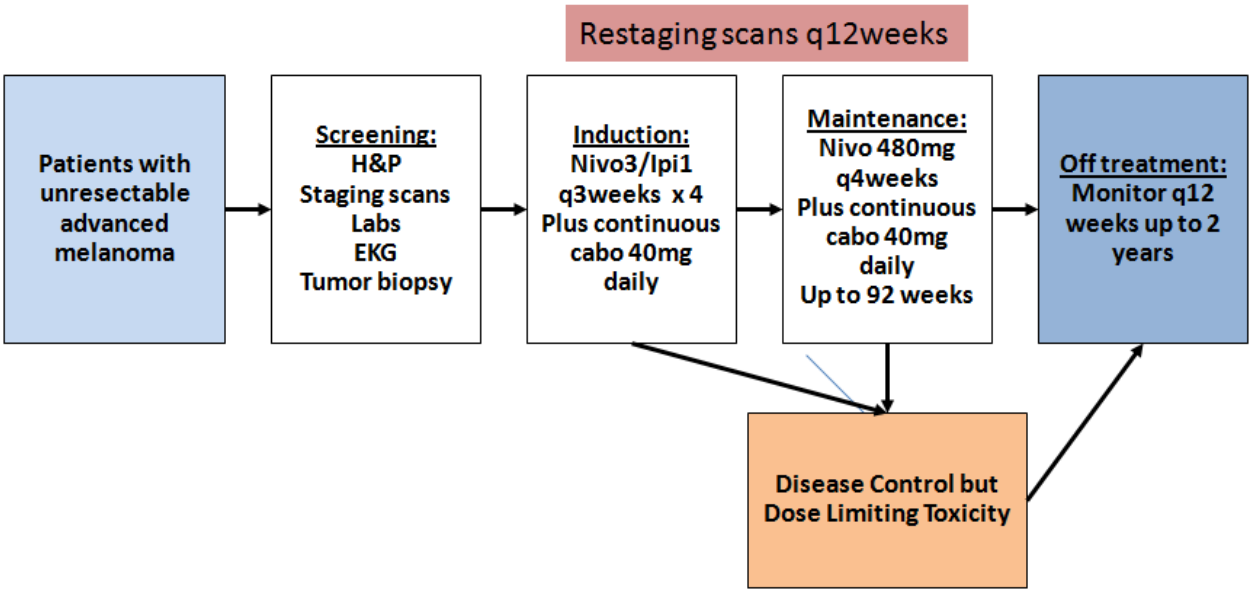
patients with unresectable advanced melanoma	
To determine the tolerability of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To determine the rate of discontinuation of study drug(s) due to adverse events
Exploratory Objectives	
To determine associations between baseline tumor mutational burden (TMB), angiogenesis pathways, and immunophenotyping with clinical activity of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To analyze molecular profiles based on whole exome sequencing (WES), PD-L1 immunohistochemistry and RNAseq from baseline tumors and correlate to ORR, PFS, and OS in patients with unresectable advanced melanoma treated with nivolumab/ipilimumab plus cabozantinib
To determine associations between baseline mutations in genes regulating anti-tumor immunity with tumor immunophenotype and clinical activity of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To determine if loss of critical immune genes (such as IFN receptor and MHC) are associated with a low IFN gamma gene expression profile and impact on baseline tumors and correlate to ORR, PFS, and OS in patients with unresectable advanced melanoma treated with nivolumab/ipilimumab plus cabozantinib
To assess on treatment biopsy for evidence of increased immune infiltration, vascularization, and MHC expression to nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma	To determine change in immune cell populations, CD31 vascularization, and MHC class I expression by multiplex immunofluorescense (IF) between baseline and on treatment tumor specimens

5.0 STUDY DESIGN

5.1 Overall Schema

Subjects with unresectable advanced melanoma meeting eligibility criteria (refer to Section 6.0) will be screened for participation on the protocol. The screening phase will include obtaining baseline imaging studies, labs, history & physical, EKG, and collection of a fresh tumor biopsy or archived tumor specimen (refer to Table 7-1). Once meeting eligibility criteria and enrolled on study, subjects will begin treatment with nivolumab/ipilimumab and cabozantinib starting on day 1 of cycle 1.The treatment schedule and follow up is outlined further in the schema Figure 5-1 and Table 7-1. Patients who attain confirmed response or stable disease and are able to tolerate study drugs will continue treatment for up to 2 years. Discontinuation after 1 year but prior to 2 years will be permitted at the discretion of the treating investigator in patients with disease control achieving either a complete or partial response.

Figure 5-1. Treatment Schema



5.2 Study Drug Dosing

Induction phase:

Nivolumab 3mg/kg IV plus Ipilimumab 1mg/kg IV every 3 weeks x 4 cycles (12 week period)

Cabozantinib 40mg PO daily for 12 weeks

When nivolumab and ipilimumab are to be administered on the same day during the induction phase, nivolumab is to be administered first over 30 minutes. 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 be the ipilimumab over 30 minutes and will start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation. Infusion window of -5 minutes/+ 10 minutes for each study drug.

Cabozantinib is an oral tablet taken by the patient daily. Participant is to self administer at the same time every day +/- 1 hour window. Participant is not to eat for at least 2 hours before and at least 1 hour after taking the medication.

A window of ± 3 days may be applied to all study visits.

Maintenance phase:

Nivolumab 480mg IV every 4 weeks for up to 92 weeks

Cabozantinib 40mg PO daily for up to 92 weeks

Maintenance therapy will continue for up to 92 weeks to complete 2 years total of treatment if tolerating therapy well and disease is controlled.

Nivolumab is administered over a 30 minute infusion without any premedication unless there is a prior history of infusion reaction. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab. Participant is to be observed following infusion to ensure no infusion reaction has occurred.

Cabozantinib is an oral tablet taken by the patient daily. Participant is to self administer at the same time every day +/- 1 hour window. Participant is not to eat for at least 2 hours before and at least 1 hour after taking the medication.

A window of ± 3 days may be applied to all study visits.

5.3 Biospecimen collection

Baseline tumor collection
Prior cycle 1 of study, all patients must have either an archived tumor specimen available or a fresh biopsy for confirmation of disease and correlative studies. Fresh tumor biopsies may be core needle, punch, or incisional/excisional biopsy. Patients without a safe site of biopsy (as assessed by treating provider) or archived specimen will be exempt from this requirement and may obtain a waiver from the principal investigator after discussion. **Refer to lab manual for specific details on handling, processing and storage.**

On treatment tumor collection
Fresh tumor collection at week 13 (refer to Table 7-1) will be optional in patients with a palpable superficial tumor in the skin, subcutaneous tissue or lymph node. This can be a core needle biopsy, punch biopsy, or incisional/excisional biopsy. Patients without a safe site of biopsy (as assessed by treating provider) will not be considered eligible for the optional biopsy. **Refer to lab manual for specific details on handling, processing and storage.**

At progression tumor collection
Fresh tumor collection at time of progression (refer to Table 7-1) will be optional. This can be a core needle biopsy, punch biopsy, or incisional/excisional biopsy. **Refer to lab manual for specific details on handling, processing and storage.**

Peripheral blood biospecimen collection
Blood samples for study of serum, peripheral blood mononuclear cells (PBMCs), and other components will be collected. Samples will be processed using standard protocols and stored at -

80 degrees Celsius for future analyses. **Refer to lab manual for specific details on handling, processing and storage.**

Stool biospecimen collection

Baseline stool samples will be collected from patients at the start of treatment. Patients will be given a stool kit (Omnigene®-Gut tube, and collection materials including a toilet hat and tool for stool transfer). Patients will need to provide the sample on day 1 of the first cycle (+/- 7 day window). **Refer to lab manual for specific details on handling, processing and storage.**

5.4 Study Treatment Discontinuation

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Sections 8.2.4.1;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator / Sponsor;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

6.0 INCLUSION/EXCLUSION CRITERIA

To be eligible for the study the subject must meet all of the inclusion and none of the exclusion criteria:

Inclusion Criteria

1. All patients must have unresectable stage IIIb-IIId or IV melanoma by AJCC 8th edition. *Note:* Patients with uveal melanoma are excluded from this study.
2. Age ≥ 18 and ECOG Performance Status of 0 or 1.
3. Measurable disease by imRECIST.
4. Baseline tumor specimen available – either archived tumor specimen collection within the past year and no intervening treatment or fresh tumor collection (A waiver may be considered for the baseline biopsy requirement after discussion with study principal investigator).
5. Recovery to baseline or ≤ Grade 1 CTCAE v4 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
6. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
   a. Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 GI/L) without granulocyte colony-stimulating factor support.
   b. White blood cell count ≥ 2500/mm^3 (≥ 2.5 GI/L).
   c. Platelets ≥ 100,000/mm^3 (≥ 100 GI/L) without transfusion.
   d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
   e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3 × upper limit of normal (ULN). ALP ≤ 5 × ULN with documented bone metastases.
   f. Total bilirubin ≤ 1.5 × ULN (for subjects with Gilbert's disease ≤ 3 × ULN).
   g. Serum albumin ≥ 2.8 g/dl.
   h. Serum creatinine ≤ 2.0 × ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:
      Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)
      Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85
   i. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol).
7. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.
8. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment.
9. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

Exclusion Criteria

1. Prior treatment with anti-PD-1/PD-L1 therapy, anti-CTLA-4 therapy or cabozantinib. Prior adjuvant anti-PD-1 and/or anti-CTLA-4 therapy is allowed if relapse is greater than 6 months from last dose.
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before first dose of study treatment.
3. Receipt of any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 4 weeks before first dose of study treatment.
4. Radiation therapy for bone metastasis or brain metastasis within 2 weeks, any other radiation therapy within 4 weeks before first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
5. Known brain metastases that are $\geq$10mm or cranial epidural disease unless adequately treated with radiosurgery and/or surgery. Patients with treated brain metastases need to be asymptomatic (no neurologic symptoms or stable neurologic deficit) and off corticosteroids prior to start of treatment. If discontinuation of corticosteroids is not feasible due to post-radiation effects, asymptomatic patients on a stable dose of dexamethasone $\leq$ 2mg daily (or equivalent) for $\geq$ 1 week prior to start of treatment will be permitted. Patients with active, asymptomatic brain metastases that are <10mm and no corticosteroid requirement will be permitted without radiosurgery or surgery based on nivo/ipi brain metastasis response data from Checkmate 204 [31]. Patients with active untreated brain metastases who are enrolled will require more frequent brain monitoring while on protocol. Refer to study schedule Table 7-1.
6. History of active autoimmune disorder requiring immunosuppressive agents. Patients with autoimmune disorders considered low risk, such as vitiligo and thyroiditis, will be allowed.
7. Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g. dabigatran), betrixaban, or platelet inhibitors (eg, clopidogrel).
   Allowed anticoagulants are the following:
   a. Prophylactic use of Low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH) are permitted.
   b. Anticoagulation with therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed in subjects without known brain metastases who are on a stable dose of anticoagulant for at least 1week before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
8. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test $\geq 1.3 \times$ the laboratory ULN within 7 days before the first dose of study treatment.
9. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
   a. Cardiovascular disorders:
      i. Congestive heart failure New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.

ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.
iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism) within 6 months before first dose.

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
   i. The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
   ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.
   Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose.
d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.
e. Lesions invading or encasing any major blood vessels.
f. Other clinically significant disorders that would preclude safe study participation.
   i. Serious non-healing wound/ulcer/bone fracture.
   ii. Uncompensated/symptomatic hypothyroidism.
   iii. Moderate to severe hepatic impairment (Child-Pugh B or C).

10. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before first dose and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment [32].
    Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.
12. Pregnant or lactating females.
13. Inability to swallow tablets.
14. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
15. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy.

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

7.0 STUDY ASSESSMENTS AND PROCEDURES

7.1 Pre-Treatment Period

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. The following assessments will be conducted before subjects receiving their first dose of study drugs on this protocol:

- History and Physical Exam
- Concurrent medication review
- Baseline laboratory assessment
- Baseline EKG
- Staging CT scan chest/abdomen/pelvis (+/- neck) and MRI brain

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

7.2 Treatment Period

During the Treatment Period subjects will receive nivolumab, ipilimumab and cabozantinib until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 5.2. Treatment will continue for up to 2 years unless there is disease progression, drug intolerance or other reason for discontinuation discussed with the principal investigator (PI). Patients with ongoing complete or partial response may discontinue therapy after 1 year on treatment at the discretion of the treating investigator. Subjects should be instructed to immediately inform the PI/sub-I of any AEs. Subjects experiencing seizures, dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

The following schedule of assessments applies to all subjects (

Table 7-1). More frequent assessments should be obtained if clinically indicated.

Table 7-1: Study Assessments

Schedule													
		Nivo-Ipi-Cabo combination treatment								Nivo-Cabo treatment		Off treatment but not progressed[9]	At progression
Cycle Week	Baseline Screening	1	1	4	4	7	7	10	10	13	Q4weeks (weeks 17-105)	Q12 weeks (+/- 4 weeks)	30 day follow up visit
Day of cycle (+/- 3 days)	-14 to 0	1	8	1	8	1	8	1	8	1	1	1	1
Nivolumab dosing q3weeks		X		X		X		X		X	X		
Ipilimumab dosing q3weeks		X		X		X		X					
Cabozantinib dosing continuous		X		X		X		X		X	X		
Medication compliance		X		X		X		X		X	X		
Prior and concomitant medications	X	X		X		X		X		X	X	X	X
Baseline tissue collection[1]	X												
Baseline stool collection		X[7]											
Physical exam	X	X		X		X		X		X	X	X	X
Vital signs	X	X		X		X		X		X	X	X	X
ECOG PS	X	X		X		X		X		X	X	X	X
Height	X												
Weight	X	X		X		X		X		X	X	X	X
Labs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[3]	X	X		X		X		X		X	X	X	
12 Lead EKG	X	X		X		X		X		X	X		
Tumor imaging assessments[4]	X[4]									X	X[6]	X[6]	
Adverse event assessment	X	X		X		X		X		X	X		X
Tumor biopsy[5]										X			X
Research blood collection[8]		X		X		X		X					X

1. Baseline tumor collection can be archived specimen if no intervening systemic therapy or fresh biopsy (core needle biopsy, punch biopsy or incisional/excisional biopsy).
2. Labs for Day 1 of each Cycle Week include CBC[a], comprehensive metabolic panel[a], free T3, free T4, TSH, INR/PT, PTT, urinalysis, spot UPCR and Creatine Kinase (CK) with Troponin I if CK is abnormal. Labs for Day 8 of each Cycle Week include only liver

function tests (ALT, AST, alkaline phosphatase, GGT, total protein, albumin, and total bilirubin).
3. Only required for premenopausal female subjects. Urine or blood HCG.
4. CT scan of the chest, abdomen and pelvis. Tumor Imaging Assessments are to be performed within 4 weeks of Cycle 1 Day 1 for the Baseline Screening Assessment. Patients with primary or metastatic disease involving the head or neck areas will require CT scan of the neck as well. MRI brain will be performed at baseline and per discretion of the treating investigator during the treatment period. In patients with a history of a prior brain metastasis, MRI brain will be performed at each reassessment. In patients with active, untreated brain metastases, MRI of the brain should be performed every 6 weeks through week 25 on protocol. Brain imaging with CT scan with IV contrast can be performed in place of MRI brain if there is a contraindication for MRI.
5. Optional core needle biopsy or punch biopsy of superficial tumor in the skin, subcutaneous tissue or lymph node that is palpable on treatment and at progression.
6. Scans every 12 weeks. Scans should occur prior to the visit. A window of -7 to +3 days is acceptable.
7. Patients will need to provide the sample on day 1 of the first cycle (+/- 7 day window).
8. Research blood collection should occur based on the calendar whenever possible and are not required to be redrawn due to treatment delays or interruptions.
9. Follow up off treatment will continue for 2 years after treatment is discontinued. Beyond this time point, progression free survival and overall survival would be assessed every 6 months via chart review or phone contact.

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PT/INR, prothrombin time/International Normalized Ratio; PTT, partial prothrombin time; UPCR, urine protein/creatinine ratio

[a] Laboratory tests should include a standard hematology panel (CBC, differential, platelets) and chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total protein)

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (eg, clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule. Regular tumor assessments should be performed in accordance to the guidelines in [Section 7.4] to determine if PD is present.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

7.3 Post-Treatment Period

Subjects will return to the study site approximately 30 days after their last dose of study drug to complete end-of-study assessments if they progressed on study while still on active treatment. If the subject is already off treatment at the time of disease progression, by either scan or exam, then the end of study assessments may occur anytime within 30 days of documented disease progression. Laboratory and physical examinations will be performed. Remaining study

treatment will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit. Patients who complete treatment will be followed as in schedule Table 7-1. Patients who are beyond 2 years from last treatment on study will be monitored for progression free survival and overall survival every 6 months via chart view or phone contact for total of 5 years from starting the study treatment. Management including but not limited to laboratory assessment, history/physical examination, imaging studies will be at the discretion of the treating provider.

Patients who come off treatment for progression should be followed for overall survival for up to 5 years from the start of study treatment. Follow up contact for survival should be performed every 6 months by chart review or phone call, unless the patient has withdrawn consent from the trial.

7.4 Laboratory Assessments

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hematocrit • platelet count • RBC count • hemoglobin	
Serum chemistry		
• albumin • ALP • amylase • ALT • AST • bicarbonate • BUN • chloride	• creatinine • GGT • Glucose • calcium • lactate dehydrogenase • lipase	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive or not available)
Other		
• TSH, Free T4 • Pregnancy test (urine or serum) for women of child-bearing potential • Creatine Kinase (CK), if CK is abnormal then Troponin-I must be drawn		• PT/INR or PTT • 24 hour urine collection for protein if elevated UPCR >1mg/mg (>113.1mg/mmol; refer to Table 8-7)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate ; GGT, γ-glutamyltransferase;

INR, International Normalized Ratio; PT, prothrombin time; PTT partial thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; UPCR, urine protein/creatinine ratio; WBC, white blood cell.

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

7.5 Treatment Response Assessment

Only those subjects who have measurable disease present at baseline, have received at least one dose nivolumab, ipilimumab and cabozantinib, and had one on-treatment scan or progressed clinically will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. Those subjects that are not evaluable for response will be replaced. Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST) will be used for the primary response assessment and for progression free survival determination [33]. Best overall response rate will be reported. Start of treatment will define the start date for calculations of PFS and OS.

7.5.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. 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, as >10 mm with CT scan, or >10 mm with 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 might or might not be considered measurable. If the site investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol).

7.5.2 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.

7.5.3 Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray. 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 subject, these are preferred for selection as target lesions.

7.5.4 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. Evaluation of target lesions as per Table 7-2.

7.5.5 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. Non-target lesion progression does not define progression of disease. It can only contribute to defining complete response (complete disappearance required).

7.5.6 New Lesions

In contrast to RECIST v1.1, new lesions that develop during treatment are not automatically captured as progressive disease in the overall response assessment with imRECIST. New measurable lesions are incorporated into the total tumor burden using the criteria in sections 7.5.1 and 7.5.2. Non-measurable new lesions preclude complete response, but are not added to the sum of diameters calculations for response evaluation.

7.5.7 Evaluation of Target Lesions

Table 7-2 summarizes the response evaluation by serial imaging using imRECIST. In patients with progressive disease, particularly on the first scan, it is recommended to confirm disease progression with a subsequent scan at least 4 weeks later. If the subsequent scan shows no progressive disease (lack of confirmation), patient would not be captured as having a progressive event and may continue on therapy per protocol. In patients with unequivocal disease progression as determined by the treating investigator, a confirmatory scan will not be required. In this situation, patient would discontinue therapy on study and be captured as a progressive event.

Table 7-2. Response evaluation by imRECIST:

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. To be assigned a status of complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than six weeks after the criteria for response is met. This can be performed at the next scheduled scans per protocol. Patients must also have complete disappearance or normalization of lymph nodes/other non-target tumor sites (e.g. resolution of a malignant pleural effusion), and no new non-measurable lesions.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters, as well as the addition of new measurable lesions. To be assigned a status of partial response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than six weeks after the criteria for response is met. This can be performed at the next scheduled scans per protocol. Patients must also not have unequivocal progression in non-target lesions and new lesions.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the baseline tumor assessment. New measurable lesions will be added to the total sum of diameters calculation (numerator). This will be used for assessment of best overall response. In patients with tumor burden decrease followed by tumor burden increase, the nadir sum of diameters will be used for assessment of progression (i.e. the new denominator). If this occurs, an increase of 20% from nadir will used for determination of progression. The sum must also demonstrate an absolute increase of at least 5 mm. Subjects with equivocal disease progression (e.g. a new lesion in the setting of major disease regression and the absence of or improvement in disease related symptoms) should have a scan confirming disease progression at least 4 weeks following the initial scan showing imRECIST defined PD. Subjects may continue on protocol therapy until repeat scan confirms PD. If repeat scan does not confirm PD, subjects should proceed with treatment and evaluation as directed by the protocol.

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. NOTE: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease). To be assigned a status of stable disease, response must be confirmed on a subsequent scan.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Table 7-3 summarizes potential outcomes.

Table 7-3. Summary of potential response outcomes by imRECIST

Target Lesions and New Measurable Lesions	Non-Target Lesions	New Lesions (Non-measurable)	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	Yes or No	PR
PR	Non-PD	Yes or No	PR
SD	Non-PD	Yes or No	SD
PD	Any	Yes or No	PD
Any	PD (unequivocal)	Yes or No	PD

7.6 Correlative studies

7.6.1 Biomarkers

A variety of factors impact the immunomodulatory properties and efficacy of immune checkpoint therapy, including nivolumab and ipilimumab, in patients with advanced melanoma. Baseline variables and changes that occur during treatment can be used to predict anti-tumor immune responses and to correlate with mechanisms of action of agents with immune modulatory properties, such as the RTK inhibitor cabozantinib. These include tumor specific factors such as tumor mutational burden, PD-L1 expression, MHC antigen presentation, interferon gamma related gene expression profiles [2, 34]. Host factors such as baseline peripheral lymphocyte counts, inhibitor immune cell levels (such as Tregs), HLA variants and dynamic changes during treatment have also been associated with responses to immune checkpoint therapy responses. Recent data on the gut microbiome indicates this may play a large

role in anti-tumor immunity as well [35]. In addition, anti-VEGF/R and anti-c-MET therapies have the ability to enhance T-cell priming and dendritic cell maturation, increase MHC antigen presentation on tumor cells, reduce immune suppressive Treg and myeloid cell populations, and activate vessel endothelium that can lead to augmented CD8+ T-cell and macrophage cell infiltration [4-8, 10, 11].

Assessment of baseline and on treatment molecular and cellular variables will serve the purpose of establishing predictive biomarkers for nivolumab/ipilimumab plus cabozantinib in patients with advanced melanoma. Exploratory analyses and comparisons to efficacy endpoints – ORR, PFS, and OS will be performed. In particular, this data will allow identification of sub-populations where clinical benefit is most often observed. We hope to show that patients typically predicted to have a low probability of response (e.g. PD-L1 IHC <1%, interferon gamma GEP low) will have substantial clinical benefit with the immunotherapy strategy investigated in this protocol. This will lead to future studies of nivolumab/ipilimumab plus cabozantinib in biomarker selected advanced melanoma patients.

Collection time points of biospecimens on protocol is outlined in Table 7-1. Refer to lab manual for specific details on handling, processing, and storage of biospecimen samples. Future assays planned for tumor specimen biomarker analyses include targeted exome sequencing (or whole exome sequencing), RNA gene expression, PD-L1 immunohistochemistry, and multiplex immunofluorescence for assessment of immune cell populations and immune markers. Peripheral blood will be analyzed by flow cytometry to characterize dynamic changes in immune cell populations, along with assessment of cytokines and other variables. Stool microbiome will be analyzed by 16s rRNA sequencing or equivalent approach. Additional biomarker analyses may be considered based on emerging data.

Samples remaining after initial protocol specific testing is completed will be banked for future unspecified cancer related research. Permission from subjects will be obtained during the consenting process. Samples that are collected will be identified by a subject's sequence ID 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.

8 TREATMENT PROCEDURES

8.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

8.2 Investigational Treatment: Cabozantinib

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 8-1.

Table 8-1: Cabozantinib Tablet Components and Composition

a

Refer to the Pharmacy Manual for details on storage and handling of cabozantinib.

8.2.1 Cabozantinib Administration

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily. Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 8.3 below.

8.2.2 Cabozantinib Dose Modifications, Interruptions, and Discontinuation

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 40 mg/day. 1 dose reduction level of cabozantinib is permitted (see Table 8-2). If cabozantinib is not tolerated at the first dose reduction level, it will then be discontinued.
- Dose modification criteria for cabozantinib are shown in Table 8-3 and 8-10. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.

- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 8-3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.
- Dose interruptions for reason(s) other than related AEs (eg, surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Guidelines for the management of specific AEs are provided in Section 8.2.4.

Table 8-2: Dose Reductions of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	No dose reduction permitted

qd, once daily
Cabozantinib will be discontinued if a qd dose of 20-mg cabozantinib (minimum dose) is not tolerated

Table 8-3: Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.4.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE, adverse event.
Note: The dose delay and modification criteria for specific medical conditions are provided in Section 8.2.4 . For re-treatment criteria of study treatment after a dose hold see Section 8.2.3.
[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

8.2.3 Cabozantinib Dose Reinstitution and Reescalation

If the subject recovers from his or her toxicities to CTCAE v.4.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 8-2 for the schedule of dose reductions).
Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 40 mg/day) may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (eg, central nervous system, cardiac, hepatic, renal).

8.2.4 Guidelines for Management of Potential Adverse Events associated with Cabozantinib

Subjects will be monitored for AEs from the time of signing informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.
Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

8.2.4.1 Cabozantinib Adverse Events

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (eg, transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs (eg, deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Section 8.2.2).

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

8.2.4.1.1 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in Table 8-4. Patients and treating providers need to be aware that diarrhea may occur as a non-immune mediated event with cabozantinib or as an immune mediated event with nivolumab/ipilimumab. Directions outlined here refer to non-immune mediated diarrhea. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 8-4: Management of Diarrhea Associated with Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (eg, small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (eg, stool sample for culture) o Administer antibiotics as needed (eg, if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose o Diarrhea not resolving: Start and or continue antidiarrheal treatment (eg, loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 9.3 for further details).

8.2.4.1.2 Non-Gastrointestinal Fistula

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.
Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

8.2.4.1.3 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study.

Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invade or encase major blood vessels. NSCLC with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. Thus, the anatomic location and characteristics of tumor as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity.
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis.
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis, hematemesis, or hematuria.

The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Though the incidence of CNS hemorrhage events in a study of subjects with glioblastoma was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of hemorrhage in glioblastoma translates to a risk of hemorrhage for subjects with brain metastases. Currently, brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment, and cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

8.2.4.1.4 Thromboembolic events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Therapeutic doses of Low molecular weight

heparins (LMWH) or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued..

Arterial thrombotic events (eg, TIA, MI) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

8.2.4.1.5 Hypertension

Table 8-5 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 8-5: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency[c]	• Discontinue cabozantinib treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (eg, myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

8.2.4.1.6 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and

appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

8.2.4.1.7 Skin and Subcutaneous Tissue Disorders

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. The decision to resume treatment with cabozantinib after surgery should be based on clinical judgment of adequate wound healing.

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.
Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in Table 8-6.

Table 8-6: Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (eg, clobetasol 0.05%) once daily and add analgesics (eg, NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (eg, clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.
[a] Permitted dose levels are defined by individual protocols.

8.2.4.1.8 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.
Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Advise subjects regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

8.2.4.1.9 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 8-7 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 8-7: Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment

RCC, renal cell carcinoma; UC, urothelial carcinoma; UPCR, urine protein/creatinine ratio.

8.2.4.1.10 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment,

hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

As neuritis, encephalitis, meningitis and other neurologic disorders have been observed with nivolumab and ipilimumab, management beyond cabozantinib drug hold may be necessary.

8.2.4.1.11 Hepatocellular Toxicity

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (eg, liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

As immune hepatitis has been observed with nivolumab and ipilimumab, management beyond cabozantinib drug hold may be necessary. If ALT or AST elevations are grade 2 or greater, immune checkpoint therapy may need to be held/discontinued and patient initiated on corticosteroids. Refer to specific guidance in section 8.5 for management of liver toxicity suspected to be potentially from cabozantinib and immune checkpoint therapy.

8.2.4.1.12 Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (eg, after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.

8.2.4.1.13 Blood and Lymphatic System Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.
Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered, but need to be used with caution in the presence of concurrent immune checkpoint therapy. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

8.2.4.1.14 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

8.2.4.1.15 Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

8.2.4.1.16 Corrected QT Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms, the following actions must be taken:

- Interrupt cabozantinib treatment
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed

- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.
Cabozantinib treatment must be permanently discontinued if either of the following applies:
- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose

8.2.4.1.17 Electrolyte Disorders
Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 8.2.2 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

8.2.4.1.18 Endocrine Disorders
Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

8.2.4.1.19 Angioedema
Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

8.3 Nivolumab
Opdivo, BMS-936558, MDX1106, anti-PD-1
Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Molecular Wt 146,221 daltons (143,619.17 daltons, protein portion).

8.3.1 Supplier/How Supplied
Standard of care nivolumab will be utilized and provided by local pharmacy. The cost of nivolumab will not be covered by the protocol. The site investigators and pharmacies will be responsible for maintenance of appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

8.3.2 Preparation
Refer to current nivolumab package insert. Nivolumab Injection: 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL solution in a single-dose 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.

During induction phase, nivolumab dosing is 3mg/kg IV every 3 weeks x 4 cycles (concurrent with ipilimumab and cabozantinib). During the maintenance phase, nivolumab dosing is 480mg IV every 4 weeks (concurrent with cabozantinib).

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
- For adult and pediatric patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micro pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection.

8.3.3 Storage and Stability

The product does not contain a preservative.
After preparation, 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.

8.3.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

8.3.5 Administration

Administer the infusion over 30 minutes through an intravenous 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.

8.3.6 Adverse Events and Management

Please see the package insert for a complete list of possible adverse events and guidance on adverse event management. Refer to Table 8-8 and ASCO/NCCN guidelines [18]. Also refer to section 8.5 for management guidance on potential overlapping adverse events from nivolumab, ipilimumab and cabozantinib.

Most common adverse reactions (≥20%) in patients were:

- Nivolumab as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain.
- Nivolumab in combination with ipilimumab are fatigue, rash, diarrhea, nausea, pyrexia, musculoskeletal pain, pruritus, abdominal pain, vomiting, cough, arthralgia, decreased appetite, dyspnea.

No dose reductions are permitted. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue in patients with severe or life-threatening infusion reactions.

Grade 2 and above immune related adverse events (irAEs) may/will require drug hold/discontinuation and administration of high dose corticosteroids (1-2mg/kg/day of prednisone or equivalent) tapered off over a 4-6 week period. Patient are to be completely off prednisone unless used for adrenal replacement purposes prior to resuming any immunotherapy, unless discussed with the Principal Investigator, Dr. Gibney. Additional immune modulatory agents may be required for treatment of irAEs that are refractory to corticosteroids, such as infliximab for immune colitis and mycophenylate for immune hepatitis. Refer to guidance below in Table 8-8 and ASCO/NCCN guidelines. After recovery from irAE during the nivolumab/ipilimumab induction phase, patients will be permitted to receive maintenance nivolumab if the irAE was most likely due to ipilimumab (e.g. immune colitis or hepatitis) and patient is receiving clinical benefit with the therapy.

During the Induction Period (Nivo-Ipi-Cabo treatment), the subject should stay on schedule and follow procedures as outlined. Drug dosing may be omitted based on toxicity guidance per protocol. If Nivolumab is restarted in the induction phase, the dose will remain at 3mg/kg for the duration of the induction phase.

During the induction phase, if an Adverse Event requires all drug to be held, and the toxicity has recovered to Grade 1 or baseline prior to the next scheduled treatment visit and the patient is eligible for Nivolumab and/or Ipilimumab, please consult study chair for approval to restart prior to the next scheduled treatment visit. If a subject is eligible to restart Nivolumab and Ipilimumab after a delay, then all subsequent visits/procedures may be shifted, including the scans, in order to complete all 4 induction cycles. The scans may be done earlier, at the investigator's discretion.

During the Maintenance phase (Nivo+Cabo treatment), starting at cycle week 13, treatment/assessment cycle date may be shifted to account for recovery from immunotherapy related toxicity. The one exception is that scans should remain every 12 weeks according to calendar days.

Table 8-8 Adverse event management for nivolumab [Package Insert, 2018].

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/ HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).
a Resume treatment when adverse reaction improves to Grade 0 or 1.
b HCC: hepatocellular carcinoma.
c Resume treatment when AST/ALT returns to baseline.

8.4 Ipilimumab

YERVOY, BMS-734016, MDX-010, anti-CTLA-4
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.

8.4.1 Supplier/How Supplied

Standard of care ipilimumab will be utilized and provided by local pharmacy. The cost of nivolumab will not be covered by the protocol. The site investigators and pharmacies will be responsible for maintenance of appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

8.4.2 Preparation

Refer to current ipilimumab package insert. Ipilimumab Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single-use vial.

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.

8.4.3 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

8.4.5 Handling and Disposal

Ipilimumab injection is available as follows:

Carton Contents	NDC
One 50 mg vial (5 mg/mL), single-use vial	NDC 0003-2327-11
One 200 mg vial (5 mg/mL), single-use vial	NDC 0003-2328-22

Store ipilimumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect ipilimumab from light by storing in the original carton until time of use. Do not freeze or shake.

8.4.6 Administration

Administration Instructions

- 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 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

When administered in combination with nivolumab, infuse nivolumab first followed by Ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

8.4.6 Adverse Events

Please see the package insert for a complete list of possible adverse events and guidance on adverse event management. Refer to Table 8-9 and ASCO/NCCN guidelines [18]. Also refer to section 8.5 for management guidance on potential overlapping adverse events from nivolumab, ipilimumab and cabozantinib.

Most common adverse reactions (≥5%) with ipilimumab as a single agent are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.

Most common adverse reactions (≥20%) with ipilimumab in combination with nivolumab are fatigue, rash, diarrhea, nausea, pyrexia, musculoskeletal pain, pruritus, abdominal pain, vomiting, cough, arthralgia, decreased appetite, dyspnea.

No dose reductions are permitted. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue in patients with severe or life-threatening infusion reactions.

Grade 2 and above immune related adverse events (irAEs) may/will require drug hold/discontinuation and administration of high dose corticosteroids (0.5-2mg/kg/day of prednisone or equivalent) tapered off over a 4-6 week period. Patient are to be completely off prednisone unless used for adrenal replacement purposes prior to resuming any immunotherapy, unless discussed with the Study Chair. Additional immune modulatory agents may be required

for treatment of irAEs that are refractory to corticosteroids, such as infliximab for immune colitis and mycophenylate for immune hepatitis. Refer to guidance below in Table 8-9 and ASCO/NCCN guidelines.

During the Induction Period (Nivo-Ipi-Cabo treatment), the subject should stay on schedule and follow procedures as outlined. Drug dosing may be omitted based on toxicity guidance per protocol. If Nivolumab is restarted in the induction phase, the dose will remain at 3mg/kg for the duration of the induction phase.

During the induction phase, if an Adverse Event requires all drug to be held, and the toxicity has recovered to Grade 1 or baseline prior to the next scheduled treatment visit and the patient is eligible for Nivolumab and/or Ipilimumab, please consult study chair for approval to restart prior to the next scheduled treatment visit. If a subject is eligible to restart Nivolumab and Ipilimumab after a delay, then all subsequent visits/procedures may be shifted, including the scans, in order to complete all 4 induction cycles. The scans may be done earlier, at the investigator's discretion.

During the Maintenance phase (Nivo+Cabo treatment), starting at cycle week 13, treatment/assessment cycle date may be shifted to account for recovery from immunotherapy related toxicity. The one exception is that scans should remain every 12 weeks according to calendar days.

Table 8-9 Adverse event management for ipilimumab [Package Insert, 2018].

Target/Organ System	Adverse Reaction (CTCAE v4)	Treatment Modification
Endocrine	Symptomatic endocrinopathy	Withhold YERVOY Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Symptomatic reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Permanently discontinue YERVOY
Ophthalmologic	Grade 2 through 4 reactions • not improving to Grade 1 within 2 weeks while receiving topical therapy or • requiring systemic treatment	Permanently discontinue YERVOY
All Other	Grade 2	Withhold YERVOY Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Grade 2 reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day • Grade 3 or 4	Permanently discontinue YERVOY

8.5 Overlapping adverse event management guidance

Many adverse events overlap between nivolumab/ipilimumab and cabozantinib. However, the mechanisms of action of the adverse events are likely different between these two classes of therapies and they require separate management plans. For example grade 3 diarrhea attributed to ipilimumab requires drug discontinuation, a course of high dose corticosteroids and supportive care, whereas grade 3 diarrhea attributed to cabozantinib requires temporary drug hold and supportive care alone. For adverse events that are most likely to occur with one class of therapy, the adverse event management should follow for that agent. An example is a grade 3-4 electrolyte abnormality, which is more common with cabozantinib. In this case, all three drugs should be temporarily held, but no corticosteroids given as this is likely not an immune related event. However, in patients with life threatening events (grade 4) or no improvement with drug hold after 5 days, then corticosteroids should be considered as it may be a rare irAE. In situations where a grade 3-4 adverse event could be due to either class of therapy, all drugs will need to be held and high dose corticosteroids administered if recommended by standard nivolumab or ipilimumab guidelines. After recovery of adverse event to grade 1 or baseline, cabozantinib can be reinitiated even if the corticosteroid taper has not been completed. The cabozantinib may need to be dose reduced if indicated by the included dosing guidelines. For some situations, such as grade 2 elevated transaminase levels, it may be appropriate to hold all study drugs, but monitor for improvement prior initiation of corticosteroids. In patients where nivolumab/ipilimumab or nivolumab cannot be restarted, cabozantinib would continue alone as outlined in the protocol treatment schema unless permanent discontinuation indicated (section 8.2). Similarly, in patients where cabozantinib cannot be restarted, nivolumab/ipilimumab or nivolumab alone may be continued as outlined in the protocol treatment schema if not meeting discontinuation rules and adverse event(s) has recovered to grade 1 or baseline and patient has successfully tapered of corticosteroids (and other immune modulatory agents). An exception is grade 2 endocrine disorders that can be treated with hormone replacement. When it is unclear how to manage the adverse event, hold drugs and consult the principal investigator.

During the Induction Period (Nivo-Ipi-Cabo treatment), the subject should stay on schedule and follow procedures as outlined. Drug dosing may be omitted based on toxicity guidance per protocol. If Nivolumab is restarted in the induction phase, the dose will remain at 3mg/kg for the duration of the induction phase.

During the induction phase, if an Adverse Event requires all drug to be held, and the toxicity has recovered to Grade 1 or baseline prior to the next scheduled treatment visit and the patient is eligible for Nivolumab and/or Ipilimumab, please consult study chair for approval to restart prior to the next scheduled treatment visit. If a subject is eligible to restart Nivolumab and Ipilimumab after a delay, then all subsequent visits/procedures may be shifted, including the scans, in order to complete all 4 induction cycles. The scans may be done earlier, at the investigator's discretion.

During the Maintenance phase (Nivo+Cabo treatment), starting at cycle week 13, treatment/assessment cycle date may be shifted to account for recovery from immunotherapy related toxicity. The one exception is that scans should remain every 12 weeks according to calendar days.

Management of Hepatocellular Toxicity Associated with Cabozantinib and Nivolumab/Ipilimumab or Nivolumab

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other causes (eg, cancer-related, infection) should be evaluated.

The following conditions require discontinuation of cabozantinib:

- Drug-related ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN without reasonable other explanation, consistent with drug-induced liver injury (DILI).
- Drug-related ALT or AST > 8 x ULN.

Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. Table 8-108-10 provides suggested guidance on management of hepatotoxicity related to cabozantinib and/or nivolumab/ipilimumab or nivolumab. However, if Grade 2 or higher abnormalities of both a serum transaminase (ALT and/or AST) and serum bilirubin are documented, all study treatment must be discontinued. Dose holds should not alter the timing of other study assessments, including but not limited to tumor imaging scheduled based on W1D1 (≤ 3 days after start of treatment).

Table 8-10: Management of Hepatotoxicity Associated with Study Treatment

Severity of LFT Elevations by CTCAE v4	Dose Modification Guidance	Management/Follow-up Guidance
Grade 1 AST or ALT > ULN to 3.0 x ULN **and/or** total bili > ULN to 1.5 x ULN	• *Cabozantinib:* – Continue cabozantinib per protocol • *Nivolumab/Ipilimumab or Nivolumab:* – Continue therapy per protocol	• Monitor LFTs per protocol • Discontinue concomitant hepatotoxic medications, if possible

Grade 2 AST or ALT > 3.0 x ULN to ≤ 5 x ULN **or** total bili > 1.5 x ULN to ≤ 3 x ULN	• *Cabozantinib*: – Interrupt cabozantinib dosing. – If LFTs return to baseline grade, resume cabozantinib at a reduced dose. • *Nivolumab/Ipilimumab or Nivolumab:* – Hold therapy per protocol. – If LFTs return to baseline grade, resume therapy per protocol	• Monitor LFTs twice weekly or more frequently as deemed clinically necessary. • If tapering off steroid therapy, monitor LFTs once weekly or more often per clinical judgment • If LFTs return to baseline grade, resume with routine monitoring • If LFT elevations persist > 7 days or worsen: – Administer 0.5-1 mg/kg/day methyl-prednisolone or oral equivalent – When LFTs return to baseline grade or CTCAE Grade ≤1, taper steroids over at least 4 weeks – Add prophylactic antibiotics for opportunistic infections if on immune suppression > 1 month or prior to 1month per investigator decision.
Grade 3-4 AST or ALT > 5 x ULN **or** total bili > 3 x ULN or as otherwise specified	• *Cabozantinib*: – Discontinue cabozantinib if: 1) ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN AND no radiographic evidence of biliary obstruction, or 2) ALT or AST > 8 x ULN. – Otherwise interrupt cabozantinib dosing and resume at a reduced dose after LFTs return to baseline grade (Study Principal Investigator approval required) • *Nivolumab /Ipilimumab or Nivolumab:* – Discontinue combination or monotherapy therapy – Exception: Can resume nivolumab after LFTs return to baseline grade if grade 3 event occurred while receiving Nivolumab/Ipilimumab (Study Principal Investigator approval required)	• Monitor LFTs twice weekly or more frequently as deemed clinically necessary • During steroid taper, monitor LFTs once weekly or more often per clinical judgment • For Grade 3: – Administer 1.0-2.0 mg/kg/day methylprednisolone IV or PO equivalent • For Grade 4: – Administer 2.0 mg/kg/day methylprednisolone IV • Add prophylactic antibiotics for opportunistic infections if on immune suppression > 1 month or prior to 1month per investigator decision. • When LFTs return to baseline grade or Grade 2, convert to oral prednisone (if not already on it) and taper steroids over at least 4 weeks • If LFT elevations do not improve in > 3-5 days, worsen or rebound: – Add mycophenolate mofetil 1g BID – If no response within an additional 3-5 days, consider other immune-suppressants per local guidelines and hepatology consultation. Taper off steroid first over at least 4 weeks and then taper off mycophenolate (decrease total 24hr dose by 500mg after every 7 days).

9 CONCOMITANT MEDICATIONS AND THERAPIES

9.1 Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the investigator's discretion.
  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 8.3.1.3.8). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
  - *Low dose low molecular weight heparins (LMWH) for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
  - *Therapeutic doses of LMWH or the direct factor Xa rivaroxaban, edoxaban, or apixaban* at the time of the first dose of study treatment are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications form the anticoagulation regimen or the tumor.
  - *Low dose LMWH for prophylactic use* after first dose of study treatment are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
  - *Therapeutic doses of LMWH or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban* after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 8.3.1.3.4.
  - Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used concomitantly with heparin or factor Xa inhibitors due

to the increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines

- For restrictions on oral anticoagulants see Section 9.2.

Potential drug interactions with cabozantinib are summarized in Section 9.3.1.

9.2 Prohibited or Restricted Therapy

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulants with coumarin agents (eg, warfarin), direct thrombin inhibitor (e.g., dabigatran), direct factor Xa inhibitor betrixaban, antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection (per local applicable guidelines) until 4 weeks after cabozantinib has been permanently discontinued.
- Any nonprotocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).
- Systemic corticosteroids above adrenal gland cortisol replacement levels (e.g. > prednisone 7.5 daily or equivalent) at study entry are not permitted. Use of corticosteroids above this level while on study may be required for management of immune related adverse events. Nivolumab and ipilimumab are held/discontinued while patients are on high dose corticosteroids and subsequent taper. Once steroid taper completed, patients may restart nivolumab and/or ipilimumab based on management guidelines in section 8.4. Patients may restart cabozantinib during steroid taper if adverse event is improved to grade 1 or better and management guidelines in section 8.3 are followed.

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per imRECIST 1.1 has been established.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 9.3.1.

9.3 Potential Drug Interactions

9.3.1 Potential Drug Interactions with Cabozantinib

Currently available data suggest that cabozantinib: (1) is not anticipated to markedly induce or inhibit CYP enzymes at clinically-relevant plasma concentrations; (2) is a substrate for CYP3A4; (3) may have the potential to inhibit the P-gp transport activity but is not a substrate of P-gp; and (4) is a substrate of drug transporter MRP2.

Cytochrome P450: Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, rand ritonavir) may increase cabozantinib plasma concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways: Http://medicine.iupui.edu/clinpharm/ddis/table.aspx http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-

administered highly protein bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. A case of a drug-drug interaction between cabozantinib and warfarin that may involve displacement of plasma protein bound drug has been reported in the literature (Foxx-Lupo et al. 2016). Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Food Effects: As food increases exposure levels of cabozantinib, subjects should fast (with the exception of water) for at least 2 hours before taking their dose of cabozantinib. After the 2 hour fast, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz. or 240 mL) with no more food intake for one hour post-dose.

Other Interactions: In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g., cyclosporine, delaviridine, efavirenz, emtricitabine) should be approached with caution, and subjects taking MRP2 inhibitors should be monitored for AEs.

9.3.2 Potential Drug Interactions with Nivolumab and Ipilimumab

There are no specific drug-drug interactions with nivolumab and ipilimumab and other drugs. Based on the mechanism of action, these agents are usually held during courses of high dose corticosteroids and patients requiring immune suppression for organ transplant, autoimmune disorders and other disease are not permitted to participate on this protocol.

9.4 Study Treatment Accountability

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all

unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

10 SAFETY

10.1 Adverse Events and Laboratory Abnormalities

10.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in this protocol. All untoward events that occur after informed consent through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits and includes the new onset of or increase in pain during this period.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE).

10.1.2 Serious Adverse Events (SAEs)

The SAE definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

- Result in death;
- Is life-threatening (i.e., in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result

in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.

- Results in persistent or significant disability or incapacity:
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

10.1.3 Relationship to Study Treatment

Assessment of the relationship of the AE to the study treatment by the investigator is based on the following two definitions:

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;
- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

10.1.4 Serious Adverse Event Reporting

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this must be documented on an SAE Report Form or in an electronic database and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures, from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment.

All SAEs and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to [redacted]

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

Serious adverse events will also be reported, and all supporting documentation sent (emailed) to the Multicenter Project Manager(s) and to the study PI, Dr. Gibney, within 24 hours.

10.1.5 Regulatory Reporting

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. Current package inserts for nivolumab and ipilimumab should be referenced as well. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;
- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.
- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The PI shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

10.2 Other Safety Considerations

10.2.1 Laboratory Data

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

10.2.2 Pregnancy/Lactation Exposure

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. Pregnancy (in subject or partner) or lactation exposure, although not an SAE, should be reported to Exelixis. Forms will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

10.2.3 Medication Errors/Overdose

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

10.2.4 Follow-Up of Adverse Events

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur more than 30 days after the decision to discontinue study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

11 STATISTICAL CONSIDERATIONS

Simon's Two-Stage Design will be used in hypothesis testing for the primary endpoint of a 1 year PFS rate. Based on the Checkmate 067 data [1], a 1 year PFS rate in the historical control is assumed to be 50% (H0: PFS rate=50%). In this trial, a target 1 year PFS rate will be 75% (improvement by 25%, H1: PFS rate >/=75%), which is deemed a clinical meaningful improvement. This will require a sample size of 23 for a one sided alpha of 0.05 and the power of 0.80. In the futility stage with the first 14 subjects, the study will be stopped if there are 7 or fewer subjects progression free at 1 year. In the final analysis, the null hypothesis will be rejected if 16 subjects or more are progression free at 1 year of the 23 total subjects. Assuming a dropout rate of 15% during the time of study, up to 27 subjects will be enrolled.

In the event of unplanned interim analyses are needed due to slow accrual or any other reasons, we will use the curtailing based SCPRT approach for statistical analysis [36].

The PFS rate in the final analysis will be calculated and a 2-sided Clopper–Pearson 95% confidence interval (CI) will be calculated. PFS and OS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS and OS will be presented with two-sided 95% CI if estimable.

Remaining analyses will be descriptive and exploratory in nature. TMB will be evaluated as a continuous variable and dichotomous breakdowns including previously reported high vs low status using a 21 nonsynonymous variants/MB cutoff [37]. PD-L1 status will use high/low cutoffs of 1% and 5% positive IHC rates [1]. Other variables will be analyzed based on published data or optimization of cutoffs. Statistical comparisons will be performed with SAS/R and looking to determine associations with biomarkers and clinical outcomes.

12 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and crosscheck of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator and/or pharmacy.

13 STUDY COMMITTEES

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Georgetown-Lombardi Comprehensive Cancer Center's DSMP.

Oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to The Georgetown-Lombardi Comprehensive Cancer Center's DSMP.

13.2 The Georgetown-Lombardi Comprehensive Cancer Center Data Safety Monitoring Committee

The Georgetown-Lombardi Comprehensive Cancer Center DSMC will review:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated Phase II study using FDA approved agents it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC). Documentation of DSMC reviews will be provided to principal investigator and sponsor. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor and principal investigator will work to address the DSMC's concerns.

14 ETHICAL ASPECTS

14.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

14.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where

the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.3 Institutional Review Board/Ethics Committee

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.
All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (eg, change in monitor or change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

At any time, the study may be terminated by the study sponsor, the sponsoring institution, or by Exelixis. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practicable.

17 STUDY DOCUMENTATION AND RECORD-KEEPING

17.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, any other records required under the Protocol, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, electroencephalogram, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these two categories of documents on file for at least the latest of (a) 2 years following the marketing application approval date for the study treatment in the indication being investigated, or (b) 2 years after the investigation is completed or discontinued, or (c) for a period of time consistent with local regulatory requirements, whichever is longest. After that period, the documents may be destroyed subject to local regulations with prior written permission from Exelixis. If the investigator wants to assign the study records to another party or move them to another location, Exelixis must be notified in advance.

17.2 Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Exelixis Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

17.4 Case Report Forms

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

18 MONITORING THE STUDY

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify both adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects should be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to Exelixis and its partners or designees for review.

20 PUBLICATIONS OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide Exelixis with a copy of any proposed publication or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of manuscripts and also comply with any provisions regarding publication that are agreed to between the PI's institution (eg, institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

21 REFERENCES

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22. APPENDIX