NCI Protocol #: NCT04197310

DF/HCC Protocol #: 19-403

TITLE: Phase II trial of cabozantinib in combination with nivolumab for advanced carcinoid tumors

Coordinating Center: Dana-Farber Cancer Institute/ Harvard Cancer Center

Principal Investigator (PI):
Kimberly Perez, MD
Dana-Farber Cancer Institute
Kimberly_Perez@dfci.harvard.edu

Other Investigators:
Jennifer Chan, MD, MPH
Dana-Farber Cancer Institute
JAng@partners.org

Matthew Kulke, MD
Boston Medical Center
Matthew.Kulke@bmc.org

Statistician:
Hui Zheng, PhD
Massachusetts General Hospital
HZHENG1@mgh.harvard.edu

Project Manager:
Alexandra Bird
Dana-Farber Cancer Institute
Alexandra_Bird@dfci.harvard.edu

Responsible Research Nurses:
Christopher Graham, RN
Dana-Farber Cancer Institute
Christopher_Graham@dfci.harvard.edu

Mark Sawin, RN
Dana-Farber Cancer Institute
Mark_Sawin@dfci.harvard.edu

Lauren Ritterband, RN
Dana-Farber Cancer Institute
Lauren_Ritterband@dfci.harvard.edu

NCI-Supplied Agent(s): N/A
Other Agent(s): Cabozatinib – Exelixis; Nivolumab – Bristol-Myers Squibb

IND #: 144470
IND Sponsor: Kimberly Perez, MD

Protocol Type / Version # / Version Date: Version #6.0 / 20-May-2022

SCHEMA

Diseases: *Well-differentiated Neuroendocrine Tumors of non-pancreatic (i.e, carcinoid) origin*	*Treatment:* ***Nivolumab intravenously every 2 weeks*** ***AND*** ***Cabozantinib orally daily*** ***28 day cycle***	*Stage I: safety run-in (N= 18);* *If more than 3 patients demonstrate response measured by RECIST 1.1 criteria then,* *Stage II: expansion (N= 17)*

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1 OBJECTIVES

1.1 Study Design

This is an open-label, single-arm, phase 2 study of nivolumab given in combination with cabozantinib. Nivolumab will be administered every two weeks at a dose of 240 mg given intravenously. Cabozantinib will be administered orally, once daily at a dose of 40 mg.

1.2 Primary Objective(s)

To evaluate the efficacy of cabozatinib in combination with nivolumab, as defined by objective response rate (ORR) according to RECIST 1.1, in patients with advanced carcinoid tumors.

1.3 Secondary Objective(s)

1.3.1 To evaluate the safety and tolerability of cabozantinib in combination with nivolumab in patients with advanced carcinoid tumors.

1.3.2 To evaluate the ORR of cabozantinib in combination with nivolumab in patients with advanced carcinoid tumors according to immune-related response criteria (irRC).

1.3.3 To evaluate the duration of response in patients with advanced carcinoid tumors receiving the combination of cabozantinib and nivolumab.

1.3.4 To evaluate progression-free survival of patients with advanced carcinoid tumors treated with the combination of cabozantinib and nivolumab.

1.3.5 To evaluate overall survival of patients with advanced carcinoid tumors treated with the combination of cabozantinib and nivolumab.

1.4 Exploratory Objective(s)

1.4.1 To explore whether baseline tumor immune cell infiltration and PD-L1 and PD-L2 staining correlates with response to therapy.

1.4.2 To explore whether changes in circulating immune cell profile correlates with response to therapy.

1.4.3 To explore whether changes in the level of angiogenic and inflammatory blood biomarkers during therapy correlate with efficacy of therapy.

2 BACKGROUND

2.1 Introduction

Neuroendocrine neoplasms are a relatively rare heterogeneous group of malignancies. These tumors arise from neuroendocrine cells located throughout the body. In current clinical practice neuroendocrine neoplasms are divided into two groups based on clinical behavior, histology, and proliferation rate: well differentiated (low grade to intermediate grade) neuroendocrine tumors (NET) and poorly differentiated (high grade) neuroendocrine carcinomas (NEC). This dichotomization is clinically relevant for therapeutic and prognostics purposes, though imprecise as the behavior (metastatic potential, local invasion, recurrence after resection) can be very heterogeneous. Furthermore, there are distinctions in the management of well-differentiated neuroendocrine tumors arising in the pancreas versus non-pancreatic primary sites, including organs such as thymus, lung, and the gastrointestinal tract. Well-differentiated neuroendocrine tumors arising in non-pancreatic sites have historically been classified as carcinoid tumors. Current therapeutic options for carcinoid tumors include somatostatin analogs, everolimus, and the radiolabeled somatostatin analog lutetium-177 dotatate. These therapies have been shown to improve progression-free survival for patients with advanced stage disease, but the benefit is finite. As such, newer therapeutic options are needed to manage this very heterogeneous disease.

2.1.1 The PD-1/PD-L1 pathway in cancer

The role of intact immune surveillance in controlling neoplastic transformation and growth has been well-described. (Restifo) There is recent evidence demonstrating a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and clinical outcomes. (Mlecnik) The PD-1 receptor ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs, natural killer cells, and a subset of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cells types. PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues and PD-L2 controls immune T-cell activation in lymphoid organs. Most healthy tissues express few PD-L1 ligands, a variety of cancer demonstrate an abundant level, thus suggesting that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and is therefore considered an attractive target for therapeutic intervention. (Intlekofer)

<u>The PD-1/PD-L1 pathway in neuroendocrine tumors</u>
The new generation of immunotherapy treatment, check-point inhibitors, has not yet been proven to be effective in patients with NETs. Prior analysis of interferon in NET, a classic immune-modulatory drug, demonstrated an ability to stimulate T-cell function, control the secretion of tumor products and inhibit tumor growth by activation of the T-cell response against the tumor and angiogenesis inhibition in NETs (Oberg). Efforts to better characterize the

immune response in NET have been undertaken, and several studies have demonstrated an association between expression of PD-L1, presence of TILs, and clinical outcome. Lamarca and colleagues recently demonstrated that 30% of a 109 patient cohort of SINETs showed expression of PD-L1 within tumor cells and/or TILs, together with a high rate of TIL presence. In this cohort, 17.2% demonstrated a concomitant presence of CD8+ lymphocyte aggregate and PD-L1 expression. (Lamarca) Other studies have demonstrated similar results, with high grade or well differentiated grade 3 NETs consistently demonstrating a higher expression of PD-L1 when compared to grade 1 or 2 NET. (Lamarca, Cavalcanti, da Silva). In contrast, in another cohort of patients with NET, including 64 with small intestinal NET (SINET) and 21 with pancreatic NET, no membranous expression of PD-L1 was identified in the SINETs group, and 11% was noted in the PNET cohort. Both groups, however, showed T-cell tumor infiltrate. (da Silva).

The therapeutic use of immune checkpoint inhibitors and NETs is currently under investigation. The results of the first completed study was presented at the ESMO 2017 Annual Conference. The Keynote-028 study evaluated the use of pembrolizumab for patients with PD-L1 positive advanced carcinoid or pancreatic NET. The study screened 276 patients for the presence of PD-L1; 36% were positive (carcinoid N=25; pancreatic NET N=16). Three carcinoid patients (12%; 95% CI, 3-31%) and one PNET (6%; 95% CI, 0-30%) had an objective response; stable disease rates were 60% (n=15) and 88% (n=14) respectively. Duration of response ranged between 6.9 to 11.1 months for the carcinoid responders; and 17.6 months for the PNET responder. (Mehnert) Other clinical trials are currently evaluating the role of checkpoint inhibitors and focusing on NETs that are both well-differentiated and poorly differentiated, and studies are also evaluating checkpoint inhibitors in combination with other immunomodulatory agents (NCT03167853, NCT02955069, NCT03095274, NCT03074513).

2.1.2 Cabozatinib in carcinoid tumors

Cabozantinib is an orally administered drug that is classified as a small-molecule tyrosine kinase inhibitor (TKI). It is a reversible competitive inhibitor of tyrosine kinase receptors including VEGFR2, MET, AXL, and RET. Cabozantinib has demonstrated efficacy in advance renal cell carcinoma and metastatic medullary thyroid cancer. (Choueiri, Brose) We recently demonstrated in a phase II trial of patients with advanced carcinoid and pancreatic neuroendocrine tumors (NET) that treatment with single agent cabozantinib was associated with encouraging response rates and progression-free survival [2]. The objective response rate, as measured by RECIST 1.1, was 15% in patients with both carcinoid tumors (6/41) and pancreatic NET (3/20). (Chan) The CABINET study, a randomized, phase III placebo-controlled clinical trial, is currently open to enrollment and will further evaluate the efficacy of cabozantinib in patients with advanced pancreatic NET and carcinoid tumors previously treated with everolimus (NCT03375320).

2.2 **Rationale**

Although NET is not typically considered to be an immunogenic malignancy, an increasing body of preclinical and clinical evidence suggests that modulation of the immune system can influence disease outcome. In particular, anti-PD-1/PD-L1 antibodies have demonstrated clinical efficacy,

and two PD-1 inhibitors (nivolumab and pembrolizumab) are FDA approved for the treatment of multiple cancer types. (Brahmer) Although immune checkpoint inhibitors have made an enormous impact on therapeutic strategies, there remain many tumor types and subsets of tumor types in which therapeutic benefit has not been clearly demonstrated. This suggests that there may be additional immunosuppressive factors causing resistance to immunotherapy, and other agents must be added to anti-PD-1/PD-L1 treatment in order to enhance the benefit of immunotherapy.

Treatment with cabozantinib has been associated with immunomodulatory changes. In a phase II study of patients with triple negative breast cancer, for example, significant and persistent increases in circulating CD3+ T-lymphocytes were observed after treatment with cabozantinib, driven primarily by increase in CD8+CD4–cytotoxic T-lymphocytes. (Tolaney) Moreover, there was a significant decrease in circulating CD14+ monocytes, an immunosuppressive myeloid-derived population. These changes in circulating immune cells provides rationale for combining cabozantinib with immune checkpoint inhibitors as an innovative treatment strategy. Similar treatment strategies are being proposed in other malignancies, including urothelial and genitourinary malignancies (NCT02496208) and renal cell carcinoma (NCT03141177).

Neuroendocrine tumors provide another ideal platform upon which to perform such a study. Given the single agent activity of cabozantinib in NET, and the potential immunomodulatory potential of cabozantinib, we propose a phase II study to evaluate the antitumor activity of cabozantinib plus nivolumab (anti-PD-1 monoclonal antibody) in patients with advanced carcinoid tumors.

2.3 IND Agent(s)

2.3.1 Cabozatinib – refer to the Investigator's Brochure (IB)/ approved labeling for detailed background information.

2.3.2 Nivolumab - refer to the Investigator's Brochure (IB for detailed background information.

2.4 Correlative Studies Background

The importance of the tumor microenvironment and immune surveillance in the natural history of cancer has proved to be significant in our therapeutic strategy. However, less than half of patients with solid tumors will derive benefit from these drugs alone. (Ribas) Thus, it is imperative to examine the mechanisms of antitumor immunity evasion in the tumor microenvironment to direct immunotherapy treatment. This effort can be moved forward by the discovery and validation of prognostic and predictive biomarkers.

Although multiple cancers have demonstrated a sensitivity to immunotherapy, there are subsets that do not appear to respond. The lack of a significant T-cell infiltrate and low expression of immune checkpoint molecules may explain the reason that certain non-inflamed tumor phenotypes are associated with de novo resistance to anti-PD-1 / anti-PD-L1 drugs. For this group of patients, therapeutic strategies that promote an increase in cytotoxic T-cell infiltration,

such as anti-angiogenic therapies, may be relevant to successfully overcoming T-cell exclusion and improve the likelihood of benefit of PD-1 blockers.

Tolaney and colleagues recently published their experience in triple negative breast cancer with single-agent cabozantinib. Although the study did not meet its pre-specified endpoint, there were notable notable biomarker changes after treatment with cabozantinib which included: significant and durable increases in plasma placental growth factor, vascular endothelial growth factor (VEGF), VEGF-D, stromal cell-derived factor 1a, and carbonic anhydrase IX, and circulating CD3+ cells and CD8 + T lymphocytes, and decreases in plasma soluble VEGF receptor 2 and CD14+ monocytes (all $p<.05$). There was a significant increase in the fraction of circulating CD3+ cells and CD3 + CD4-CD8+ T lymphocytes at days 22 and 64 ($p=.04$ and $p=.01$, respectively), and a decrease in percentage of CD14+ monocytes at days 22 and 64 ($p=.01$). (Tolaney) Although none of these findings, except baseline soluble MET levels, were associated with outcome measures, this is the first description of cabozantinib induced modulation of immune cells in the clinical setting. We propose analysis of potential biomarkers of cabozantinib and nivolumab activity in carcinoid and the impact on the immune environment. We intend to explore changes in angiogenic/inflammatory biomarkers during treatment, the characteristics of potential immune biomarkers and expression of immune checkpoint molecules, and TILs to explore the activity of cabozantinib and nivolumab in carcinoid tumors.

3 PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with locally unresectable or metastatic well-differentiated neuroendocrine tumor of non-pancreatic (ie, carcinoid) origin

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have evidence of radiographic disease progression within the past 12 months.

3.1.4 Patients who have received at least one line of therapy, which can include somatostatin analog therapy. Participants should be adequately recovered from acute toxicities of prior treatment.

- Prior somatostatin analog therapy is allowed. Continuation of somatostatin analog therapy is allowed provided that the dose has been stable for 2 months.
- Prior chemotherapy: Participants must have been off treatment with cytotoxic chemotherapy for at least 14 days prior to registration.
- Prior biologic therapy: Patients must have discontinued all biologic therapy at least 28 days prior to registration. Duration may be shorted to 14 days for agents with short half-lives.
- Prior radiolabeled somatostatin analog therapy: Participants must have completed radiolabeled somatostatin analog therapy at least 6 weeks prior to registration.
- Prior hepatic artery embolization or ablative therapies is allowed if measurable disease remains outside the treated area or there is documented disease progression in a treated site. Prior liver-directed or ablative treatment must be completed at least 28 days prior to registration.
- Prior radiation therapy: Radiation therapy must be completed per the following timelines
  i) Radiotherapy to the thoracic cavity or abdomen within 4 weeks prior to registration.
  ii) Radiotherapy to bone lesions within 2 weeks prior to registration.
  iii) Radiotherapy to any other site within 4 weeks prior to registration.
  NOTE: In all cases, there must be complete recovery and no ongoing complications from prior radiotherapy.

3.1.5 Age ≥ *18* years.

3.1.6 ECOG performance status ≤1 (Karnofsky ≥60%, see Appendix A)

3.1.7 Participants must have normal organ and marrow function as defined below:

- absolute neutrophil count	≥1,500/mcL
- platelets	≥100,000/mcL
- total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (or 2.0 x ULN in patients with documented Gilbert's Syndrome)
- AST (SGOT)/ALT (SGPT)	≤2.5 × ULN or ≤ 3 × ULN for participants with documented liver metastases
- creatinine Or creatinine clearance	<1.5 × ULN ≥40 mL/min (using Cockcroft-Gault formula) for participants with creatinine levels above institutional normal
- Urine protein/creatinine ratio (UPCR)	≤ 1
- PT/INR or partial thromboplastin time (PTT) test	< 1.3 × the laboratory ULN within 7 days before the first dose of study treatment.

3.1.8 Negative urine pregnancy test for women of childbearing potential.

3.1.9 Participant must be able to swallow pills.

3.1.10 The participant is capable of understanding and complying with the protocol and has signed the informed consent document.

3.2 Exclusion Criteria

3.2.1 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.

3.2.2 Participants who are receiving any other investigational agents.

3.2.3 Participants who have received a prior cabozantinib.

3.2.4 Participants who have received prior therapy with an anti-PD-1, anti-PD-L1, anti- PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including nivolumab, pembrolizumab, ipilimumab, and any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

3.2.5 Participants with known Central Nervous System(CNS) metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.6 The participant has tumor in contact with, invading, or encasing major blood vessels or radiographic evidence of significant cavitary pulmonary lesions.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib or nivolumab.

3.2.8 Participants receiving any strong inhibitors or inducers of CYP3A4 within 14 days prior to registration are ineligible. Chronic treatment with strong inhibitors or inducers of CYP3A4 is not allowed.

3.2.9 Cardiovascular disorders including:

- Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening;
- Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;
- Any history of congenital long QT syndrome;
- QTcF interval >500 msec
- Any of the following within 6 months before the first dose of study treatment:
  - unstable angina pectoris;
  - clinically-significant cardiac arrhythmias;

- stroke (including transient ischemic attack (TIA), or other ischemic event);
- myocardial infarction;

3.2.10 GI disorders particularly those associated with a high risk of perforation or fistula formation including:

- Tumors invading the GI tract, active peptic ulcer disease, active inflammatory bowel disease (eg, Crohn's disease), active diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
- Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before screening

3.2.11 Thromboembolic events within 6 months of registration.
Note: Low dose aspirin ≤ 81 mg/day is allowed. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks prior to registration. Treatment with warfarin is not allowed.

3.2.12 The subject has experienced any significant bleeding episodes, including:

- Clinically significant gastrointestinal bleeding within 6 months before the first dose of study treatment
- Clinically significant hemoptysis (> 0.5 teaspoon) within 3 months of the first dose of study treatment
- Any other signs indicative of pulmonary hemorrhage within 3 months before the start of study treatment
- Individuals with a history of different malignancy are ineligible except for the following circumstances: Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy.

3.2.13 Participant has an active infection requiring IV antibiotics

3.2.14 Any active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (e.g. celiac disease) are permitted to enroll.

3.2.15 Patient has a medical condition that requires chronic systemic steroid therapy or on any other form of immunosuppressive medication. Adrenal replacement steroid disease are permitted in the absence of autoimmune disease.

3.2.16 The participant is known to be positive for the human immunodeficiency virus (HIV), HepBsAg, or HCV RNA. HIV-positive participants with non-detectable viral loads on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cabozantinib and nivolumab.

3.2.17 The participant has received a live vaccine within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. The use of the inactivated seasonal influenza vaccine (Fluzone®) is allowed.

3.2.18 Pregnant or lactating females are excluded from this study because cabozantinib and nivolumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib and nivolumab, breastfeeding should be discontinued if the mother is treated with cabozantinib and nivolumab. These potential risks may also apply to other agents used in this study.

3.2.19 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 following treatment. Women of childbearing potential receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab. Contraception must be used for 4 months after last dose of cabozantinib.

3.3 Inclusion of Women and Minorities

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

4 REGISTRATION

4.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally by the Project Manager at the Coordinating Center. All sites should call the Project Manager at 617-632-5728 to verify dose level availabilities. The required Registration Request Cover Sheet and External Site Subject Registration forms will be provided to sites. Following registration, participants should begin protocol therapy within 5 days.* Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed to 617-582-7988 or e-mailed to the Project Manager, DanielleE_Stonely@dfci.harvard.edu:

- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Registration Request Coversheet
- External Site Subject Registration form

- Screening provider note including medical/ surgical history, ECOG performance status, vital signs, and physical exam findings
- Pathology report to support inclusion criteria
- Laboratory reports including:
    - CBC with differential
    - Chemistry panel
    - Pregnancy test (if applicable)
    - Thyroid panel
    - Coagulation panel
    - LDH
- Screening radiology reports (CT and/or MRI scans)
- Screening EKG

The participating site will then call 617-632-5728 or e-mail DanielleE_Stonely@dfci.harvard.edu, the Project Manager to verify eligibility. The Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Project Manager will fax or e-mail the participant study number and confirmation of registration to the participating site. The participating site will then register the patient per their local requirements.

5 TREATMENT PLAN

5.1 Treatment Regimen

This is an open-label, single-arm, phase 2 study of nivolumab given every 14 days intravenously in combination with cabozantinib given orally once daily for 28 days. Up to 35 participants will be enrolled to the study to assess the efficacy of the combination as defined by objective response rate (ORR) according to RECIST 1.1, in patients with carcinoid tumors.

No investigational or commercial agents of therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	Not routinely necessary unless prior infusion reaction.	240mg	IV	Every 14 days	28 days (4 weeks)
Cabozantinib	Not necessary	40mg	oral	Continuous, once daily*	

*The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Participants do not need to re-meet eligibility criteria on Cycle 1, Day1 if screening laboratory evaluations were completed within 3 days of Cycle 1 Day 1.

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- hemoglobin ≥ 9 g/dl
- total bilirubin ≤1.5 × institutional upper limit of normal (ULN) (or 2.0 x ULN in patients with documented Gilbert's Syndrome)
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN or ≤ 3 × institutional ULN for participants with documented liver metastases
- Creatinine <1.5 ×within normal institutional ULN OR creatinine clearance ≥40 mL/min (using Cockcroft-Gault formula) for participants with creatinine levels above institutional ULN.
- urine protein/creatinine ratio (UPCR) ≤ 1.
- Urine pregnancy test in women of child-bearing age

5.2.2 Subsequent Cycles

- absolute neutrophil count ≥1,000/mcL
- total bilirubin ≤1.5 × institutional upper limit of normal (ULN) (or 2.0 x ULN in patients with documented Gilbert's Syndrome)
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN or ≤ 3 × institutional ULN for participants with documented liver metastases
- Urine pregnancy test in women of child-bearing age every 4 weeks (+/- 1 week)

5.3 **Agent Administration**

On days when Nivolumab and Cabozantinib are administered on the same day (i.e. Day 1 of each cycle) the order of agent administration does not matter.

5.3.1 Nivolumab Administration

Nivolumab is available as 100 mg vials (10 mg/mL), which include an overfill. It is supplied in 10 mL type I flint glass vials with butyl stoppers and aluminum seals. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP (USP to a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.) or 5% Dextrose.

Nivolumab will be administered every 14 days at a dose of 240 mg given intravenously over 30 minutes (+/- 10 minutes) using a volumetric pump with 0.2 to 1.2 micron pore size, low- protein binding polyethersulfone membrane in-line filter. Please refer to the Investigational Brochure for further details regarding storage, preparation and administration. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

5.3.2 Cabozantinib administration

Cabozantinib will be administered orally, once daily for 28 days at a dose of 40 mg. Cabozantinib should be taken 2 hours after a meal (water is permitted) with a full glass of water (8oz/240mL). Participants should continue to fast for 1 hour after taking cabozantinib. Participants will be provided with dosing instructions, a drug diary and a sufficient supply of cabozantinib for continuous daily dosing. Cabozantinib should be dosed on an outpatient basis even on days where Nivolumab and Cabozantinib are dosed together (i.e. Day 1 of each cycle). While taking Cabozantinib, participants should avoid consumption of grapefruit and Seville oranges. Cabozantinib should not be crushed, chewed, or dissolved in water.

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.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.4 **General Concomitant Medication and Supportive Care Guidelines**

5.4.1 Concomitant Medications Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or

vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the overall PI.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care and documented in the medical record. Selected medications of interest received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment, including dosage, frequency, route, and dates of administration will be recorded.

Concurrent use of somatostatin analogs is allowed, provided that the patient has been on a stable dose for at least two months.

Concomitant medications that are known to prolong the QTcF interval and should be used with caution 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 QTcF interval).

Drugs known to be P-glycoprotein substrates (e.g. fexofenadine, aliskiren, ambrisentan digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.) should be used with caution as cabozantinib can cause increased P-glycoprotein substrate plasma concentrations.

MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, and emtricitabine should be used with caution during treatment with cabozantinib as coadministration can cause increased cabozantinib plasma concentrations.

Highly protein-bound medications (e.g. diazepam, furosemide, dicloxacillin, propranolol, etc.) should be used with caution during treatment with cabozantinib.

Bisphosphonates should be used with caution due to the nephrotoxic potential and potential for osteonecrosis of the jaw previously described in association with these agents.

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than nivolumab and cabozantinib
- Radiation therapy
- Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. The use of the inactivated seasonal influenza vaccine (Fluzones, BCG, and ty
- Systemic glucocorticoids should be avoided for any purpose other than to modulate symptoms from radiation or an event of clinical interest of suspected immunologic

etiology. If corticosteroids are required for this purpose, the minimum effective dose should be used.

- Full dose oral anticoagulation/antiplatelet therapy is not permitted. Low dose aspirin ≤ 81mg/day is allowed. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks. Treatment with warfarin is not allowed.
- CYP3A4 Inhibitors

  Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with cabozantinib.

  - Indinavir
  - Clarithromycin
  - Ketoconazole

  CYP3A4 inhibiting foods such as grapefruit/grapefruit juice and Seville oranges may increase plasma concentrations of cabozantinib and should be avoided during treatment with cabozantinib.

  Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4.

- CYP3A4 Inducers

  Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with cabozantinib

  - Rifampin
  - Carbamazepine

  Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4.

5.4.2 Supportive Care Guidelines – general medications

Patients should receive full supportive care while on this study.

This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose must be recorded in the medical records.

Antiemetics may be used at the discretion of the treating physician.

Antiemetic agents, along with supportive care, may be used as clinically appropriate at the first sign of nausea and vomiting. 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone due to possible CYP3A4 interactions.

Diarrhea management is per the discretion of the treating physician.

Diarrhea may need to be managed conservatively with medications such as loperamide, diphenoxylate/atropine, deodorized tincture of opium, or octreotide as clinically appropriate at the first sign of diarrhea. Treating physicians may wish to instruct patients to notify their physician immediately at the first signs of poorly-formed or loose stool or an increased frequency of bowel movements.

Patients with severe diarrhea may need to be assessed for intravenous hydration, correction of electrolyte imbalances, and dietary adjustments.

Prevention of Skin Toxicity

Patients could be advised to use prophylactic measures for skin care. These measures may include: the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF $\geq$ 30: avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick, cotton gloves and socks to prevent injury and to keep the palms and soles dry. Treating physicians may wish to carefully monitor patients with skin disorders for signs of infection (e.g. abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical, red and swollen areas on the palms and soles. Treating physicians may wish to consider adequate interventions to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas, including aggressive management of symptoms and an early dermatology referral.

Recommendations for treatment of palmar-plantar erythrodysesthesia (hand-foot) syndrome include urea 20% cream twice daily and clobetasol 0.05% cream once daily. Analgesics (e.g. NSAID, GABA agonist, narcotic) can be used for pain control if needed.

Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

Treating physicians may wish to consider carefully monitoring patients for episodes of abdominal pain, especially in patients with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis.

Prevention of Mucositis and Stomatitis

Comprehensive dental examination may be used as a preventative measure to identify any potential complications prior to initiation of protocol therapy, and, if indicated, the appropriate correction may need to be implemented such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, treating physicians may wish to advise patients to maintain good oral hygiene and standard local treatments such as non-traumatic cleansing and oral rinses (e.g. with a weak solution of salt and baking soda), as well as noting that the oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque.

Prevention of Osteonecrosis of the Jaw (ONJ)

Patients using concomitant antiangiogenic drugs, bisphosphonates, or denosumab may need to be monitored for ONJ more frequently, and treating physicians may wish to advise patients who have previously been treated with or concomitantly receive these medications to avoid invasive dental procedures if possible. In cases where dental procedures are unavoidable, treating physicians may wish to consider the risks and benefits of a dental procedure, the extent of the procedure, as well as the risk of developing osteonecrosis of the jaw when deciding how long to hold protocol therapy.

Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.

White Blood Cell Growth Factors and other FDA-approved White Blood Cell Growth Factor biologics may not be used to avoid dose reductions, delays or to allow for dose escalations specified in the protocol.

5.5 Criteria for Taking a Participant Off Protocol Therapy

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

1. Disease progression by RECIST 1.1 Criteria
   Although the primary endpoint is ORR as defined by RECIST 1.1, patients may remain on protocol therapy until the time of disease progression by irRC criteria. The immune criteria allows treatment beyond initial radiographic worsening of disease in order to distinguish between pseudoprogression and true disease progression.

2. Participants who have attained a confirmed complete response (CR) and who have been treated for at least 24 weeks on protocol therapy and had at least four treatments with nivolumab beyond the date when the initial CR was declared. Participants who stop nivolumab with CR may be eligible for additional nivolumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase Therapy, as summarized below.

3. Intercurrent illness that prevents further administration of treatment

4. Unacceptable adverse event(s). 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.

5. Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements. OR Significant noncompliance with the protocol schedule in the opinion of the investigator. OR Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued.

6. Participant decides to withdraw from the protocol therapy

7. General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

8. 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 5 months (women) or 7 months (men) after discontinuation of nivolumab and 4 months after discontinuation of cabozantinib

9. Women who become pregnant or are breastfeeding

10. Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol

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

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

Second Course Phase (Retreatment Period)

Participants may elect to stop nivolumab and cabozantinib with confirmed CR after at least 24 weeks of treatment.

Subjects who stop nivolumab and cabozantinib with CR may be eligible for additional nivolumab and cabozantinib therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Stopped initial treatment with nivolumab and cabozantinib after attaining an investigator-determined confirmed CR according to RECIST 1.1, was treated for at least 24 weeks with nivolumab before discontinuing therapy, and received at least four treatments with nivolumab beyond the date when the initial CR was declared

AND

- experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with nivolumab

- did not receive any anti-cancer treatment other than cabozantinib since the last dose of nivolumab

- meets all other study inclusion/exclusion criteria, as per Section 3.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they

last received nivolumab. Visit requirements are as outlined for subjects on the initial treatment phase of the trial.

5.6 Duration of Follow Up

Participants will be followed for initiation of a new regimen of anti-neoplastic therapy, first disease progression event after removal from protocol therapy or until death . Tumor assessments should continue to be performed every 12 weeks on these participants until first disease progression event or until death, whichever occurs first.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dosing/Delays/Omission/Modification

- The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications.
- If multiple adverse events are seen, administer dose based on the greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If more than one of these apply, use the most stringent (i.e. the greatest dose reduction).
- Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Participants held for these reasons require prior approval from the PI and should resume therapy within 6 weeks of the scheduled interruption. The reason for interruption should be documented in the participant's study record.

- If treatment is withheld > 8 weeks from the last dose of cabozantinib or nivolumab, the patient should discontinue study therapy.
- For management of AEs which can be clearly attributed to cabozantinib or nivolumab, independent dose modification for either agent is allowed as described. For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications or delay of both agents.
- Participants who require dose delay should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met.
- Delayed doses of nivolumab and cabozantinib should be administered as soon as the participant meets criteria to resume treatment. If a dose has been delayed, the participant should not wait until the next scheduled dosing date.
- Dosing interruptions will not impact assessments or cycle/day scheduling.
- Restarting of treatment after dose interruption must be discussed with the PI.
- In order to standardize the management of adverse events, treatment management algorithms recommended for utilization in this study are included in Appendix B.

6.2 Dose Levels

Dose Level	Nivolumab (IV)	Cabozantinib (tablet dose expression)
0 (starting dose)	240 mg	40mg daily
-1	-	20mg daily

Dose reductions are permitted for cabozantinib but not for nivolumab.

6.3 Hematologic Toxicities

For **grade 3 neutropenia with documented infection, grade 3 neutropenia ≥ 5 days, or grade 4 neutropenia**, delay cabozantinib and nivolumab until toxicity resolves to grade ≤ 1, then resume cabozantinib with one dose level reduction and nivolumab without dose reduction.

For **grade 3 febrile neutropenia**, delay cabozantinib and nivolumab until ANC grade ≤ 1 and temperature to ≤ 38.0°C, then resume cabozantinib with one dose level reduction and nivolumab without dose reduction.

For **grade 4 febrile neutropenia**, discontinue cabozantinib. Resume nivoluamb when ANC grade ≤ 1.

For **grade 3 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia**, continue nivolumab but delay cabozantinib until platelet count ≥ 100,000/mm^3, then resume cabozantinib with one dose level reduction.

For **grade 4 anemia**, continue nivolumab but delay cabozantinib and use supportive care (e.g. red blood cell transfusions) as clinically indicated according to institutional guidelines until toxicity resolves to grade ≤ 1, then resume cabozantinib with one dose level reduction.

6.4 **Diarrhea/Colitis**

Participants experiencing intolerable Grade 2 diarrhea or Grade 3 diarrhea unable to be managed with standard antidiarrheal treatments should consult a gastrointestinal (GI) doctor for potential endoscopy and biopsy to help distinguish between cabozantinib vs. nivolumab mediated toxicity.

If a biopsy is performed and:

- there is T cell infiltration indicative of nivolumab-induced colitis, nivolumab should be held and managed with corticosteroids. Once diarrhea returns to Grade 1, restart cabozantinib and nivolumab as indicated in the management table below.
- there is no T cell infiltration indicative of nivolumab-induced colitis, when diarrhea returns to Grade 1 nivolumab should be resumed at the same dose at the discretion of the investigator. Cabozantinib should also be resumed at a reduced dose.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose <10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea.

Table: Management of Diarrhea/Colitis

Grade	Management
Grade 1	• Continue nivolumab and cabozantinib. • Start Anti-diarrheal agent (e.g., Imodium) – up to 3 agents are permitted • Close monitoring.
Grade 2	• Hold nivolumab and cabozantinib • Administer anti-diarrheal agent (e.g., Imodium). • If symptoms persist > 5 days or recur, initiate therapy with Prednisone 60 mg/day or equivalent • If improved to Grade ≤1 within 8 weeks: o Taper steriods over ≥ 1 month o Restart Nivolumab when corticosteroids have been reduced to the equivalent of prednisone ≤ 10 mg/day. o Restart Cabozantinib at a reduced dose when corticosteroids have been reduced to the equivalent of prednisone ≤ 10 mg/day.
Grade 3	Hold nivolumab and cabozantinib. • Treat with IV steroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or

	equivalent) after improvement • If improved to Grade ≤1 within 8 weeks: o Taper steriods over ≥ 1 month o Restart Nivolumab when corticosteroids have been reduced to the equivalent of prednisone ≤ 10 mg/day. o Restart Cabozantinib at a reduced dose when corticosteroids have been reduced to the equivalent of prednisone ≤ 10 mg/day.
Grade 4	• Permanently discontinue nivolumab and hold cabozantinib. • Treat with IV steroids (1−2 mg/kg/day methylprednisolone or equivalent) and convert to oral steroids (prednisone 60 mg/day or equivalent) after improvement • When symptoms improve to Grade ≤ 1, taper steroids over ≥ 1 month • If symptoms are not improving after 48 hours of initiating steroids or are worsening, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. • If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at reduced dose as determined by the investigator.

6.5 **Hepatobiliary Disorders**

It is recommended that participants 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 participants who develop increased values of ALT, AST, or bilirubin.

Guidelines in the following table should be used for dose modifications.

Transaminase elevation CTCAE v. 5.0	**Intervention**
≤ Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN – 1.5x ULN	Continue study treatment, monitor liver function tests (LFTs) weekly for at least 4 weeks
Grade 2 AST or ALT > 3.0 to </= 5.0 x ULN and/or Total bilirubin >ULN – 1.5x ULN to </= x 3ULN	Hold cabozantinib and nivolumab Monitor LFTs at least twice weekly until return to baseline or Grade </= 1 Consider referral to a hepatologist If persistent > 5 days, start prednisone 60 mg/day or equivalent. When LFTs resolve to baseline or Grade ≤1 and steroid dose is

Transaminase elevation CTCAE v. 5.0	**Intervention**
	prednisone ≤ 10 mg/day or equivalent, restart nivolumab and cabozantinib at a reduced dose. * Permanently discontinue protocol therapy for conditions fulfilling Hy's law with elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation
Grade 3 AST or ALT > 5.0 to ≤ 20.0 x ULN and/or Total bilirubin > ULN – 3.0 x ULN to ≤10.0 x ULN	Hold cabozantinib and nivolumab. Monitor LFTs every 48−72 hours until LFTs return to baseline or Grade ≤1 Consider referral to hepatologist and liver biopsy to establish etiology of hepatic injury Start prednisone 60 mg/day or equivalent With first occurrence: . If LFTs do not resolved to Grade < 3 within 7 days, permanently discontinue nivolumab and continue holding cabozantinib. . When LFTs resolve to baseline or Grade ≤ 1, taper steroids over ≥1 month. When steroid dose is prednisone ≤ 10 mg/day or equivalent, restart Nivolumab and Cabozantinib at a reduced dose. Subjects receiving cabozantinib at a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the principal investigator. If recurs: permanently discontinue nivolumab . If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at reduced dose as determined by the investigator. * Permanently discontinue protocol therapy for conditions fulfilling Hy's law with elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation
Grade 4 AST or ALT > 20.0 x ULN and/or Total bilirubin > ULN 10.0 x ULN	Permanently discontinue nivolumab and hold cabozantinib and inform the principle investigator. Obtain hepatology consult and liver biopsy to establish etiology of hepatic injury. Start prednisone 60 mg/day or equivalent. If LFT results do not decrease within 48 hours after initiation of systemic steroids, consider addition of an alternative immunosuppressive agent (e.g., mycophenolate) to the corticosteroid regimen. If LFTs resolve to baseline or Grade ≤ 1, taper steroids over ≥1 month.

Transaminase elevation CTCAE v. 5.0	**Intervention**
	If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at reduced dose as determined by the investigator.

6.6 Elevated Amylase and/or Lipase

Patients may develop symptomatic and/or radiographic evidence of pancreatitis, diabetes mellitus, or pancreatic dysfunction related to cabozantinib or nivolumab. Amylase and lipase should be checked if there is clinical suspicion for pancreatitis. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations related to nivolumab.

Patients with symptomatic or radiographic pancreatitis should discontinue nivolumab and consider consulting a gastroenterologist for management.

Table: Management of elevated amylase and/or lipase

Grade	Management/ Next Dose for Cabozantinib and Nivolumab
≤3	For asymptomatic ≤ grade 3 lipase or amylase elevation, continue protocol therapy. Ensure that participants have associated symptoms consistent with pancreatitis, such as abdominal pain, or hyperglycemia or radiographic pancreatic inflammation.
4	Hold nivolumab and cabozantinib. Ensure that participants have associated symptoms consistent with pancreatitis, such as abdominal pain, or hyperglycemia or radiographic pancreatic inflammation. If patient remains asymptomatic, resume treatment when ≤ Grade 1.

6.7 Fatigue, Anorexia and Weight loss Disorders

Fatigue has been reported during treatment with cabozantinib and nivolumab, the dose modifications are recommended for both drugs. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms.

- For Grade ≥ 3 fatigue despite optimal management, hold nivolumab and cabozantinib. When fatigue improves to ≤ Grade 2, resume treatment with nivolumab at the same dose and cabozantinib at one dose level reduction.

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement.

- For Grade ≥ 3 anorexia and weight loss despite optimal management, delay therapy. Treatment with nivolumab and cabozantinib with one dose level reduction may be resumed when symptoms improve to grade ≤ 2.

6.8 **Stomatitis and Mucositis**

Refer to Section 5.4 for guidance regarding supportive care of mucositis and stomatitis.

For **grade 2 mucositis or stomatitis that is subjectively tolerable**, continue cabozantinib and nivolumab in addition to providing supportive care.

For **grade 2 mucositis or stomatitis that worsens, lasts ≥ 10 days, or interferes with adequate nutrition (and supportive care is insufficient)**, continue nivolumab but delay cabozantinib until toxicity improves to grade ≤ 1, then resume cabozantinib with one dose level reduction.

For **grade 3 mucositis or stomatitis that interferes with adequate nutrition (and supportive care is insufficient)**, continue nivolumab but delay cabozantinib until toxicity improves to grade ≤ 1, then resume cabozantinib with one dose level reduction.

For **grade 4 mucositis or stomatitis that interferes with adequate nutrition (and supportive care is insufficient)**, discontinue cabozantinib permanently, resume nivolumab when toxicity improves to grade ≤ 1.

6.9 **Palmar-plantar erythrodysesthesia (PPE) syndrome**

Palmar-plantar erythrodysesthesia syndrome (also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, and erythema have been reported in cabozantinib-treated participants. Refer to Section 5.4 for guidance regarding supportive management of skin toxicity.

Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

CTCAE v.5.0 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. Maintain dosing of nivolumab.
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 or is intolerable, proceed to the intervention guidelines for Grade 3. Maintain dosing of nivolumab.
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. Maintain dosing of nivolumab.

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.

6.10 **Other dermatologic disorders**

Treatment-emergent skin rash has been associated with nivolumab. The majority of cases of rash have been mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Table 5: Management of Skin Rash

Grade	**Intervention**
≤ Grade 1	No change in dose
Grade 2	Continue protocol therapy and monitor.
Grade 3	Omit dose of nivolumab and cabozantinib until < grade 1.
Grade 4	Discontinue nivolumab and hold cabozantinib If the subject is unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at one dose level below prior dose once resolves to grade ≤ 1.
. Patients with bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome,	

Grade	Intervention
	TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. . Pruritus may occur with or without skin rash and should be treated symptomatically. . Note skin rash typically occurs early and may be followed by additional events particularly during steroid taper.

6.11 **GI perforation/fistula and non-GI fistula formation**

GI perforation/fistula and non-GI fistula formation have been reported with cabozantinib and other approved drugs that inhibit VEGF pathways.

After starting 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 are present.

• Discontinue cabozantinib treatment in participants diagnosed with GI or non-GI perforation/fistula. Nivolumab can be resumed after perforation/fistula has healed.

6.12 **Treatment-emergent hypertension**

Guidelines for hypertension management:

- For patients who require a delay of greater than 6 weeks for management of hypertension, discontinue cabozantinib.
- Patients may have up to 3 agents for management of hypertension prior to any dose reduction in cabozantinib.
- 24 to 48 hours should elapse between modifications of anti-hypertensive therapy.
- Treating physicians should not add antihypertensive medications that are strong inducers or inhibitors of CYP3A4.

Criteria for dose modification	**Intervention**

> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	Maintain dose of cabozantinib and nivolumab; however, please see below for recommendations regarding anti-hypertensive therapy. Recommended Antihypertensive Therapy • Increase existing antihypertensive therapy or initiate a new antihypertensive agent if needed after 24-48 hours of treatment; increase dose in stepwise fashion every 24-48 hours until BP is controlled or at the maximum dose of therapy. • If BP is still not controlled, add another antihypertensive agent; increase dose of this drug as described in Step 1. • If BP is still not controlled, add a 3rd agent; increase dose of this drug as described in Step 1. • If BP is still not controlled after maximal medical management, proceed with one dose level reduction.
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	Maintain dosing of nivolumab. Delay cabozantinib until systolic BP ≤ 159 mmHg and diastolic BP ≤ 99 mmHg. Once blood pressure is controlled to this level, resume cabozantinib with one dose level reduction and consider the recommended antihypertensive therapy outlined above. For patients who require a delay of greater than 6 weeks for management of hypertension, discontinue cabozantinib. If the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110, then discontinue cabozantinib and recommend inpatient management as clinically indicated with IV medications.Maintain dosing of nivolumab. Delay cabozantinib until systolic BP ≤ 159 mmHg and diastolic BP ≤ 99 mmHg. Once blood pressure is controlled to this level, resume cabozantinib with one dose level reduction and consider the recommended antihypertensive therapy outlined above. NOTE: Discontinuing or reducing the dose of cabozantinib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.
Hypertensive crisis or hypertensive encephalopathy	Discontinue cabozantinib treatment. Hold nivolumab until resolution.

BP, blood pressure.

6.13 **Thromboembolic Event**

Maintain dosing of nivolumab.

For **grade 2 or 3 venous thrombosis requiring anticoagulation**, delay cabozantinib. If the planned duration of full dose anticoagulation is ≤ 2 weeks, then delay cabozantinib until

anticoagulation is completed. If the planned duration of full dose anticoagulation is > 2 weeks, then resume cabozantinib during anticoagulation therapy if all of the following are met:

- The patient must be on a stable dose of LMWH prior to restarting cabozantinib. Warfarin or a novel oral anticoagulation drug may not be used for anticoagulation.
- The patient must not have any pathological condition that carries a high risk of bleeding.
- The patient must not have had any hemorrhagic events while on study.

For **recurrent/worsening venous thromboembolic events after resuming cabozantinib**, discontinue cabozantinib.

For **grade 4 venous thromboembolic events**, discontinue cabozantinib.

For **any grade arterial thromboembolic events including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia**, discontinue cabozantinib.

6.14 **Hemorrhagic Events**

Maintain dosing of nivolumab.

For **grade 2 CNS or pulmonary hemorrhage**, discontinue cabozantinib.

For **any other grade 3 or 4 hemorrhage**, discontinue cabozantinib.

6.15 **Proteinuria**

Proteinuria is an expected AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies. Nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways.

Management of Proteinuria:

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in protocol 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 • Continue nivolumab dosing • 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 and nivolumab 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 and nivolumab treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart nivolumab and 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. • If treatment is delayed for more than 6 weeks due to proteinuria, discontinue cabozantinib and nivolumab treatment.
Nephrotic syndrome	• Discontinue cabozantinib and nivolumab treatment.

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

6.16 **Hypophosphatemia**

Hypophosphatemia has been reported during treatment with cabozantinib.

Mild hypophosphatemia is usually asymptomatic or symptoms can be non-specific such as weakness, bone pain, rhabdomyolysis, or altered mental status. Other causes of hypophosphatemia such as poor nutrition, chronic alcoholism, malabsorption, excessive antacid use, glucocorticoids use, kidney dysfunction, respiratory alkalosis, vitamin D deficiency should be ruled out and/or these causes treated according to standard of care.

Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements according to standard clinical practice guidelines.

6.17 **Osteonecrosis of the Jaw**

To minimize the risk of osteonecrosis of the jaw, it is recommended that, if possible, cabozantinib be stopped at least 4 weeks prior to dental procedures such as tooth extractions, implants, and major jaw surgery whenever possible. Cabozantinib does not need to be held for routine dental fillings and cleanings.

6.18 **QTcF Prolongation**

For **QTcF interval > 500 msecs**, (confirm with triplicate EKG) continue nivolumab but delay cabozantinib, stop any medications that may prolong the QTcF interval (if possible), and consider checking calcium, potassium, and magnesium levels and correcting any abnormalities. Once QTcF interval ≤ 500 msecs, correction of electrolyte abnormalities has been considered, and symptoms have resolved, cabozantinib may be resumed with one dose level reduction.

6.19 **Pulmonary Toxicity**

Mild-to-moderate events of pneumonitis have been reported with nivolumab. Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Management of pneumonitis is as summarized in the following table:

Grade	Management
≤1	Continue protocol therapy if radiologic findings only; dose may be held for further evaluation per investigator discretion
2	Hold nivolumab pending evaluation. Patient should discontinue nivolumab if prolonged steroids are required unless an alternative etiology of findings is identified. Withhold cabozantinib until resolved to ≤ Grade 1.
3	Discontinue nivolumab. Withhold cabozantinib until resolved to ≤ Grade 1.
4	Discontinue nivolumab. Withhold cabozantinib until resolved to ≤ Grade 1.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza inactivated vaccine for all patients.	

6.20 **Neurologic Events**

The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin. Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), Guillain-Barre syndrome, and myasthenia gravis should discontinue nivolumab. If reversible posterior leukoencephalopathy syndrome (RPLS) is diagnosed then discontinue cabozantinib.

Table: Management of Neurologic Events

Grade	Management
≤1	Continue protocol therapy
2	Hold nivolumab. Hold cabozantinib. If treatment with steriods is required, permanently discontinue nivolumab. If no treatment with steroids is required, and it has resolved to ≤ Grade 1, resume nivolumab and caboantinib at same dose. Participants are permitted to resume treatment with nivolumab for peripheral isolated CN VII (Bell's palsy) when stable.
3	Discontinue nivolumab. Hold cabozantinib. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at a lower dose as determined by the investigator.
4	Discontinue nivolumab. Hold cabozantinib. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at a lower dose as determined by the investigator.

6.21 **Endocrinopathy including hypophysitis and adrenal insufficiency**

Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI or aseptic meningitis or encephalitis should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored.

Table: Management of Endocrinopathy including hypophysitis and adrenal insufficiency

Grade	Management
≤2	Asymptomatic abnormalities do not require dose delay*. If symptomatic, hold until on a stable replacement hormone regimen. If treated with steroids patients, must be stable off of steroids for two weeks with the exception of adrenal replacement therapy.
3	Hypophysitis: Hold nivolumab and cabozantinib* until ≤ Grade 1, then resume at same dose. Other endocrinopathies: Hold nivolumab and cabozantinib* until ≤ Grade 1 and stable on replacement hormones, then resume at same dose.

4	Discontinue nivolumab. Discontinue cabozantinib. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume cabozantinib at a lower dose as determined by the investigator.

*Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement, and steroids including baseline serum: cortisol, ACTH, TSH and free T4

6.22 **Thyroid Dysfunction**

- Cabozantinib and nivolumab do not need to be held for asymptomatic participants. Management of thyroid dysfunction should follow accepted clinical practice guidelines.
- For **grade 3 hyper- or hypothyroidism**, delay cabozantinib until toxicity improves to grade ≤ 2, then resume nivolumab and cabozantinib with one dose level reduction.
- For **grade 4 hyper-or hypothyroidism**, discontinue cabozantinib and nivolumab.

6.23 **Creatinine Levels/ Renal Insufficiencies**

Table: Management of Creatinine Levels/Renal Insufficiencies

Grade	Management
≤1	Continue protocol therapy. Monitor weekly until return to baseline.
2-3 (>1.5 baseline to ≤ 6 3.0 x ULN)	Hold nivolumab and cabozantinib until ≤ Grade 1. Monitor creatinine every 2-3 days. Start 0.5 to 1.0 mg/Kg/day methylprednisolone IV or oral equivalent. Consider consulting nephrology and obtaining a renal biopsy.
4 (>6.0 x ULN)	Discontinue nivolumab and hold cabozantinib. Monitor creatinine daily. Start 1.0 – 2.0 mg/Kg/day methylprednisolone IV or oral equivalent. Consult nephrologist and consider obtaining a renal biopsy.

6.24 **Infusion Reactions**

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study PI and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE (version 5.0)) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

Table: Management of Infusion Reaction

Grade	Management
≤1	Continue nivolumab infusion, remain at bedside. Continue cabozantinib.

	Institute prophylactic medications with subsequent infusions.
2	Hold nivolumab until resolution to ≤ Grade 1. Refer to management and rechallenging instructions below. Continue cabozantinib.
3	Discontinue nivolumab. Continue cabozantinib.
4	Discontinue nivolumab. Continue cabozantinib.

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

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

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. Restart the infusion at 50% of the original infusion rate when symptoms resolve to Grade ≤ 1; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administration. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms:

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

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, treat with bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids)

6.25 **Fever**

Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.

Table 16: Management of Fever

Grade	Management
≤1	Continue nivolumab and cabozantinib and monitor.
2	Hold nivolumab and cabozantinib until ≤ Grade 1
3	Hold nivolumab and cabozantinib until ≤ Grade 1
4	Hold nivolumab and cabozantinib until ≤ Grade 1

6.26 **Management of other toxicities attributable to cabozantinib**

General guidance for management of non-hematologic toxicity not described above and considered at least possibly related to cabozantinib only:

CTCAE v.5.0 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. Continue nivolumab
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care. Continue nivoliumab.
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. Continue nivolumab. 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 Contiue nivolumab.

AE, adverse event.
[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.

6.27 Management of other toxicities attributable to nivolumab

General guidance for management of other non-laboratory adverse events not described above attributed to nivolumab only:

Grade	Management/Next Dose for Nivolumab
≤ 1	Continue protocol therapy.
2	Hold nivolumab until ≤ Grade 1 OR baseline (exceptions as noted below). Continue cabozantinib.
3	Omit dose of nivolumab if not recurrent (exceptions as noted below). Continue

Grade	Management/Next Dose for Nivolumab
	cabozantinib.
4	Discontinue nivolumab therapy. Continue cabozantinib.
Recommended management: Low-grade events that are considered drug related and any high-grade events of unclear etiology should be fully evaluated and treated with systemic corticosteroids if an alternative etiology is not identified.	

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events Lists

7.1.1 Expected adverse events for cabozantinib

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (eg, pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal [GI] perforation and rectal/perirectal abscess. Additionally, events of arterial thromboembolism (transient ischemic attack [TIA], myocardial infarction [MI]) have been reported. For a full listing of safety events please refer to the Cabozantinib Investigational Brochure.

7.1.2 Expected adverse event for nivolumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 DF/HCC Adverse Event Reporting Guidelines

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

7.3.4 Reporting to the Food and Drug Administration (FDA)

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

7.3.5 Reporting to Hospital Risk Management

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

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the

toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.5 Expedited Reporting to BMS

All SAEs that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

All SAEs must be reported to BMS within 24 buiness hours of the awareness of the event. SAEs must be recorded on a Medwatch Form 3500A.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

If only limited information is initially available, a follow-up report is required and should include the same investigator term(s) initially reported.

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

All SAEs should be followed to resolution or stabilization.

7.6 Expedited Reporting to Exelexis

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 that are assessed by the PI as **related** to drug or study procedure 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, on a MedWatch 3500A Form, must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- 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.

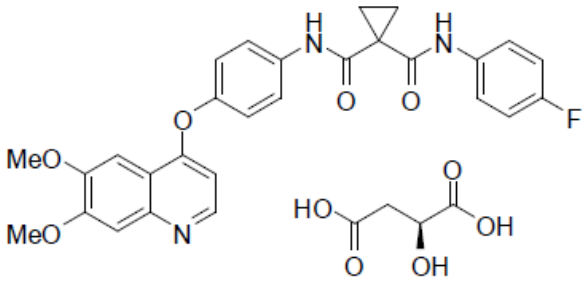
8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 Cabozantinib

8.1.1 Description

Cabozantinib is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is C28H24FN3O5·C4H6O5 and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is:



In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

8.1.2 Form

Cabozantinib/XL184 Tablets

The manufacturer will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 20-mg yellow film-coated tablets. The 20-mg tablets are round. The components of the tablets are listed in the table below. The sponsor is requiring pharmacy to dispense cabozantinib in original containers; if needed, it is permissible for DF/HCC pharmacy to remove and destroy the tablets in excess of the dosing requirement per standard practice, while still dispensing the drug in the original container.

Table: Cabozantinib Tablet Components and Composition

Ingredient	Function	%w/w
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910/Hypromellose 6cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

8.1.3 Storage and Stability

Store cabozantinib at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

8.1.4 Compatibility

Not applicable

8.1.5 Handling

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

8.1.6 Availability

Cabozantinib is an investigational agent and will be supplied free-of-charge from Exelixis.

8.1.7 Preparation

Not applicable

8.1.8 Administration

Cabozantinib is administered once daily as an oral tablet. Participants will be provided with a

sufficient supply of study treatment and instructions for taking the study treatment on days without scheduled clinic visits. After fasting (with exception of water) for 2 hours, participants will take study treatment daily each morning with a full glass of water (minimum of 8 oz/ 240 mL) and continue to fast for 1 hour after each dose of study treatment. If doses are withheld, the original schedule of assessments should be maintained when cabozantinib is restarted. The participant should be instructed to not make up the missed doses and to maintain the planned dosing schedule. Participants must be instructed to not make up missed doses that are vomited.

8.1.9 Ordering

Cabozantinib will be provided by Exelixis.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

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.

8.1.11 Destruction and Return

At the end of the study, unused supplies of cabozantinib and nivolumab should be destroyed according to institutional policies. Expired supplies of cabozantinib and nivolumab will be destroyed according to DF/HCC instititutional SOP. Destruction will be documented in the Drug Accountability Record Form.

8.2 **Nivolumab**

8.2.1 Description

Nivolumab is also referred to as BMS-936558-01 or BMS-936558. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are provided in the table below. The geometric mean of terminal T-HALF was 25.6 days and the typical clearance was 8.8 mL/h, which are consistent with those of full human immunoglobulin antibodies.

Table: Nivolumab Physical and Chemical Properties

BMS Number	**BMS-936558-01**
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, Anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

8.2.2 Storage and Stability

Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking. Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

8.2.3 Compatibility

No incompatibilities between Nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

8.2.4 Handling

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

8.2.5 Availability

Nivolumab is available as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

8.2.6 Preparation

Nivolumab is available as 100 mg vials (10 mg/mL), which include an overfill. It is supplied in 10 mL type I flint glass vials, with butyl stoppers and aluminum seals. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5%

Dextrose, USP to a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.

8.2.7 Administration

Nivolumab will be delivered in infusion bags with IV infusion lines over 30 minutes (+/- 10 minutes) using a volumetric pump with 0.2 to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

8.2.8 Ordering

Nivolumab will be provided by BMS.

8.2.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

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.

8.2.10 Destruction and Return

At the end of the study, unused supplies of nivolumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlative Science Objectives

- To explore whether baseline tumor immune cell infiltration and PD-L1 and PD-L2 staining correlates with response to therapy.
- To explore whether changes in circulating immune cell profile correlates with response to therapy
- To explore whether changes in the level of angiogenic and inflammatory blood biomarkers during therapy correlate with efficacy of therapy

9.2 **Hypothesis:**

Based on what has been described in breast cancer with single agent exposure to Cabozantinib, we hypothesize the following:

(1) there will be an increase in CD3+ T-lymphocytes, primarily CD8CD4- cytotoxic T lymphocytes
(2) a decrease in monocytes
(3) impairment of neutrophil recruitment

In all patients in the run-in phase (first 18 patients) for whom tumor is safely accessible, a baseline and on-treatment tumor biopsy during cycle 2 is required. Based on concerns for biopsy associated complications, a safety evaluation will be performed after 6 patients have undergone an on-treatment biopsy.

For those undergoing a biopsy the following criteria must be met:

- Biopsy should be done only in patients in whom the tumor is safely accessible.
- Due to the risk of perforation and fistula with cabozantinib,
  - transesophageal and transintestinal biopsies should not be performed
  - biopsies should not be performed in areas of prior fistula formation, surgery or radiation.
- **To minimize risks of bleeding, the on-treatment biopsy should be performed with a 20 gauge (or smaller) needle.**

Serial blood draws for correlative science are required on this trial; blood draws will be obtained the first day of cycles 1 and 2 prior to the infusion of study drugs, at the end-of-treatment visit in patients who go off study for progressive disease, and all efforts will be made to obtain an additional blood draw at the time of progressive disease in patients who went off study for anything other than progressive disease.

Summary of Specimens

Research Sampling	Timepoint	Contents	Destination
Archival Tissue	Anytime on study	1 FFPE block or 10-20 5 micron unstained slides	DFCI Clinical Research (Dr. Perez)
Fresh Tissue	Baseline	5-7 cores	DFCI Clinical Research (Dr. Perez) / DFCI Rodig Lab
	End of cycle 2	5-7 cores	DFCI Clinical Research (Dr. Perez) / DFCI Rodig Lab
Stool Sample	Pre-treatment	1 Stool sample	CIO Immune Assessment Lab of Mariano
	At time of on treatment biopsy	1 Stool sample	

Blood	Baseline, cycle 2 day 1, cycle 3 day 1, and at progression	5 – Green Top 10 ml Sodium Heparin tubes (REF 366480) (PBMCs)	CIO Immune Assessment Lab of Mariano Severgnini

9.3 **Archival Tissue**

1 block or 10-20 5 micron unstained, charged slides will be collected for future research.

9.4 **Fresh Tissue Biopsy**

Objectives:

- Characterizing immune markers in metastatic well differentiated carcinoid tumors.
- Compare MET and phospho-MET expression in tumor tissue at baseline and after tumor exposure to the combination of MET and PD-1 inhibition.

Collection and Storage of Fresh Tissue

Tissue biopsy samples will be processed with 4-6 cores put in FFPE as per usual institutional practice and a separate core to be put in FFPE to be set to BWH Pathology.

Details on processing and shipping of samples are provided in Appendix C.

Potential Testing:

Assay 1: Immune population characterization by Multiplex Immunofluorescence (mIF)

Objective: identify subsets of different immune populations (effector/memory CD8 cells, T regulatory cells, dendritic cells, tumor associated macrophages, and Tie-2 expressing monocytes) and changes in these populations in response to cabozantinib and nivolumab at baseline versus 4-6 weeks post initiation of treatment.

Methods: The CIO Tissue Biomarker Laboratory (TBL) led by Dr. Scott Rodig and Ana Lako offers multiplex immunofluorescence biomarker imaging for multi-label analysis of formalin- FFPE tissue biopsy samples. We use the PerkinElmer's multiplex biomarker imaging systems to precisely measure and quantify multiple fluorescent molecular markers simultaneously, even when co-localized within a single tissue section. The data for each marker is spectrally unmixed, generating clear and accurate images for each of the individual labels in a multi-labeled tissue section with no crosstalk. Specifically, we will use the Opal chemistry and multispectral microscopy Vectra™ 3.0 and Polaris™ systems (Perkin-Elmer), which includes the Nuance software; analysis will be performed using the inForm software. T-cell and other immune cell subpopulations are defined by co-expression of specific markers and are evaluated as cell density per tumor tissue (number of positive cells by mm square of tumor area. The staining procedure is

performed by specialized technicians under pathologist supervision, and the scanning and analysis is done by senior scientists and a pathologist trained in the use of Vectra and InForm.

The following antibodies will be assessed by mIF to identify the presence of the immune subsets:

T Cell Panel: CD4, CD8, FoxP3
Tumor Characteristics Panel: Chromogranin, PD-L1, PD-L2, TIM-3, and LAG-3
Monocyte Panel: CD68, CD 163, Indoleamine 2,3 deosygenase -1 (IDO-1), CD11c, CD14, CD16, CD56

Assay 2: CyTOF

Objective: analyze the characteristics of the TILs present in carcinoid tumors

Methods: The CIO Immune Assessment Lab led by Mariano Severgnini and Dr. Emily McWilliams offers CyTOF; a single-cell proteomic technology that allows for the analysis of 30+ cellular parameters using antibodies tagged with heavy metal isotopes to elucidate complex phenotypic and functional characteristics of heterogeneous immune populations as well as their activation status and checkpoint marker expression. The technology is closely related to flow cytometry, but the readout is based on mass spectrometry rather than fluorescence. CyTOF technology currently allows us to analyze over 35 parameters in parallel while being significantly less affected by spillover between channels, natural background, and cell-based autofluorescence. Each CyTOF panel includes 12 immunological core markers: CD3, CD4, CD8, CD11C, CD14, CD16, CD19, CD25, CD45, CD56, CD127, and HLA-DR that will identify CD8, CD4 T cells, regulatory T cells, B cells, NK cells, and myeloid cell subsets including dendritic cells, basophils, and neutrophils. Panels can then be customized on a per trial basis to over 30+ parameters including identification of checkpoint molecules (PD-1, PD-L1, etc), and markers for memory, activation, trafficking, and cytotoxicity. The samples will be run on a CyTOF2 mass cytometer (Fluidigm) housed at DFCI and analyzed by DFCI scientists using tools such as Cytobank and Astrolabe.

TILs isolated from the biopsy specimen will be assessed and the following antibodies will be used, with the potential to alter based on novel developments in the field of cancer immune profiling:

Panels to include: CD8, PD-1, PD-L1, PD-L2, CD4, CD25, CD127

Assay 3: c-Met expression

Objective: Evaluate c-Met and phosphor-c-Met expression in the tumor tissue at baseline vs. 4-6 wks post treatment.

Methods: tumor tissue sections will be de-parrafinized prior to antigen retrieval, blocking and incubation with primary antibodies to determine: (1) Qualification of c-Met expression; (2) association between expression and response to therapy

9.5 **Blood Collection**

Research blood collection is mandatory for all patients for flow cytometry and potential DNA isolation. The samples will be banked in the DFCI CIO Immune Assessment Labfor these and future research purposes. These specimens will become the property of the DF/HCC.

Potential Testing:
Assay 1: CyTOF

Objective: analyze the characteristics of the PBMCs present in patients with active carcinoid tumors.

Methods: Surface staining with a panel of antibotides on PBMCs will be performed utilizing a previously developed panel that includes the following:

Assay 2: Evaluate potential plasma biomarkers of cabozantinib

Objective: conduct an exploratory analysis of potential biomarkers of cabozantinib activity.

Methods: The CIO IAL offers FLEXMAP 3D: Luminex's most advanced and versatile multiplexing platform. Capable of multiplexing up to 500 analytes (cytokines, chemokines, growth factors, etc) in a single sample. Analytes of interest will include a panel of circulating angiogenic and inflammatory molecules previously identified as potential biomarkers of response to therapy.

> *Biomarkers specific to anti-VEGF therapy:* VEGF, placental-derived growth factor (PIGF), VEGF-C, VEGF-D, sVEGFR1, basic granulocyte-macrophage colony stimulating factor (GM-CSF), interferon gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), and interleukin (IL)-1B, IL-2, IL-6, IL-8, IL-10, and IL-12 heterodimer p70, and stromal-derived factor 1 alpha.
> *Biomarkers specific to cabozantinib activity:* HGF, s-MET, s-c-KIT and sVEGFR2

9.6 **Stool Collection**

Research stool collection is mandatory for all patients. The samples will be banked in the DFCI CIO Immune Assessment Labfor these and future research purposes. These specimens will become the property of the DF/HCC.

Each participant will provide two stool samples, one obtained during screening and the other between the time of the on treatment biopsy and the next planned treatment visit. Participants should be instructed to collect the stool samples once eligibility has been confirmed. This will be proceeded and analyzed by the DFCI Center for Immuno-Oncology, Immune Assessment Laboratory, under the direction of Mariano Severgnini, PhD. The purpose of which is to evaluate

participant's microbiome as a possible predictive marker for immunotherapy treatment.

9.7 **Statistical Considerations**

All tissue and circulating biomarkers will be correlated with clinical outcome in collaboration with our statistician. Descriptive statistics will be provided for all outcome measurements, as appropriate.

9.8 **Additional analysis**

The plans for tissue and blood analyses will be altered based on novel developments in the field of cancer immune profiling at the time of correlative science. Additional markers or alternative technologies (based on scientific developments and/or novel technologies) may also be used, to explore potential prognostic or predictive candidate markers/panels or markers related to treatment benefit and/or safety, to improve diagnostic tests, or to understand carcinoid biology.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Screening	Cycle 1		Cycle 2			Cycle 3+		End of Treatment (Within 30 Days of Last Dose)	Safety Follow Up (100 Days After Last Dose)[c]
		Day 1	Day 15	Day 1	Day 15	Day 16-28[j]	Day 1	Day 15		
Cabozantinib[A]		X	X	X	X		X	X		
Nivolumab[B]		X	X	X	X		X	X		
Informed consent	X									
Medical history	X									
Concurrent Medications[l]	X									
Physical exam[d]	X	X	X	X	X		X	X	X	X
Vital signs[e]	X	X	X	X	X		X	X	X	X
Performance status	X	X		X			X		X	X
CBC w/diff, plts[f]	X	X	X	X	X		X	X	X	X
Serum chemistry[a]	X	X	X	X	X		X	X	X	X
Urine protein creatinine ratio	X	X		X			X			
TSH/fT4[g]	X	X		X			X			
Pregnancy Test[b]	X	X[b]		X[b]			X[b]			
Coagulation Panel (PT/PTT)	X									
LDH	X									
EKG	X	X		X			X			
Research Biopsy[j]	X					X				
Research Blood[k]	X			X			X		X	
Research Stool	X[m]					X[n]				
Adverse event evaluation		X----------X								X
Tumor measurements[h]	X	Tumor measurements are repeated every 8 (+/- 1) weeks for the first 24 weeks, then every 12 (+/- 1) weeks thereafter as indicated below. Documentation (radiologic) must be provided for participants removed from study for progressive disease.								X

A: Cabozantinib: 40mg PO days 1-28 of a 28 day cycle
B: Nivolumab: 240 mg IV on days 1, 15 of a 28 day cycle.

a. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b. In female subjects of child-bearing potential as defined in the eligibility criteria, pregnancy test must be performed within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 1 week.
c. Off-study evaluation.
- follow up visits or other contact required in order to identify SAEs during the 100 days following the end of study treatment.
- Male and Female subjects must be educated on contraception post treatment: women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab. Contraception must be used for 4 months after last dose of cabozantinib.

d. A complete physical examination will be performed at baseline. A limited physical exam will be completed prior to therapy on Days 1 and 15 for Cycles 1 and 2 and on Day 1 of every cycle beginning with cycle 3.
e. Vital sign assessments include measurements of heart rate, systolic and diastolic blood pressures, respiratory rate, temperature and weight.
f. Hematology includes: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute

	differential count. Results must be available prior to the administration of study drug. ANC must be ≥1500 for eligibility and Cycle 1 Day 1. Subsequent ANC must be ≥1000. g. TSH and free T4 will be performed during screening, on Day 1 of Cycles 1-4 and then every other cycle on Day 1. h. Tumor assessments should consist of 1) CT chest/abdomen/pelvis and/or MRI of the abdomen/pelvis, and 2) any other imaging studies (CT neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Tumor assessments will be performed every 8 weeks (+/- 1 week) calculated from C1D1 for the first 24 weeks, then every 12 weeks (+/- 1 week) thereafter. Additional scans are permitted as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments will occur as outlined regardless of dose holds or treatment delays. i. End of treatment visit is to occur within 30 days of final administration of study treatment. End of treatment assessments do not have to be repeated if the same assessments were performed within 7 days (28 days for tumor assesments) prior to the visit. j. For the first 18 patients during the run-in phase: The first biopsy of a metastatic site should occur during the 2 weeks before initiating treatment on cycle #1. Please see section 9.2. Preferably, the same metastatic lesion will be biopsied twice. k. Five 10mL whole blood sample for research will be collected at baseline, C2D1, C3D1, and progression The sample will be collected at the end of treatment visit for all patients who discontinue due to progressive disease, and all efforts will be made to obtain an additional blood draw at the time of progressive disease in patients who went off study for anything other than progressive disease. l. If new medications or changes are prescribed while patient is receiving treatment on study, these medications should be recorded. m. Stool sample will be collected during screening, prior to C1D1. Sample should be received within 1 day of collection. n. Stool sample will be collected between the time of the on treatment biopsy and the next planned treatment visit. Sample should be received within 1 day of collection.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every *8* weeks (+/- 1 week) for the first 24 weeks, then every 12 weeks (+/- 1 week) thereafter. In addition to a baseline scan, confirmatory scans should also be obtained *8* (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

Evaluable Non-Target Disease Response. Participants who have lesions present at

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

11.1.2 Disease Parameters

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

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

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

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

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

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

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

11.1.3 Methods for Evaluation of Disease

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

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

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

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

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

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

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes

reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must

normalize for a patient to be considered in complete clinical response.

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

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

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

11.1.4.3 Evaluation of New Lesions

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

11.1.4.4 Evaluation of Best Overall Response

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

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

11.1.5 Duration of Response

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

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

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

11.1.6 Survival and Time to Progression Definitions

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.2 Other Response Parameters

11.2.1 Definition of Tumor Response Using Immune-Related Response Criteria (irRC)

The sum of the longest diameter of lesions (SPD) at tumor assessment using the immune- related response criteria (irRC) for progressive disease incorporate the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

11.2.2 Impact of New Lesions on irRC

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

11.2.3 Definition of Target Lesions Response Using irRC

. **irComplete Response (irCR):** Complete disappearance of all target lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
. **irPartial Response (irPR):** Decrease, relative to baseline, or 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable target lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SBD increases by >25% when compared to SPD at nadir.
. **irStable Disease (irSD):** Does not meet criteria for irRC or irPR, in the absence of progressive disease.
. **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e. taking SPD of all target lesions and any new lesions) when compared to SPD at nadir.

11.2.4 Definition of Non-Target Lesions Response Using irRC

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

11.2.5 Definition of Overall Response Using irRC Overall response using irRC will be based on these criteria:

. **Immune-Related Complete Response (irCR):** Complete disappearance of all tumor lesions (target and non-target) together with no new measurable/unmeasurable lesions for at least 4 weeks from the date of documentation of complete response.
. **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all target lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline, of the irSPD compared to the previously SPD baseline of 50% or greater is considered an irPR.
. **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease
. **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute PD:
    - At least 25% increase in the SPD of all target lesions over baseline SPD calculated for the target lesions.
    - At least 25% increase in the SPD of all target lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the target lesions.

Criteria for determining overall response by irRC are summarized as follows:

Immune-Related Response Criteria Definitions

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

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

irBOR is the best confirmed overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

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

12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix D.

13 ETHICAL ASPECTS

13.1 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.”

13.2 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.

13.3 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.

14 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 and Bristol Myers Squibb 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).

15 CONDITIONS FOR TERMINATING THE STUDY

At any time, the study may be terminated by the study sponsor(s), the sponsoring institution, or by Exelixis and/or Bristol Myers Squibb. Should this be necessary, Exelixis and/or Bristol Myers Squibb and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and/or Bristol Myers Squibb 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.

15.1 Collaborative Agreements Language

N/A

16 STATISTICAL CONSIDERATIONS

16.1 Study Design/Endpoints

The study intends to examine the clinical efficacy and tolerability of cabozantinib and nivolumab in the treatment of patients with advanced carcinoid. The study includes an interim analysis after 18 patients to assure tolerability and to evaluate response rate of combining cabozantinib and nivolumab. This combination is likely to be well tolerated based on prior studies in patients with breast cancer and renal cell carcinoma, but these data require confirmation in patients with carcinoid tumors. This is a one-arm study without randomization. If objectives of the interim analysis are met then enrollment will be expanded to include 17 additional patients.

16.1.1 Primary endpoint:

The primary efficacy endpoint is the objective response rate (ORR) in patients with advanced carcinoid tumors treated with the combination of cabozantinib and nivolumab. ORR is defined using the RECIST 1.1 criteria as the proportion of subjects with a confirmed CR or a confirmed PR.

16.1.2 Secondary endpoint:

The secondary endpoints are safety, response rate according to immune-related response criteria, duration of response, progression free survival (PFS), and overall survival (OS) for patients with advanced carcinoid tumors treated with the combination of cabozantinib and nivolumab.

16.2 Sample Size, Accrual Rate and Study Duration

The primary objective of this study is to investigate the safety and tolerability of the combination of cabozantinib and nivolumab. Based on the results of a phase II trial of cabozantinib as monotherapy for patients with advanced carcinoid and pancreatic NET and other trials examining anti-PD-1 agents in patients with other malignancies not selected by PD-L1 status, a true objective response rate (ORR) of 10% or less would not be of clinical interest and represents the null hypothesis of this study. A true rate of 30% would be considered a clinically meaningful level of response. The sample size for this study was chosen to have 95% power to declare the combination effective at this rate with a one-sided Type 1 error of no more than 5%.

Using a Simon's two-stage design, 18 patients will be enrolled in the first stage. If in this first stage there are at least 3 patients with an objective response (ORR), accrual will continue to the second stage where an additional 17 patients will be enrolled. If there are at least 7 patients with an objective response among the total 35 patients, the regimen will be considered worthy of further study.

If the true response rate is 10%, the chance the regimen is declared worthy of further study is less than 5% (exact alpha = 0.047). If the true response rate is 30%, the chance that the regimen is declared worthy of further study is 95%

16.3 **Analysis Plan**

The primary endpoint is the objective response rate (ORR). We will calculate the frequency and percentage of responses. The point estimate of the ORR with a 9% confidence interval based on the exact binomial distribution will be presented.

With a sample size of 35, if the observed ORR is 30%, we will estimate the 95% confidence interval for the ORR to be 14.8% to 45.2%.

Below is a table for the 95% CIs corresponding to varying observed ORR

	95% CI
15%	**3.2% to 26.8%**
20%	**6.8% to 33.3%**
30%	**14.8% to 45.2%**
40%	**23.8% to 56.2%**

The secondary endpoints are safety, response rate according to immune-related response criteria, duration of response, progression free survival (PFS), and overall survival (OS) for patients with advanced carcinoid tumors treated with the combination of cabozantinib and nivolumab.

Safety will be assessed by analysis of adverse event (AE) and toxicity data. AE and toxicity data, including laboratory values, will be graded using CTCAE version 5.0. Tabulations of toxicities will be provided by organ system and attribution.

Response rate according to immune-related response criteria will be analyzed using the same method for ORR. Duration of response will be summarized using mean, standard deviation, median, and inter-quartile range.

Progression free survival and overall survival will be defined from time of randomization to time of progression or date of death, respectively. Any patients who have not died by the analysis cut-off date or are lost to follow up will be censored at their last date of contact. Any patient that withdraws consent for follow up will be censored on the date of withdrawal of consent. Kaplan-Meier method will be employed to obtain survival estimates and median survival times will be provided. Greenwood's formula will be used to construct 95% confidence intervals around these estimates.

16.4 Interim Monitoring Plan

If in the first stage there are at least 3 patients with an objective response (ORR), accrual will continue to the second stage where an additional 17 patients will be enrolled.

16.5 Evaluation of Toxicity

For the safety analysis, all enrolled patients who receive at least one dose of cabozantinib and nivolumab will have information collected on adverse events, which will be summarized by severity as assessed by the Common Toxicity Criteria for Adverse Events (CTCAE), v. 5.0 and relationship to study drugs.

17 PUBLICATION PLAN

A final study report will be provided within 12 months of the first visit of the last patient enrollled. The results should be made public within 12 months of reaching the end of the study.

The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B GI ADVERSE EVENT MANAGEMENT ALGORITHM

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

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

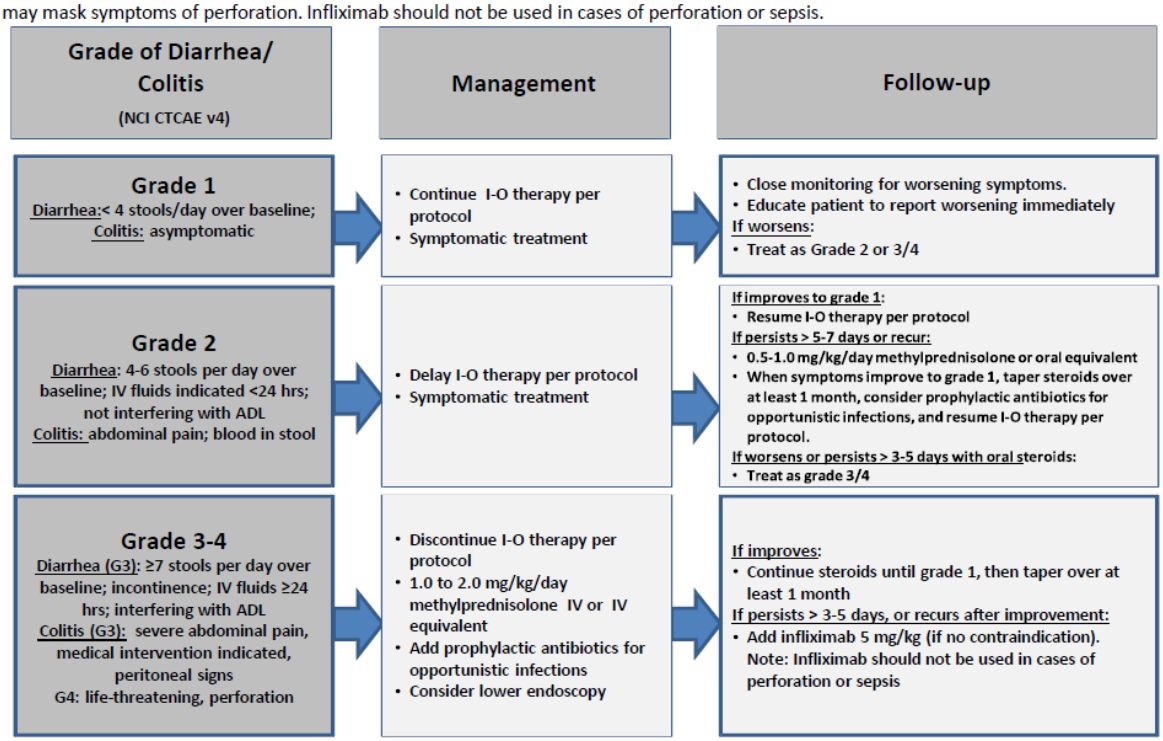
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

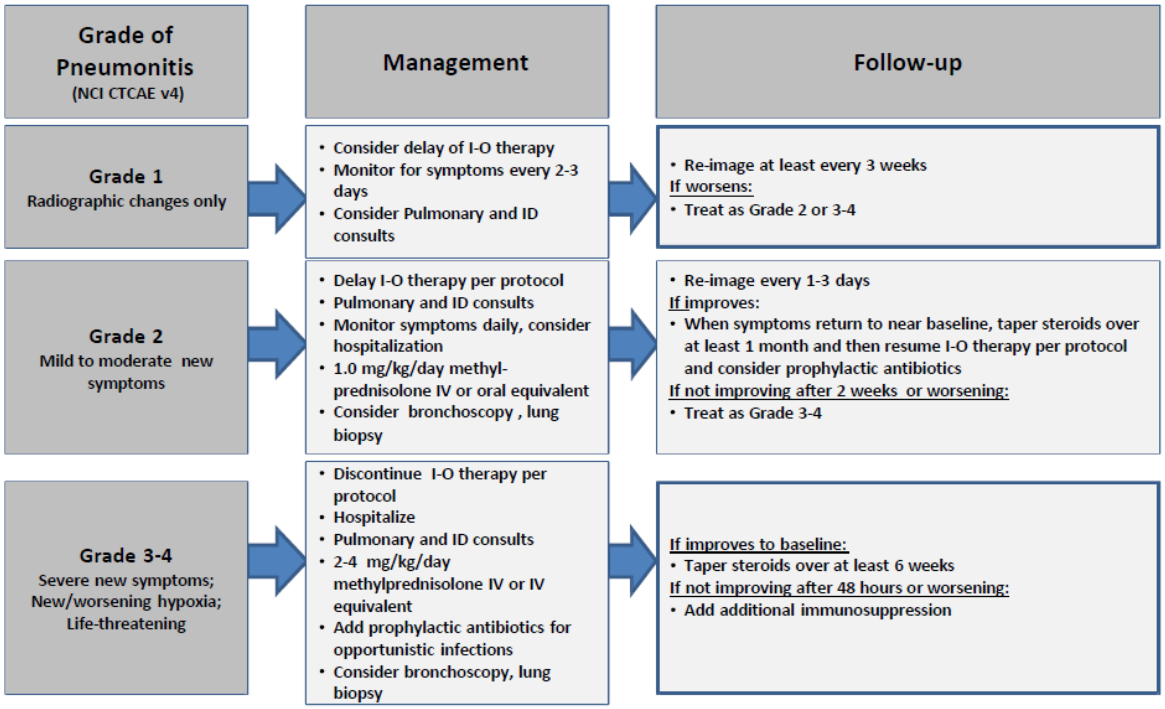
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Pulmonary Adverse Event Management Algorithm

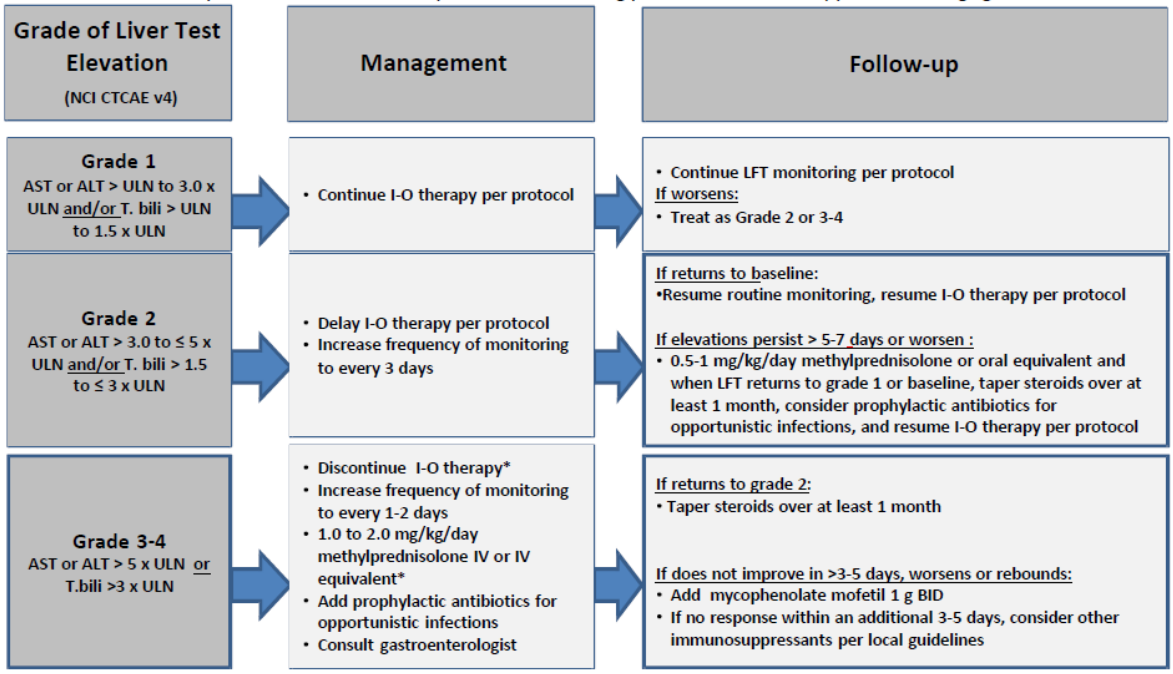
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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

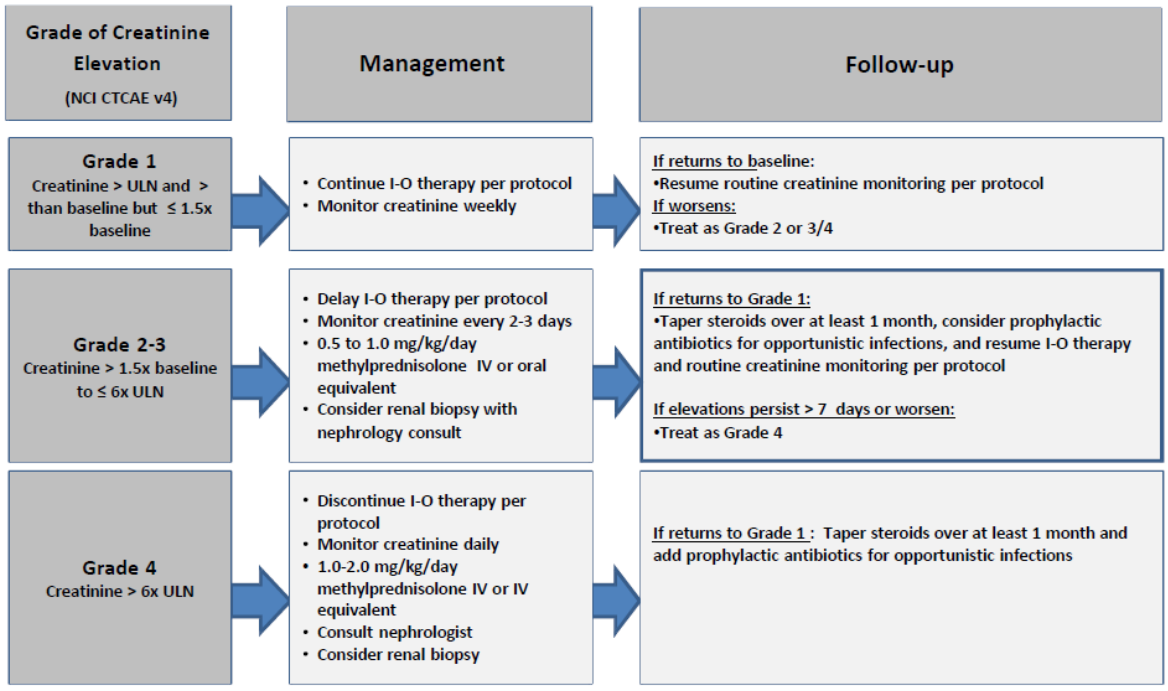


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Renal Adverse Event Management Algorithm

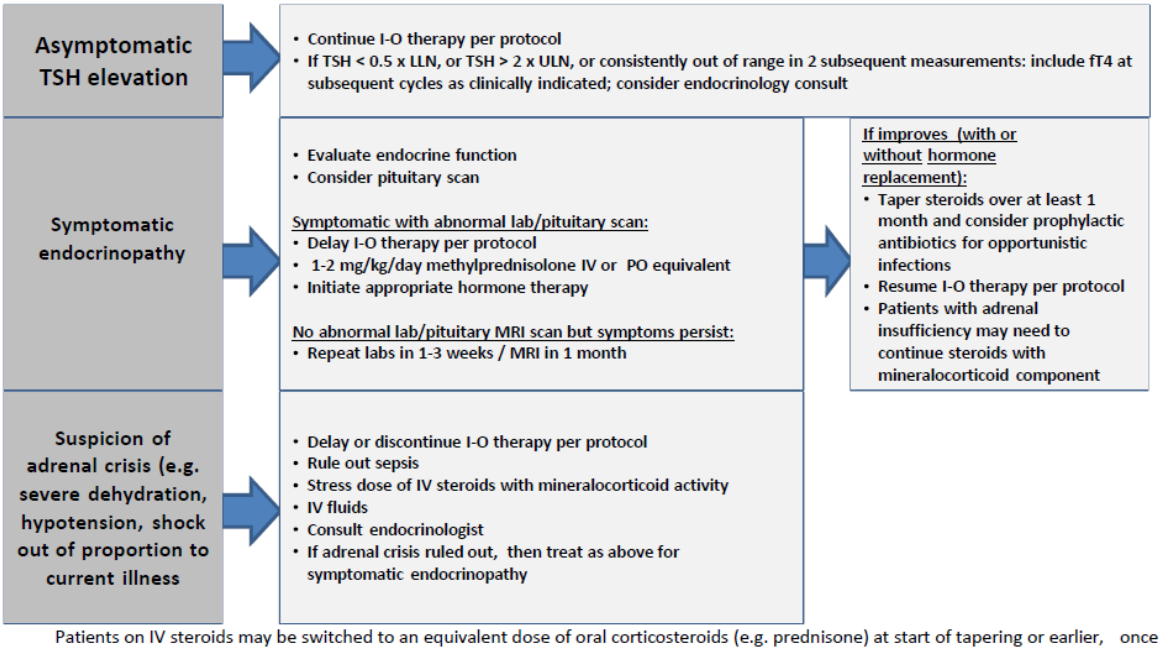
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Endocrinopathy Adverse Event Management Algorithm

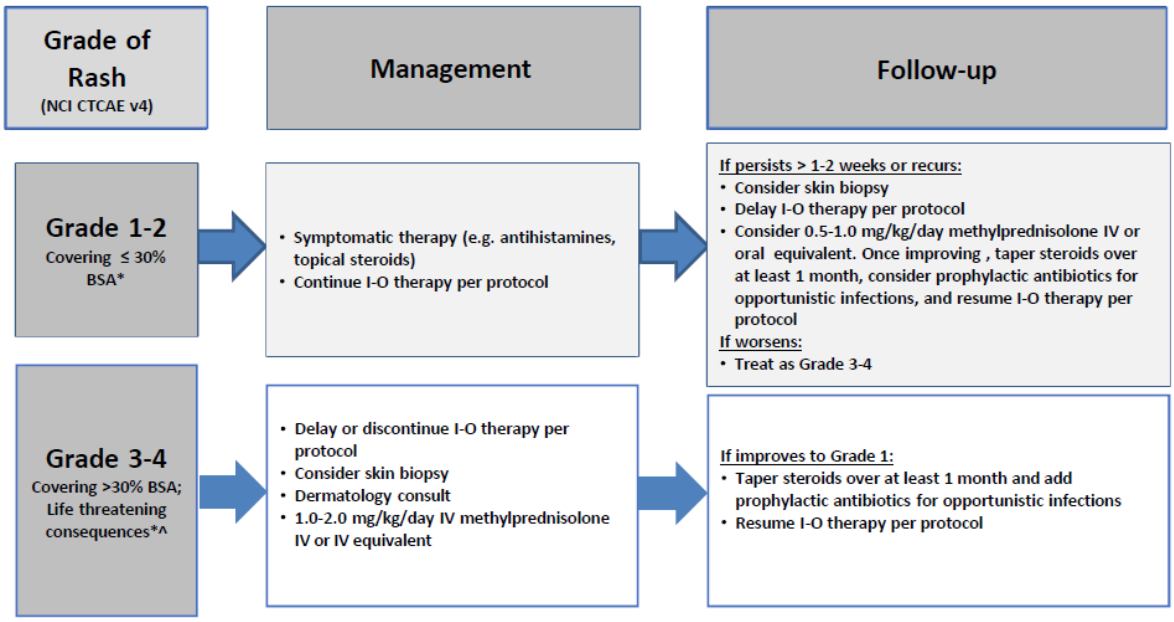
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



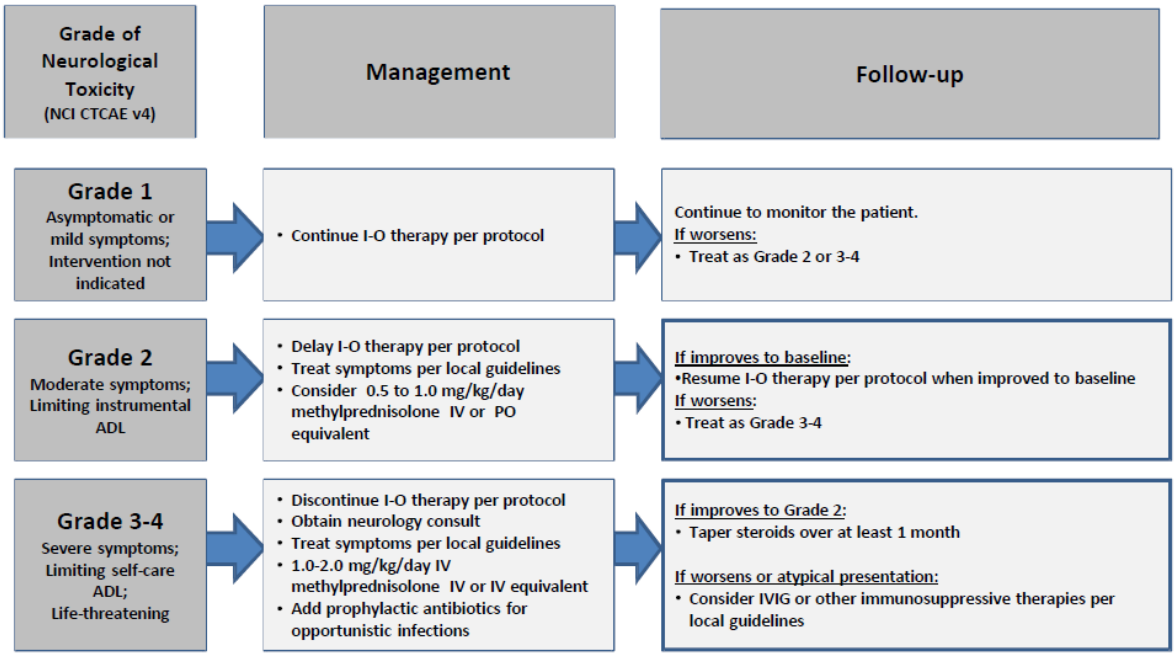
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

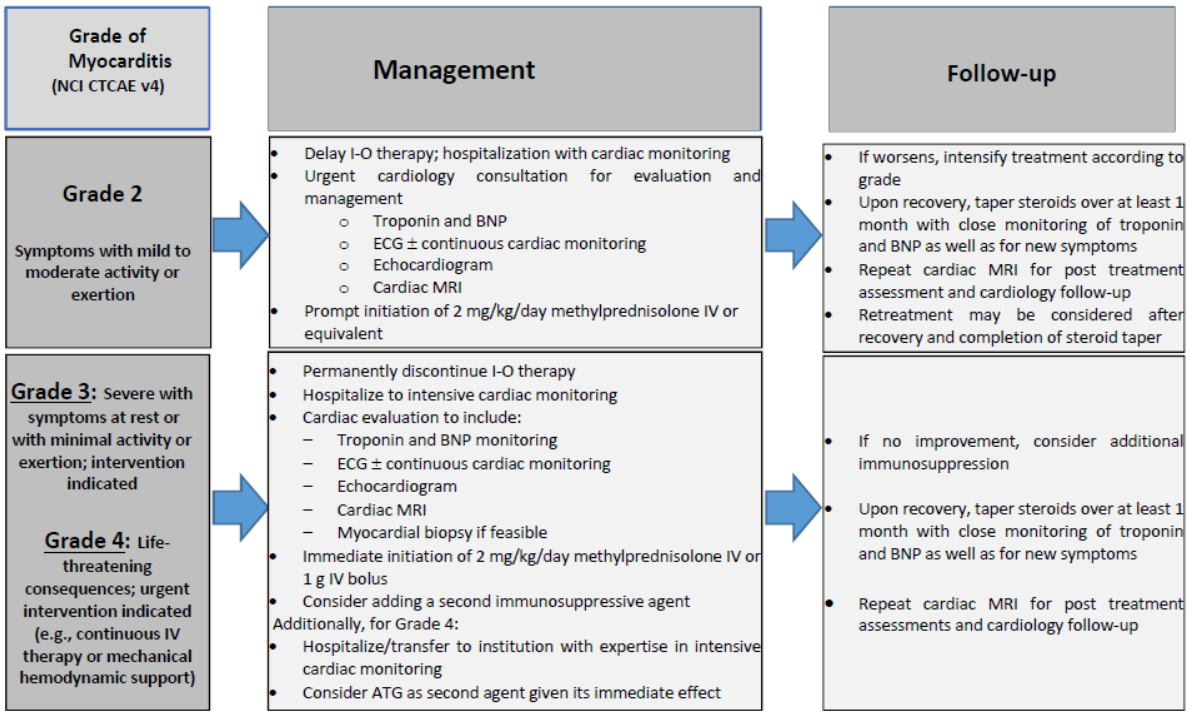
Neurological Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

APPENDIX C BIOSPECIMEN PREPARATION

Processing Guidelines for Tissue Biopsies

1. Five to seven cores will be collected utilizing a 16-18 gauge needle is recommended, a 20 gauge core needle biopsy is also acceptable at the discretion of the interventionalist performing the procedure. Collection of less than the goal amount of tissue will not be considered a protocol violation and should be based upon the clinical judgement of the clinician performing the biopsy procedure.
2. Tissue mass is placed on a sterile saline soaked Telpha pad
3. Using forceps or scalpel, tumor tissue is separated into multiple fragments, if necessary
4. Distinct tissue fragments will be allocated for the following, in order of protocol priority:

    a. Two to three samples placed in room temperature formalin for processing to a FFPE block to be set to the DFCI Rodig Lab.
    b. One sample placed in room temperature formalin to be set to BWH Pathology per BWH CSIR SOP.
    c. Two to three samples placed in room temperature formalin for processing to additional FFPE block(s) to be stored by the DFCI Clinical Trials Team (Dr. Perez).

5. Samples will be annotated with only a unique de-identified study subject number, protocol number, and the date of collection. Links to identifying information for each sample will be stored centrally on a password-protected firewall secured database in accordance with institution tissue bank protocols.

Processing Guidelines for Whole Blood and Plasma Samples

1. Samples will be collected as follows:
    a. Green Top 10 ml Sodium Heparin Tubes for PBMCs
2. Samples will be delivered immediately to the CIO Immune Assesment Lab to be processed within 1.5 hours of being drawn.

CIO Immune Assessment Lab of Mariano Severgnini:

Center for Immuno-Oncology
Dana-Farber Cancer Institute
1 Jimmy Fund Way, JF0406
Boston, MA 02215
Phone: (617) 632-2421
Pager: 42093

Processing Guidelines for Stool Samples

1. Samples will be collected per kit instructions.
2. Samples will be delivered immediately to the CIO Immune Assesment Lab to be processed.

CIO Immune Assessment Lab of Mariano Severgnini:

Center for Immuno-Oncology
Dana-Farber Cancer Institute
1 Jimmy Fund Way, JF0406
Boston, MA 02215
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Pager: 42093

APPENDIX D

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

1 INTRODUCTION

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

1.1 Purpose

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

2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 External Site

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

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- *Document the delegation of research specific activities to study personnel.*
- *Commit to the accrual of participants to the protocol.*
- *Submit protocol and/or amendments to their IRB of record.*
- *Maintain regulatory files as per ICH GCP and federal requirements.*
- *Provide the Coordinating Center with regulatory documents or source documents as requested.*
- *Participate in protocol training prior to enrolling participants and throughout the trial as required.*
- *Update Coordinating Center with research staff changes on a timely basis.*
- *Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.*
- *Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.*
- *Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable.*
- *Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.*
- *Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.*
- *Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.*
- *Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.*

3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- ***Protocol revisions:*** *External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.*

- ***Protocol closures and temporary holds:*** *External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.*

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3 IRB Re-Approval

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

The Coordinating Center will not register participants if a re-approval letter is not received for the External Site on or before the anniversary of the previous approval date.

3.4 DF/HCC Multi-Center Protocol Confidentiality

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

the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5 Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and faxed or e-mailed to the Coordinating Center.
Email: DanielleE_Stonely@dfci.harvard.edu; Fax: 617-582-7988.

- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Registration Request Coversheet
- External Site Subject Registration form
- Screening provider note including medical/ surgical history, ECOG performance status, vital signs, and physical exam findings
- Pathology report to support inclusion criteria
- Laboratory reports including:
    - CBC with differential
    - Chemistry panel
    - Pregnancy test (if applicable)
    - Thyroid panel
    - Coagulation panel
    - LDH
- Screening radiology reports (CT and/or MRI scans)
- Screening EKG

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

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

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

3.5.1 Initiation of Therapy

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

3.5.2 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.6 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web-based training for all eCRF users.

3.6.1 Data Forms Review

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

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

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

3.7 Protocol Reporting Requirements

3.7.1 Protocol Deviations, Exceptions and Violations

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

3.7.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

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

3.7.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4 MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in regular Coordinating Center initiated teleconferences. Overall protocol progress and important announcements will be distributed regularly as minutes from these teleconferences.

Remote Monitoring will be conducted as agreed upon per the Remote Monitor Plan……. External Sites may be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification.

4.2 Monitoring Reports

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

4.3 Accrual Monitoring

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

The following **minimum** accrual requirements are recommended:

1) Phase II-III: 3 per site/annually.

However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site annually should be a minimum target for each site.

5 AUDITING: QUALITY ASSURANCE

5.1 DF/HCC Internal Audits

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

5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

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

5.4 External Site Performance

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

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.