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**Title: A phase II, single-arm clinical trial evaluating the triplet combination of ipilimumab, nivolumab and cabozantinib in patients with anti-PD-1(L1) refractory cutaneous melanoma.**

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# 1 BACKGROUND INFORMATION

**Introduction:**

## 1.1 Background on the indication

*PD-1 and CTLA-4 immune checkpoint inhibitors*

Tumor antigen-specific T cells exposed to chronic antigenic stimulation develop an exhausted phenotype characterized by increased surface expression of various co-inhibitory checkpoint molecules (including PD-1, LAG-3, TIM-3, and others) and loss of effector function[1]. Blockade of co-inhibitory checkpoint molecules can reinvigorate exhausted T cells and produce dramatic anti-tumor effects[2].

Over the past decade, treatment with immune checkpoint inhibitors has revolutionized the treatment of patients with advanced cancer. The combination of ipilimumab plus nivolumab has been shown to be one of the most effective treatment regimens for patients with advanced metastatic melanoma[2,3]. Over half of patients with metastatic cutaneous melanoma treated with the combination of ipilimumab + nivolumab achieve at least a partial response and are alive 5 years later[2]. The Checkmate 511 clinical trial showed that treatment with a reduced dose of ipilimumab (1 mg/kg) in combination with nivolumab (3 mg/kg) resulted in similar progression free survival and overall survival compared with Ipilimumab 3 mg/kg + nivolumab 1 mg/kg. The Ipi 1 mg/kg + Nivo 3 mg/kg regimen was far better tolerated with significantly less toxicity[4].

Despite the success of immune checkpoint inhibitors and targeted therapeutics, melanoma continues to claim the lives of thousands each year. For patients with metastatic melanoma who are refractory to anti-PD-1 monotherapy, treatment with the combination of Ipilimumab plus nivolumab or pembrolizumab results in a median progression free survival of 3-5 months[5-7]. As such, improved therapy options for patients with PD-1 refractory cutaneous melanoma is a significant unmet clinical need.

*Vascular endothelial growth factor (VEGF)*

VEGF signaling within the tumor microenvironment results in profound local immunosuppression. VEGF signaling promotes tumor infiltration of regulatory T cells (Treg) and myeloid derived suppressor cells (MDSC) which suppress adaptive anti-tumor immune responses. VEGF signaling also inhibits dendritic cell maturation resulting in impaired antigen presentation and T cell activation[8]. Activated T cells upregulate VEGF cell surface receptors. VEGF signaling in activated T cells results in upregulated surface expression of co-inhibitory receptors as well as reduced cytotoxic activity and proliferative capacity[9,10].

Given that VEGF signaling has multiple pro-tumorigenic and immunosuppressive effects in cancer progression – there is a strong rationale for combining VEGF inhibition with immune checkpoint inhibition. Several recent clinical trials have demonstrated improved anti-tumor activity with combination therapies blocking VEGF and PD-1/PD-L1 signaling. We recently published the results of our phase Ib/II clinical trial with the combination of lenvatinib + pembrolizumab[11]. This clinical trial showed impressive anti-tumor activity in heavily pre-treated patients including those with metastatic renal cell carcinoma and endometrial cancer[12].

**1.2 Background on the compounds**

*Ipilimumab*

Ipilimumab is a fully human IgG1 kappa monoclonal antibody that binds the co-inhibitory receptor CTLA-4. Antibody binding prevents interaction with the CTLA-4 ligands CD80 and CD86[13]. Blockade of CTLA-4 results in increased T cell activation and proliferation. Ipilimumab was the first immune checkpoint inhibitor to receive FDA approval as a cancer therapy. Treatment of patients with advanced metastatic melanoma with ipilimumab monotherapy resulted in improved overall survival[14]. Subsequent clinical trials with ipilimumab alone and in combination with anti-PD-1 antibodies have demonstrated impressive clinical activity in patients with melanoma, renal cell carcinoma, non-small cell lung cancer and other cancers[2,15,16]. Side effects of ipilimumab result from autoimmune attack on healthy tissues. Side effects may include dermatitis, colitis, hepatitis, hypophysitis, pneumonitis, endocrinopathies, nephritis, arthritis, neuropathies and others.

*Nivolumab*

T cell activation results in upregulation of counter regulatory co-inhibitory receptors including PD-1 and CTLA-4. Ligation of these co-inhibitory receptors with their corresponding ligands results in diminished cytotoxicity and proliferative capacity. These regulatory mechanisms serve to prevent excessive immune activation and autoimmune disease. However, in some diseases such as cancer and chronic viral infections, chronic antigenic stimulation of T cells results in high expression of co-inhibitory checkpoint receptors which leads to T cell exhaustion. Nivolumab is a fully human IgG4 kappa monoclonal antibody that binds the co-inhibitory receptor PD-1. Nivolumab binding to PD-1 blocks interaction with the PD-1 ligands PD-L1 and PD-L2. PD-1 blockade can lead to reinvigoration of exhausted T cells and prevent T cell exhaustion of newly activated T cells. Nivolumab has been shown to have excellent clinical efficacy in treating a wide range of cancers as monotherapy and in combination with ipilimumab[2,15,16].

*Cabozantinib*

Cabozantinib is a potent small molecule inhibitor of multiple receptor tyrosine kinases. Cabozantinib inhibits VEGFR2, MER, KIT, and MET at single digit nanomolar $IC_{50}$ concentrations. Other kinases including ROS1, RET, FLT3, RON, AXL, and TIE2 are also inhibited with nanomolar concentrations of cabozantinib. Cabozantinib has been shown to have clinical activity in a variety of solid tumors and has been approved by the FDA for treatment of medullary thyroid cancer, renal cell carcinoma and hepatocellular carcinoma[17-19].

### 1.3 Rationale for the proposed study

In this clinical trial, we will evaluate the clinical efficacy and safety of the combination of VEGF inhibition (cabozantinib 40 mg/day) with immune checkpoint inhibition (ipilimumab 1 mg/kg + nivolumab 3 mg/kg) for patients with metastatic cutaneous melanoma who are refractory to anti-PD-1/PD-L1 therapy. The hypothesis is that concurrent blockade of distinct and inter-related signaling pathways (VEGF and co-inhibitory immune checkpoint pathways), will result in improved anti-tumor immune reactivity and clinical efficacy. Inhibition of VEGF signaling in the tumor microenvironment will increase CD8+ T cell infiltration, reduce infiltration of Treg and MDSC populations, and block the direct immunosuppressive effects of VEGF on activated T cells. Blockade of PD-1 and CTLA-4 immune checkpoint pathways will facilitate reinvigoration of exhausted T cells and allow expansion and activation of a broader repertoire of tumor antigen-specific T cells.

## 2 STUDY OBJECTIVES AND ENDPOINTS

Recent clinical trials have demonstrated median PFS as high as 5 months with the combination of low dose ipilimumab (1 mg/kg IV every 3 weeks) in combination with anti-PD-1 therapies in patients with anti-PD1 refractory cutaneous melanoma. As such, we will use the 5 month mPFS as the benchmark for the design of this clinical trial. In order to show a 4 month improvement in mPFS (with a power of 0.8 and a one-sided test given a type I error rate of 0.05), a total of 41 subjects would need to be enrolled. This signal seeking pilot study will initially enroll 25 subjects at our site (single institution) in less than 2 years. If this treatment combination results in a ***mPFS of at least 8 months or an ORR of 45% or higher***, we will review these results with BMS and Exelixis and propose protocol and budget amendments to add 1-2 additional sites to expedite enrollment to a total of at least 41 subjects.

**Primary Objective**

The primary objective of this clinical trial is to evaluate the clinical efficacy and progression free survival of the triplet combination of ipilimumab + nivolumab + cabozantinib in patients with anti-PD-1/PD-L1 refractory metastatic cutaneous melanoma.

**Secondary Objectives:**

- Safety/Tolerability (CTCAE v5.0)
- Objective response rate (iRECIST)
- Overall survival
- Correlative translational studies (paired pre-treatment and day #15 on-treatment tumor biopsies for characterization of tumor infiltrating immune cell profiling and gene expression changes)

**Primary endpoint**:

Progression free survival will be defined as the time between the date of enrollment and the first date of documented progression (per iRECIST), as determined by the investigator, or death due to any cause, whichever occurs first. Cumulative incidence functions will be displayed and summarized for the median time to progression as well as percentage of patients without disease progression at 12, 18, and 24 months.

**Secondary endpoints**:

1. Objective response rate (iRECIST)
2. Duration of response
3. 6, 12 and 24 month progression free survival
4. 12 month overall survival
5. Incidence of grade ≥3 treatment related adverse events (CTCAE v5.0)
6. Correlative molecular profiling

**STUDY DESIGN**: This is a phase II, single arm, single institution clinical trial. Adults (age ≥18 years-old) with anti-PD-1 refractory, unresectable/metastatic cutaneous melanoma will be evaluated for eligibility. Eligible participants will be treated with the triplet combination of ipilimumab 1 mg/kg + nivolumab 3 mg/kg every 3 weeks for 4 cycles in addition to cabozantinib 40 mg/day. For cycles 5+, treatment will

consist of nivolumab 480 mg IV every 4 weeks in combination with cabozantinib 40 mg/day. The total duration of therapy will be 24 months.

- Ipilimumab 1 mg/kg + Nivolumab 3 mg/kg IV every 3 weeks + Cabozantinib 40 mg PO daily for 4 cycles followed by:
- Nivolumab 480 mg IV every 4 weeks + Cabozantinib 40 mg PO daily for up to 24 months

### 2.1 Study Treatment Discontinuation

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

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

- An AE or intercurrent illness that in the opinion of the Investigator warrants the subject's withdrawal from study treatment.
- The Investigator believes it is not in the best interest of the subject to continue on study.
- Specific conditions described in the Management of Adverse Events Section 5.4.
- Necessity for treatment with other anticancer treatment prohibited by protocol.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the study and for 4 months after the last dose of cabozantinib and 3 months after the last dose of ipilimumab and 5 months after the last dose of nivolumab.
- Women who become pregnant or are breastfeeding.
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the Principal Investigator.
- Necessity for interrupting all study treatment for greater than 12 weeks for study-treatment-related AEs unless approved by the Principal Investigator.

- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol.
- Significant noncompliance with the protocol schedule in the opinion of the Investigator.
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued.
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the Investigator. Patients who continue study treatment beyond progression must be reconsented into the study.
- Subject participation in another clinical study using an investigational agent, investigational medical device, or other intervention.
- Subject request to discontinue all study treatments (with or without concurrent withdrawal of informed consent).

# 3 INCLUSION/EXCLUSION CRITERIA

## 3.1 Inclusion Criteria

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

1. Histologically (or cytologically) confirmed diagnosis of metastatic cutaneous melanoma.
2. Prior therapy:
    a. Must have been treated previously with an immune checkpoint inhibitor targeting PD-1 or PD-L1.
    b. Disease progression following treatment with prior anti-PD-1/PD-L1 therapy must be confirmed at least 4 weeks after the first imaging showing disease progression to rule out pseudoprogression.
    c. Prior therapy with BRAF/MEK inhibitors (before or after anti-PD-1(L1) therapy) is allowed but not required.
    d. Patients who develop unresectable/metastatic disease ***while*** receiving or following completion of adjuvant systemic anti-PD-1/PD-L1 therapy are eligible.
3. Recovery to baseline or ≤ Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
4. Men and women, aged ≥ 18 years
5. Measurable disease meeting the following iRECIST criteria:
    a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or >1.5 cm in the short-axis diameter for a lymph node metastasis that is serially measurable according to

iRECIST using computed tomography/magnetic resonance imaging (CT/MRI).

b. Lesions that have had external beam radiotherapy must show evidence of disease progression to qualify as a target lesion.

6. ECOG performance status ≤ 1
7. Adequate cardiac function, as defined by:
    a. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
    b. Baseline QTc interval ≤ 480 ms
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days before first dose of study treatment:
    a. Absolute neutrophil count (ANC) ≥ 1500/µL without granulocyte colony-stimulating factor support.
    b. White blood cell count ≥ 2500/µL.
    c. Platelets ≥ 100, 000/µL without transfusion.
    d. Hemoglobin ≥ 9 g/dL (≥ 90 g/L).
    e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤ 3x upper limit of normal (ULN). ALP ≤ 5x ULN with documented bone metastases.
    f. Total bilirubin $\leq$ 1.5 x ULN. Note: Individuals who have a total bilirubin level >1.5 X ULN will be allowed if their indirect bilirubin level is < 1.5 x ULN (i.e., participants with suspected or known diagnosis of Gilbert's Syndrome)
    g. Serum albumin ≥ 2.8 g/dl.
    h. (PT)/INR or partial thromboplastin time (PTT) test < 1.3x the laboratory ULN
    i. Serum creatinine ≤ 1.5x ULN or calculated creatinine clearance ≥ 40mL/min (≥ 0.675mL/sec) using the Cockcroft-Gault equation:
    *Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)*
    *Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85*
    j. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h urine protein ≤ 1 g.
9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.
10. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of

cabozantinib and 3 months after the last dose of ipilimumab and 5 months after the last dose of nivolumab.

11. Participants of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at screening, within 24 hours prior to receiving the first dose of study medication, and then every 4 weeks while on treatment.
12. Participants of child-bearing potential agree to use highly effective methods of contraception starting with the first dose of assigned study intervention through 5 months after the last dose of study therapy. Participants of childbearing potential are those who are not proven postmenopausal. Postmenopausal is defined as any of the following:

    a. Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    b. Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50
    c. Radiation-induced oophorectomy with last menses >1 year ago
    d. Chemotherapy-induced menopause with >1 year interval since last menses
    e. Surgical sterilisation (bilateral oophorectomy or hysterectomy

### 3.2 Exclusion Criteria

1. Prior therapy:
    a)
    b) Prior therapy with a VEGF(R) inhibitor alone or in combination with immune checkpoint inhibitor(s).
    c) Prior therapy with an anti-CTLA-4 antibody
2. Participants with active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
3. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
4. History of allergy or hypersensitivity to any monoclonal antibody
5. Previous or concurrent malignancy within 3 years of study entry, with the following exceptions:
    a) adequately treated basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, or other noninvasive or indolent malignancy; OR
    b) other solid tumors treated curatively in which the expected rate of recurrence within 5 years is < 5%.

6. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:

    a) History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to screening,

    b) Symptomatic congestive heart failure (i.e. Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening. Exceptions include asymptomatic/well-controlled atrial fibrillation/flutter or paroxysmal supraventricular tachycardia;

    c) Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, despite medical therapy

7. History of thromboembolic or cerebrovascular events ≤ 6 months prior to the first dose of study treatment. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e., massive or sub-massive) deep vein thrombosis or pulmonary emboli.

    ***Note:*** *Individuals with either deep vein thrombosis or pulmonary emboli that does not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.*

    ***Note:*** *Individuals with thromboembolic events related to indwelling catheters or other procedures may be enrolled.*

8. Impaired gastrointestinal function or disease that may significantly alter the absorption of cabozantinib (e.g., uncontrolled vomiting or malabsorption syndrome)

9. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)

10. Any other condition that would, in the Investigator's judgment, contraindicate an individual's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

11. Participants who have undergone major surgery (e.g., intracranial, intrathoracic, or intra-abdominal surgery) ≤ 3 weeks prior to starting study drug, minor surgery ≤ 10 days prior to starting study drug or who have not recovered from side effects of such procedure. Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment.

12. Participants that are pregnant or nursing (lactating)

13. Prisoners or individuals who are involuntarily incarcerated

14. Medical, psychiatric, cognitive or other conditions that may compromise the participant's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study

15. Patients with leptomeningeal involvement by melanoma

16. Participants with CNS metastases or leptomeningeal carcinomatosis are not eligible unless:

16.1. CNS metastases have been treated and remained stable by radiographic evaluation at least 4 weeks after CNS directed therapy and/or:

16.2. There are ≤5 asymptomatic untreated CNS metastases measuring no larger than 10 mm each.

16.3. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment."

17. Radiation therapy for bone metastases within 2 weeks, any other radiation therapy within 4 weeks, or systemic treatment with radionuclides within 6 weeks before first dose of study treatment; ongoing clinically relevant complications from prior radiation therapy are not eligible
18. Concomitant anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following:
    18.1. Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).
    18.2. Therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.
19. Administration of a live, attenuated vaccine within 30 days prior to first dose of study treatment
20. Evidence of tumor invading the GI tract, active peptic ulcer disease, IBD, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of pancreatic duct or common bile duct, or gastric outlet obstruction
21. Abdominal fistula, GI perforation, bowel obstruction or intra-abdominal abscess within 6 months before first dose of study treatment. Complete healing of intra-abdominal abscess must be confirmed before first dose of study treatment
22. Clinically significant hematuria, hematemesis, or hemoptysis of >0.5 tsp (2.5ml) of red blood, or other history of significant bleeding within 12 weeks before first dose of study treatment
23. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation
24. Lesions invading or encasing any major blood vessels.
25. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
26. Serious non-healing wound/ulcer/bone fracture.
27. Moderate to severe hepatic impairment (Child-Pugh B or C).
28. Requirement for hemodialysis or peritoneal dialysis.
29. History of solid organ or allogenic stem cell transplant.

30. QTcF > 500 msec within 14 days before first dose of study treatment (Note: Could also be listed in Inclusion as ≤ 500 msec)

# 4 STUDY ASSESSMENTS AND PROCEDURES

## 4.1 Pre-Treatment Period

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

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

| Screening Procedures | Pre-treatment Period Day -28 through initiation of treatment | Instructions |
|---|---|---|
| Informed Consent | X | |
| Medical History | X | All medical history relevant to the disease under study including smoking history, alcohol use, AJCC M stage, recreational drug use |
| Adverse Event Collection | X | |
| Concomitant Medications | X | Complete review of current medications with patient including herbal and dietary supplements, and over the counter (OTC) |
| Comprehensive Physical Exam | X | To include basic body systems |

| | | |
|---|---|---|
| Vital Signs | X | Height, weight, blood pressure, pulse, 02 saturation, respiration |
| ECOG Performance Status | X | |
| Disease Assessment | X | Contrast enhanced CT of the chest, abdomen, pelvis Or MRI abdomen,w/wo gadolinium contrast including non contrast CT are acceptable for patients with iodine contrast allergies. |
| Cardiac Assessment | X | ECHO and ECG |
| Biopsy | X | Optional biopsy prior to initiation of treatment. In patients who do not consent then archival tissue will be requested. |
| Laboratory Assessments | X | See Clinical Safety Laboratory Assessments. |
| Tumor Markers | X | LDH |
| Specimen Collection or Optional Specimen Banking | X | Serum for banking ( 4ml lavender top and 4ml red top ) |

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

### 4.1.1 Clinical Safety Laboratory Assessments

| **Clinical Safety Laboratory Assessments** | |
|---|---|
| **Hematology – CBC with Hemoglobin, Hematocrit, Total leukocyte count, including differential and Platelet count** | |
| **Chemistry** | |
| **Aspartate aminotransferase (AST)**<br>**Alanine aminotransferase (ALT)**<br>**Total bilirubin**<br>**Alkaline phosphatase (ALP)** | **Albumin**<br>**Sodium**<br>**Potassium**<br>**Chloride** |

| | |
|---|---|
| **Lactate dehydrogenase (LDH)**<br>**Creatinine**<br>**Blood Urea Nitrogen (BUN) or serum UREA**<br>**Glucose**<br>**Bicarbonate**<br>**Total Protein** | **Calcium**<br>**Phosphorus**<br>**CK**<br>**GGT- screening**<br>**Magnesium-screening**<br>**Troponin - screening**<br>**TSH, and free T4 - screening**<br>**TSH, with reflexive fT4 if TSH is abnormal - on treatment**<br>**Lipase and /or amylase** |
| PT/INR/PTT, and drug adherence checks | |
| **Serology** | |
| **Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA), - screening only**<br>**(Testing for HIV-1 and HIV-2 must be performed where mandated by local requirements)** | |
| **Other Analyses** | |
| **Serum Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).** | |
| **Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55)** | |
| **Urinalysis with UPCR (urine protein creatinine ratio) - screening and at each study visit** | |

### 4.2 Treatment Period

During the Treatment Period subjects will receive treatment for up to 24 months or until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 2.1. Subjects should be instructed to immediately inform the Investigator of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant and should be documented. If laboratory values constitute part of an

event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

Regular tumor assessments should be performed to determine if PD is present. Tumor assessments should continue on the protocol-defined schedule, relative to the date of first dose of study treatment, regardless of whether study treatment is given, reduced, held or discontinued. The same imaging modalities used at screening will be used for subsequent tumor assessments after first dose.

If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

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

The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated.

**Study Assessments**

| Study Day/Visit Day | Cycles 1-4 ( 21 days) Day 1 ( +/- 4 days) | Cycles 5 + Day 1 ( +/- 4 days) | Instructions |
|---|---|---|---|
| **Adverse Event Assessment** | **X** | **X** | |
| **Concomitant Medications** | **X** | **X** | **Review of prohibited medications prior to each study drug dosing** |
| **Physical Exam** | **X** | **X** | |
| **Vital Signs** | **X** | **X** | **Weight, blood pressure, pulse, 02 saturation, respirations at each visit** |
| **ECOG Performance Status** | **X** | **X** | |
| **Questionnaire(s)** | **X** | **X** | **FACT-M (Version 4)** |
| **Cabozantinib 40 mg PO daily Continuous** | **X** | **X** | |

| | | | |
|---|---|---|---|
| **Ipilimumab 1 mg/kg IV Day 1 Every 3 weeks (cycles 1-4 )** | **X** | | |
| **Nivolumab 3mg/kg IV Day 1 Every 3 weeks (cycles 1-4 )** | **X** | | |
| **Nivolumab 480mg IV Day 1 every 4 weeks** | | **X** | |
| **Disease Assessment** | **Refer to instructions for interval** | **Refer to instructions for interval** | **Contrast enhanced CT of the chest, abdomen, pelvis. Restaging will occur every 12 weeks ( +/- 1 week)** |
| **Cardiac Assessment** | **X** | | **ECG/EKG – day 1 of cycles 1-4 only** |
| **Specimen Collection or Optional Specimen Banking** | **X** | **X** | **Serum for banking ( 4ml lavender top and 4ml red top )** |
| **Biopsy** | **x** | | **(prior to treatment start and on treatment for 10 patients) prestudy and on day 15 for consenting patients** |
| **Complete Blood Count (CBC)** | **X*** | **X** | **See Clinical Safety Laboratory Assessments. *Repeat CBC/CMP on D14 of cycles 1-4.** |
| **Blood Chemistry** | **X*** | **X** | **See Clinical Safety Laboratory Assessments. *Repeat CBC/CMP on D14 of cycles 1-4.** |
| **Thyroid Function Tests** | **X** | **X** | **See Clinical Safety Laboratory Assessments. *TSH with reflex to free T4 day 1 of odd numbered cycles*** |
| **Tumor Markers** | | | **LDH** |
| **Immune Parameters** | **X** | **X** | **Immune parameters assessment. Refer to Section 4.4** |
| **Study Labs Serum Sample Pharmacokinetics (PK)** | | | **Please see PK section of the protocol. Section 4.4** |
| **Urinalysis UPCR** | **X** | **X** | **UA to evaluate for proteinuria** |
| **Pregnancy Test (HCG)** | **X** | **X** | **For WOCBP** |

### 4.3 Post-Treatment Period

Subjects will return to the study site approximately 30 days after their last dose of treatment to complete end-of-study assessments. Patients will be followed for residual toxicity for 100 days post last day of treatment even if they start a new anticancer therapy. Patients who are removed from study early will be followed for residual toxicity for 100 days post last day of treatment even if they start a new anticancer therapy.

Laboratory and physical examinations will be performed. Remaining study drug will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

| Study Day/Visit Day | 30 days (+/- 7 days) last study treatment | 12 weeks after last study treatment (+/- 14 days ) | Instructions |
|---|---|---|---|
| **Adverse Event Assessment** | **X** | **X** | |
| **Concomitant medications** | **X** | **X** | |
| **Physical Exam** | **X** | **X** | |
| **Vital Signs** | **X** | **X** | |
| **ECOG Performance Status** | **X** | **X** | |
| **Disease Assessment** | | | **Contrast enhanced CT of the chest, abdomen, pelvis.**<br><br>**Restaging will occur every 12 weeks (+/- 14 days) through 3 years from the start of treatment and then every 6 months until 5 years from start of treatment.** |

| | | | |
|---|---|---|---|
| **Complete Blood Count (CBC)** | **X** | **X** | **See Clinical Safety Laboratory Assessments.** |
| **Blood Chemistry** | **X** | **X** | **See Clinical Safety Laboratory Assessments.** |
| **Thyroid Function Tests** | **X** | **X** | **See Clinical Safety Laboratory Assessments.** |
| **Tumor Markers** | **X** | **X** | **LDH** |

### 4.4 Correlative Studies

Translational studies will be performed on fresh tumor biopsies and peripheral blood specimens and correlated with clinical response to therapy.

- Paired tumor biopsies (pre-treatment and day #15) on 10 subjects with accessible tumors amenable to safe biopsy.
- PBMCs and serum will be collected pre-treatment and on day 1 of each cycle for the first 6 cycles.
- Analysis may include multiplex immunofluorescent tissue staining for characterization of tumor infiltrating immune profile, RNAseq to evaluate global gene expression changes within tumor resulting from treatment, and characterization of peripheral blood immune cell profiles, T cell activation status, and cytokine analysis. Scope of work and budgets will be negotiated with BMS and Exelixis separate from this clinical trial protocol.

### 4.5 Research Participant Registration and Subject Number Assignment Procedures

**Research Participant Registration**

Patients must meet all of the eligibility requirements and undergo all screening procedures. If a patient enrolls in the study, but does not receive study therapy, the patient's enrollment may be canceled. Reasons for cancellation will be documented in writing. Any patient whose enrollment was canceled before receiving study therapy will be replaced.

**Assignment of Subject Numbers**

Subject numbers will be assigned at enrollment based on order of enrollment. For example:

- MFH is the 4th patient enrolled to study. Subject number INC– 04
- B-A is 9th patient enrolled to study. Subject number INC – 09

All case report forms, study reports, and laboratory samples for research tests, including immune parameters or pharmacokinetics, will be labeled with the full patient subject number.

Each Consented participant will be assigned only 1 identification number. Numbers must not be reused for different participants. Any participant who is screened multiple times will retain their original identification number.

# 5 TREATMENT PROCEDURES

## 5.1 Composition, Formulation, and Storage

All study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations. Please refer to the most up to date Investigator Brochure in regards to storage conditions, handling, and preparation specifications for all study agents.

### 5.1.1 Investigational Treatment: Cabozantinib

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

**Cabozantinib Tablet Components and Composition**

| Ingredient | Function | % w/w[a] |
|---|---|---|
| Cabozantinib Drug Substance (25% drug load as free base) | Active Ingredient | 31.68 |
| Microcrystalline Cellulose (Avicel® PH-102) | Filler | 38.85 |
| Lactose Anhydrous (60M) | Filler | 19.42 |
| Hydroxypropyl Cellulose (EXF) | Binder | 3.00 |
| Croscarmellose Sodium (Ac-Di-Sol®) | Disintegrant | 6.00 |
| Colloidal Silicon Dioxide | Glidant | 0.30 |
| Magnesium Stearate | Lubricant | 0.75 |
| Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow | Film Coating | 4.00 |
| [a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose | | |

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

### 5.1.2 Nivolumab

Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Nivolumab is produced from cell culture using a CHO cell line. The physical and chemical properties of nivolumab drug substance are provided below:

**Physical and Chemical Properties of Nivolumab Drug Substance**

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

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

### 5.1.3 Ipilimumab

Ipilimumab (BMS-734016, MDX-010) is a fully human IgG1 consisting of 4 polypeptide chains; 2 identical heavy chains primarily consisting of 447 amino acids each with 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds. Ipilimumab is produced from cell culture using a Chinese Hamster Ovary (CHO) cell line. The physical and chemical properties of the ipilimumab drug substance are provided below:

**Physical and Chemical Properties of Ipilimumab Drug Substance**

BMS Number BMS-734016-01 or BMS-734016

Other Names/Laboratory Codes Yervoy®, MDX-010, MDX-CTLA-4

Molecular Weight 147,991 Daltons

Appearance Clear to slightly opalescent, colorless to pale yellow liquid, may contain particles
Solution pH 7.0
pI The isoelectric focusing analysis generates a banding pattern in the pI range of 8.5 to 8.8, with the major isoform at an approximate pI of 8.7
Abbreviations: pI = isoelectric point.

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

## 5.2 STUDY TREATMENT ADMINISTRATION

### 5.2.1 Cabozantinib Administration

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily.

Cabozantinib tablets should only be taken whole by mouth and should not be cut, chewed, or crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity. Cabozantinib should not be taken with food (subjects should not eat for at least 2 h before and at least 1 h after taking cabozantinib) and should be taken with a full glass (at least 8 ounces or 240 mL) of water. If a dose is missed, the missed dose should not be taken less than 12 h before the next dose. Cabozantinib tablets should be stored at controlled room temperature and inventoried according to applicable regulations

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 5.4 below.

### 5.2.2 IO Therapy Administration

Participants will be treated with ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for 4 cycles . For cycles 5+, treatment will consist of nivolumab 480 mg IV every 4 weeks. The total duration of therapy will be 24 months.

## 5.3 Study Treatment Accountability

The Investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, and how

much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

Drug accountability records will be maintained by the Providence Health & Services Oregon Region Investigational Drug Services pharmacy.
Unused investigational drug will be returned or destroyed at study close or when drug expires as per the site's policy.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug (Nivolumab and Ipilimumab) to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study."

All investigational drug accountability records, physical inventory and other supporting documents (such as temperature monitoring logs) will be made available to the monitor and applicable regulatory agencies for auditing and monitoring purposes.

## 5.4 Study Treatment Dose Modifications, Interruptions, and Discontinuation

The following should be taken into consideration in decisions regarding management for treatment-related side effects: cabozantinib and IO agents have class-specific safety profiles based on their mechanisms of action but may also cause AEs that overlap. In the case of AEs clearly attributed to cabozantinib or the IO agent, independent dose modification for either agent is allowed.

- Examples of VEGFR TKI associated AEs caused by cabozantinib are hypertension and hand-foot syndrome.
- Examples of irAEs caused by IO agents are pneumonitis and endocrinopathies.
- Examples of overlapping AEs are diarrhea and elevations in liver function tests.

As a general approach all AEs should be managed with supportive care including both pharmacological and non-pharmacological treatments according to consensus management guidelines at the earliest signs of toxicity considered related to study treatment.

Study treatment may be continued for mild AEs if appropriate supportive care has been initiated to ameliorate symptoms. Should this be ineffective and toxicities become unacceptable, dose modifications of study treatment should be considered to prevent worsening of toxicity. Moderate to severe AEs usually require dose modifications including dose reductions and/or interruptions.

Dose interruptions of cabozantinib or IO agents for AEs may occur independent of the other agent at the discretion of the Investigator. If all study treatment is interrupted for more than 12 weeks, treatment should be discontinued unless approved by the Principal Investigator.

### 5.4.1 Management of AEs Associated with Cabozantinib

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

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- The assigned starting dose for cabozantinib is 40 mg/day. Two dose reduction levels of cabozantinib are permitted (see “Dose Reductions of Cabozantinib” table).
- Dose modification criteria for cabozantinib are shown in the “Dose Reductions of Cabozantinib” table. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in the “Dose Modifications of Cabozantinib for Treatment-Related AEs” table, if the Investigator feels it is in the interest of a subject’s safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per Investigator discretion. If treatment is interrupted due to related AEs for more than 12 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is

benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity, with approval from the Principal Investigator.

- Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 12 weeks per the discretion of the Investigator.
- Guidelines for the management of specific AEs of cabozantinib such as GI disorders, non-GI fistula formation, hemorrhage, thromboembolic events, hypertension, stomatitis and mucositis, skin disorders, osteonecrosis, proteinuria, nervous system disorders, infections and infestations, blood system disorders, fatigue, weight loss, QTc prolongation, electrolyte disorders, endocrine disorders, respiratory disorders and hepatic adverse events begin in Section 5.4.1.2.

**Dose Reductions of Cabozantinib**

| Assigned Dose | First Dose Level Reduction | Second Dose Level Reduction | Third Dose Level Reduction |
|---|---|---|---|
| 40 mg daily (qd) | 20 mg daily (qd) | 20 mg every other day (qod) | No dose reduction permitted |
| Cabozantinib will be discontinued if a dose of 20-mg cabozantinib every other day (minimum dose) is not tolerated | | | |

**Dose Modifications of Cabozantinib for Treatment-Related AEs**

| Event | Management |
|---|---|
| Grade 1 AEs | Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable. |
| Grade 2 AEs which are tolerable and are easily managed | Continue cabozantinib treatment at the current dose level with supportive care. |
| Grade 2 AEs which are **intolerable** and **cannot be adequately managed** | At the discretion of the Investigator, cabozantinib should be dose reduced or interrupted.<br><br>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.<br><br>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.<br>Discontinue cabozantinib unless the following criteria are met:<br>• Subject is deriving clear clinical benefit as determined by the Investigator, and approved by the Principal Investigator.<br>• Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care . |
| Note: The dose delay and modification criteria for specific medical conditions are provided in Section 5.4.1.2. | |

#### 5.4.1.1 Cabozantinib Dose Reinstitution and Reescalation

If the subject recovers from his or her toxicities to CTCAE v.5.0 Grade $\leq 1$ or to the baseline value (or lower) and the toxicity was unrelated to cabozantinib, then cabozantinib may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade $\leq 1$ or to the baseline value (or lower) the toxicity was deemed possibly related to cabozantinib, then cabozantinib may be restarted at a reduced dose.

Subjects who initiated treatment with cabozantinib at 40 mg and experience a possibly related AE of Grade 1 or 2 severity may be restarted with no dose change after recovery of the toxicities to ≤ Grade 1 or to the baseline value (or lower) if appropriate supportive care can prevent or minimize the risk of the AE.

Subjects receiving a dose of 20 mg qod may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a dose of 20 mg qod should discontinue cabozantinib.

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

#### 5.4.1.2 Guidelines for Management of Potential Adverse Events Associated with Cabozantinib Treatment

Subjects will be monitored for AEs from the time of 1$^{st}$ treatment through their last follow-up visit (100 days after the date of the last dose of study treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the Investigator. AE severity will be graded by the Investigator in accordance with CTCAE v.5.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

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

Subjects may also experience other medically important but less frequent AEs including arterial and venous thrombotic AEs (e.g., deep vein thrombosis [DVT], pulmonary embolism, transient ischemic attack [TIA], and myocardial infarction [MI]), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistulae formation, osteonecrosis, and RPLS).

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

Many AEs can occur early (within the first few weeks) in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting. In addition, earlier onset for events of dehydration was observed in subjects with castrate-resistant prostate cancer (CRPC) when compared with subjects with other tumor types.

Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic

events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and reversible posterior leukoencephalopathy syndrome (RPLS).

A population pharmacokinetics analysis of cancer subjects with RCC, HCC, MTC, glioblastoma, and other solid tumors predicted a terminal half-life of approximately 99 h for cabozantinib when administered as repeated once-daily doses. Thus, as described above, it will take most subjects 2 to 3 weeks (5 half-lives) to reach steady state with daily dosing after initiating therapy with cabozantinib. AEs attributable to cabozantinib may be expected to occur by the time maximum plasma concentrations are reached, and therefore early intervention with dose modifications within the first 15-21 days of daily dosing may be justified.

#### 5.4.1.2.1 Gastrointestinal Events

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess:
Prior to initiation of treatment with cabozantinib, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Tumors invading GI or respiratory tracts.
- Active peptic ulcer disease, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis.
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.
- Ongoing visceral complications from prior radiation therapy.
- Prior GI surgery (particularly when associated with delayed or incomplete healing).

Complete healing following abdominal surgery and radiation therapy and/or resolution of intra abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

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[20] are present.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown below.

Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per Investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

**Management of Diarrhea Associated with Cabozantinib**

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

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 6 for further details).

#### 5.4.1.2.2 Hepatic Events

See section 5.4.3 for guidance regarding both cabozantinib and IO agent.

#### 5.4.1.2.3 Non-Gastrointestinal Fistula

Radiation therapy (in certain areas of the body) has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (e.g., radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib until these complications have resolved.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 4 weeks of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non GI fistula.

#### 5.4.1.2.4 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

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

- History of clinically significant hemoptysis, hematemesis, or hematuria.

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

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

#### 5.4.1.2.5 Vascular Disorders

Thromboembolic Events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the Investigator and according to individual protocols. Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed for management of thrombotic events. Other oral anticoagulants including coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardioprotection per local

applicable guidelines are not allowed, until 4 weeks after cabozantinib has been permanently discontinued. See Section 6.2 for additional restrictions on anticoagulation therapy.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Subjects should be evaluated for pre-existing risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac and/or thromboembolic events that occurred prior to initiation of study treatment. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

Hypertension

The below table provides treatment guidelines for hypertension deemed related to cabozantinib. Subjects with known hypertension should be optimally managed prior to entry into clinical trials with cabozantinib according to entry criteria of specific protocols. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

**Management of Hypertension Associated with Cabozantinib**

| Event | Management |
|---|---|
| **Subjects NOT receiving optimized anti-hypertensive therapy** | |
| > 140 mm Hg (systolic)[a] and < 160 mm Hg<br><br>OR<br><br>> 90 mm Hg (diastolic) and < 110 mm Hg | • Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications.<br>• Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <140 mm Hg systolic or <90 mm Hg diastolic.<br>• If subject is symptomatic interrupt cabozantinib treatment |
| ≥ 160 mm Hg (systolic)<br><br>OR<br><br>≥ 110 mm Hg (diastolic) | • Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per Investigator discretion.<br>• Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 140 mm Hg systolic or < 90 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted.<br>• Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic.<br>• Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic. |
| Hypertensive emergency[c] | • Discontinue cabozantinib treatment. |

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

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

#### 5.4.1.2.6 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

#### 5.4.1.2.7 Skin and Subcutaneous Tissue Disorders

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

Treatment with cabozantinib should be stopped at least 3 weeks prior to elective surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until complete wound healing.

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral.

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

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

#### 5.4.1.2.8 Angioedema

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

#### 5.4.1.2.9 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib treatment. Advise subjects regarding oral hygiene practice and to quickly report symptoms to Investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 3 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Withhold cabozantinib for development of ONJ until complete resolution.

#### 5.4.1.2.10 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. The below table provides treatment guidelines for proteinuria deemed related to cabozantinib. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

**Management of Proteinuria Associated with Cabozantinib**

| Event | Management |
|---|---|
| UPCR ≤ 1 mg/mg<br>(≤ 113.1 mg/mmol) | • No change in cabozantinib treatment or monitoring. |
| UPCR > 1 and < 3.5 mg/mg<br>(> 113.1 and < 395.9 mg/mmol) | • Consider confirming with a 24-h protein assessment within 7 days.<br>• No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection.<br>• 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.<br>• 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. |
| UPCR ≥ 3.5 mg/mg<br>(≥ 395.9 mg/mmol) | • Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein.<br>• If ≥ 3.5 mg/mg on repeat UPCR, continue to hold cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated. |
| Nephrotic syndrome | • Discontinue cabozantinib treatment. |

#### 5.4.1.2.11 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes. RPLS has been reported.

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

#### 5.4.1.2.12 Infections and Infestations

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

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

#### 5.4.1.2.13 Blood and Lymphatic System Disorders

Hematological toxicities (i.e., neutropenia, thrombocytopenia, and anemia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

#### 5.4.1.2.14 Fatigue

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

#### 5.4.1.2.15 Weight Loss

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

#### 5.4.1.2.16 Corrected QT Prolongation

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

Unless otherwise specified, only subjects with a baseline QTcF ≤ 500 msec are eligible for cabozantinib research studies. Cabozantinib should be used with caution in subjects with QT prolongation risk, a history of QT interval prolongation, or who are taking antiarrhythmics or drugs known to prolong the QT interval. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Interrupt cabozantinib treatment.
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management.
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated.
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org).

- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 ms and the average increase is ≤ 60 ms above baseline, or otherwise determined by consultation with a cardiologist or appropriate expert.

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

- Symptoms are determined to be unrelated to the QT interval prolongation.
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved.
- Principal Investigator has reviewed all available information and has agreed to the continuation of study treatment

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.
Cabozantinib treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation.
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose.

#### 5.4.1.2.17 Endocrine Disorders

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

#### 5.4.1.2.18 Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and approved by the Principal Investigator. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

#### 5.4.1.2.19 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible cause of new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

#### 5.4.1.2.20 Electrolyte Abnormalities

Electrolyte abnormalities, including hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia have been noted in subjects treated with cabozantinib. In some cases these have been Grade 3 or 4 and/or serious. These laboratory values should be evaluated routinely. Deficits should be corrected when an electrolyte abnormality is noted in order to avoid worsening. Correction of electrolyte abnormalities should be accompanied by increased frequency of monitoring.

### 5.4.2 Management of AEs Associated with Nivolumab and Ipililumab

The assigned dose for Nivolumab 3 mg/kg IV every 3 weeks followed by 480mg every 4 weeks.

The assigned dose for Ipilimumab 1 mg/kg for a maximum of up to 4 doses.

Dose reductions are not allowed for the IO agents. AEs associated with the IO agents are managed with dose delays.

For more detailed guidance on management of non-hepatocellular AEs associated with IO agents please see Appendix A. For recommendations on management of hepatocellular toxicity and dose modifications of both cabozantinib and IO agents, see Section 5.4.3.

#### 5.4.2.1 Dose Delay Criteria for the Nivolumab and Ipililumab

Administration of the Nivolumab and Ipililumab should be delayed, for any of the following:

- Any Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia does not require dose delay
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
    - Grade 3 AST, ALT or total bilirubin may require dose discontinuation. (See Section 5.4.3)
- Grade 4 amylase or lipase value necessitates dose delay for the anti-PD-(L)1 and anti-CTLA-4 and abdominal imaging to rule out pancreatitis regardless of presence or absence of symptoms. If the diagnostic radiology scan shows no evidence of pancreatitis, the anti-PD-(L)1 and anti-CTLA-4 may

be resumed once the amylase and lipase values return to Grade 3 or lower as long as the subject remains asymptomatic.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Immuno-oncology agents are associated with AEs that differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms or tables (Section 5.4.3 and Appendix A) have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis
- Infusion-related Reactions

#### 5.4.2.2 Criteria to Resume Nivolumab and Ipilimumab

Delayed doses of Nivolumab and Ipilimumab should be administered as soon as the subject meets criteria to resume treatment. If a dose has been delayed, the subject should not wait until the next scheduled dosing date.

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Systemic corticosteroids for control of infusion reactions or irAEs must have been tapered to a dose level ≤ 10 mg/day of prednisone equivalent before resuming treatment with Nivolumab and Ipilimumab.

- For subjects with AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline grade and corticosteroid therapy has been tapered to no higher than the equivalent of 10 mg of prednisone per day.
  *Note: Drug-related ALT or AST > 3x ULN in combination with total bilirubin > 2x ULN without reasonable other explanation, consistent with DILI mandates permanent discontinuation of all study drugs.*
  *Note:* Nivolumab and Ipilimumab*, or Ipilimumab alone, may be continued after a Grade 3 ALT or AST has been observed and managed appropriately after a positive benefit risk ratio has been determined and the Principal Investigator has been consulted (See Section 5.4.3)*
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Principal Investigator.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If all study treatment is interrupted for > 12 weeks, the subject must be permanently discontinued from study treatment unless approved by the Principal Investigator.

#### 5.4.2.3 Criteria for Discontinuation of Nivolumab and Ipilimumab

Criteria for discontinuation of both Nivolumab and Ipilimumab during the combination therapy period or the Nivolumab alone after no additional Ipilimumab is to be given are specified in this section. If a subject meets criteria for discontinuation and the Investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both Nivolumab and Ipilimumab with the exception of certain cases of liver function test elevation (See Section 5.4.3).

Nivolumab and Ipilimumab should both permanently discontinued for any of the following reasons:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment;
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration;
- Any Grade 3 adrenal insufficiency regardless of control with hormone replacement.
- Any Grade 3 drug-related non-skin AE lasting > 7 days or recurs;
- Grade 3 diarrhea or Grade 3 colitis

- *Note: Nivolumab alone can be continued if grade 3 colitis or diarrhea lasts ≤ 7 days or if, upon permanent discontinuation of ipililumab, the Principal Investigator approves continued use due to a possible favorable benefit/risk ratio.*

- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding;
- Grade ≥ 3 drug-related AST**, ALT**, or total bilirubin;

  *** In most cases of Grade 3 AST or ALT elevation,* Nivolumab and Ipililumab *will be permanently discontinued. Nivolimab alone or* Nivolumab and Ipililumab *may be continued with approval from the Principal Investigator if there is a possible favorable benefit/risk ratio.*
- Drug-related ALT or AST > 3x ULN in combination with total bilirubin > 2x ULN without reasonable other explanation, indicative of potential DILI, mandates permanent discontinuation of all study drugs;
- Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin);
- Any grade meningoencephalitis, myasthenia gravis, or Guillain-Barré syndrome
- Any event that leads to delay in dosing lasting > 12 weeks from the previous dose.

The following scenarios do not require discontinuation of the ipililumab and/or nivolumab:

- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement;
- Grade 4 neutropenia ≤ 7 days;
- Grade 4 lymphopenia or leukopenia;
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset;
- Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Principal Investigator;
- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Drug-related adverse events are any toxicity temporally associated with administration of the investigational agent that may be at least possibly related to study treatment;

- Dosing delays lasting > 12 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue as clinically indicated during such dosing delays.

### 5.4.3 Management of Hepatocellular Toxicity Associated with Cabozantinib and Nivolumab and Ipililumab

Elevations of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib, anti-PD-(L)1 agents, and anti-CTLA-4 agents. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other causes (e.g., cancer-related, infection) should be evaluated.

The following condition requires discontinuation of all study drugs:

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

The table below provides suggested guidance on management of hepatotoxicity related to cabozantinib, Nivolumab and Ipililumab.

In the event cabozantinib is interrupted and Nivolumab and Ipililumab delayed due to a Grade 2 abnormality in a serum transaminase (ALT and/or AST) or serum bilirubin, Nivolumab and (if fewer than 4 ipilulumab doses have been administered and no AE has occurred that led to discontinuation of the ipililumab alone) the ipililumab should be resumed upon return of liver function tests to baseline grade, at which time cabozantinib should be resumed with a dose reduction (from either 40 mg qd to 20 mg qd, or 20 mg qd to 20 mg qod as appropriate).

If no additional ipililimab is to be administered, the dose of cabozantinib may be re escalated no sooner than 10 days after re-initiation of cabozantinib. And then can be further escalated no sooner than 14 days thereafter.

Consult with the Principal Investigator to discuss further management should re-challenge be followed by any recurrence of a Grade 2 or higher liver function test.

Dose delays should not alter the timing of other study assessments, including but not limited to tumor imaging.

For additional information on dose modifications of Nivolumab and Ipililumab, refer to Section 5.4.2 or Appendix A.

**Suggested Management of Hepatotoxicity Associated with Study Treatment**

| Severity of LFT[a] Elevations | Dose Modification Guidance | Management/Follow-up Guidance |
|---|---|---|
| AST or ALT<br>> 1 – ≤ 3x ULN<br>**and/or**<br>total bili<br>> 1 – ≤ 1.5x ULN | • *Cabozantinib:*<br>– Continue cabozantinib per protocol<br>• *Nivolimab/Ipilulimab:*<br>– Continue therapy per protocol | • Monitor LFTs per protocol.<br>• Discontinue concomitant hepatotoxic medications, if possible. |
| AST or ALT<br>> 3 – ≤ 5 x ULN<br>**or**<br>total bili<br>> 1.5 – ≤ 3x ULN | • *Cabozantinib*:<br>– Interrupt cabozantinib dosing.<br>– If LFTs return to baseline grade, resume cabozantinib at a reduced dose. After completion of ipililumab, re-escalate cabozantinib dose as per protocol. If no additional ipililumab doses are to be administered, the dose of cabozantinib may be re-escalated no sooner than 10 days after re-initiation of cabozantinib.<br>– See above section for additional guidance.<br>• *Nivolimab/Ipilulimab:*<br>– Delay therapy per protocol.<br>– If LFTs return to baseline grade, resume therapy per protocol. | • Monitor LFTs twice weekly or more frequently as deemed clinically necessary.<br>– If tapering off steroid therapy, monitor LFTs once weekly or more often per clinical judgment[b].<br>– If LFTs return to baseline grade, resume with routine monitoring.<br>• If LFT elevations persist > 3 days or worsen:<br>– Administer 0.5-1 mg/kg/day methylprednisolone or oral equivalent.<br>– When LFTs return to baseline grade or CTCAE Grade ≤1, taper steroids over at least 1 month[b].<br>– Consider prophylactic antibiotics for opportunistic infections. |
| AST or ALT<br>> 5x ULN<br>**or**<br>total bili > 3x ULN or as otherwise specified | • *Cabozantinib*:<br>– Discontinue cabozantinib if ALT or AST > 8x ULN.<br>– Otherwise interrupt cabozantinib dosing and resume at a reduced dose after LFTs return to baseline grade (Sponsor approval required)<br>• *Nivolimab/Ipilulimab:*<br>– Discontinue therapy for Grade 3 ALT/AST, unless the Investigator in consultation with the Principal Investigator determines a favorable risk/benefit ratio that warrants continuation of both Nivolumab and Ipililumab or of Nivolumab alone | • Monitor LFTs twice weekly or more frequently as deemed clinically necessary.<br>• During steroid taper, monitor LFTs once weekly or more often per clinical judgment[b].<br>• For Grade 3:<br>– Administer 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent.<br>• For Grade 4:<br>– Administer 2.0 mg/kg/day methylprednisolone IV or IV equivalent.<br>• Add prophylactic antibiotics for opportunistic infections.<br>• Consult Gastroenterologist.<br>• When LFTs return to baseline grade or Grade 2, taper steroids over at least 1 month[b]. |

| | | |
|---|---|---|
| | | • If LFT elevations do not improve in > 3 days, worsen or rebound:<br>– Add mycophenolate mofetil 1g BID.<br>– If no response within an additional 3-5 days, consider other immune-suppressants per local guidelines. |
| ALT or AST > 3x ULN AND total bilirubin > 2x ULN **AND** no radiographic evidence of biliary obstruction | • All study drugs must be discontinued. | • Follow the above management/follow-up guidance by grade. |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bili, bilirubin; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; LFT, liver function tests; ULN, upper limit of normal

[a] LFTs include AST, ALT and total bilirubin.

[b] Subjects 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 should be taken into account when switching to the equivalent dose of oral corticosteroids.

# 6 CONCOMITANT MEDICATIONS AND THERAPIES

## 6.1 Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., ASCO or ESMO guidelines).
- Bisphosphonates or RANK-L inhibitors can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the Investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 5.4.1.2.9). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended. Withhold cabozantinib for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.

- Inhaled, intranasal, intra-articular, and topical corticosteroids are allowed if minimal systemic absorption. Systemic corticosteroids are allowed for control of infusion reactions or irAEs and must be tapered to a dose level ≤ 10 mg/day of prednisone equivalent before next administration of the IO agent. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed.
- Individualized anticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
    - At the time of first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
    - After first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
    - Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed

### 6.2 Prohibited or Restricted Therapy

*The following therapies are <u>prohibited</u> until study treatment has been permanently discontinued*:

- Any investigational agent or investigational medical device.
- Any non-protocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 6.1.
- Live vaccines are prohibited while on study and until 5 months after last dose of IO agent (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines). The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.
- Metamizole (dipyrone) because of its potential for causing agranulocytosis.
- Anticoagulants: Prohibits coumarin agents, direct thrombin inhibitors, direct factor Xa inhibitor betrixaban, platelet inhibitors, and aspirin above low-dose levels for cardio-protection until 4 weeks after cabozantinib has been permanently discontinued

*The following therapies should be <u>avoided</u> until study treatment has been permanently discontinued or until otherwise specified*:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin[21].
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).
- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

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

### 6.2.1 Potential Drug Interactions with Cabozantinib and Effects of Food

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

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

Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, rand ritonavir) may increase cabozantinib plasma concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be avoided.
Please refer to the drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Protein Binding: Cabozantinib is highly bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. A case of a drug-drug interaction between cabozantinib and warfarin that may involve displacement of plasma protein bound drug has been reported in the literature[22]. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses is not allowed in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

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

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

Concomitant administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, $H_2$ receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

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

### 6.2.2 Potential Drug Interactions

No drug interactions between cabozantinib and ipilimumab and nivolumab have been observed in previously reported clinical trials. Cabozantinib does not affect metabolism or the serum half-life of ipilimumab or nivolumab. Cabozantinib has overlapping toxicity with ipilimumab/nivolumab including the potential to cause diarrhea, elevated liver enzymes, skin rash, and hypothyroidism.

## 7 SAFETY

### 7.1 Adverse Events and Laboratory Abnormalities

### 7.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical trial subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. This requirement includes specific events or symptoms associated with cancer progression or general clinical deterioration to ensure potential toxicities are not overlooked. Radiographic progression without associated clinical sequalae is not considered an AE: terms such as ‘disease progression’ should be avoided. An adverse event can arise from any use of the drug (eg off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in this protocol.

All untoward events that occur after start of study therapy through 30 days (100 days for SAEs and certain other events [See AEs of Special Interest Table]) after the last study treatment are to be recorded by the investigational site.

At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report. Seriousness, severity grade, and relationship to study treatment will be assessed by the Investigator. Severity grade will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE). This study will use the NCI CTCAE v5.0.

Assessment of the relationship of the AEs to individual study treatment by the Investigator is based on the following two definitions:

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

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the ISR agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

### 7.1.2 Laboratory Abnormalities

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

appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry to the study.

## 7.2 Serious Adverse Events (SAEs)

### 7.2.1 Definitions

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

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

- Result in death.
- Is immediately life-threatening (i.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.
- Results in significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event (IME).
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of IMEs include

intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE

### 7.2.2 SAEs Reporting

As soon as an Investigator becomes aware of an AE that meets the criteria for an SAE, the Investigator will document the SAE on an SAE Report Form in REDCap. SAEs must be recorded as Adverse Events using the electronic case report form in REDCap a clinical data management system (CTMS).

In addition, SAEs regardless of causal relationship, must be reported to Exelixis and BMS within one (1) business day of the Investigator's knowledge of the event by submitting a completed MedWatch report form.

**Exelixis Reporting**: The reports must be emailed to **drugsafety@exelixis.com** or faxed to **650-837-7392** with the below:

- Required Information:
    - Identity of Investigator
    - Site name
    - Subject identifiers
    - Drug name and dosage
    - Event description
    - Event terms (i.e., as recorded in the electronic database)
    - Investigator's assessment of the relationship of the event to study treatment (Section 7.1)
    - The reason why the event is considered to be serious (i.e., the seriousness criteria) (Section 7.2.1)

- Recommended Information:
    - Medications or therapeutic measures used to treat the event
    - Action taken with the study treatment because of the event

- Outcome/resolution of the event
- Any additional SAE information

Note – Medical records should **not** be sent to Exelixis unless requested.

**BMS Reporting**: All SAEs that occur from first study treatment through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug, including those thought to be associated with protocol-specified procedures (eg, a follow-up skin biopsy) within 24 hours \ 1 business day to comply with regulatory requirements. MedWatch 3500 form should be completed and submitted to BMS to report the SAEs.

Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission. Medical Records should **not** be sent to BMS unless requested.

An SAE report should be completed for any event where doubt exists regarding its seriousness;

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to the below email address and the BMS Protocol number must be included on the SAE form or on the cover sheet with the SAE form transmission

**SAE Email Address: Worldwide.Safety@BMS.com**

**SAE Facsimile Number: +1-609-818-3804**

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

The Sponsor-Investigator will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all AE and SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

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).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol.

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

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

SAEs that must be recorded on an SAE Reporting form include the following:

- SAEs that occur after initiation of study therapy and through 100 days after the date of the decision to permanently discontinue study treatment
- SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 100 days after the date of the decision to permanently discontinue study treatment.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Exelixis and/or BMS.

When reporting SAEs, the following additional points will be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator will report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated, and the diagnosis amended when the etiology has been identified. If an autopsy was performed, the autopsy report should be provided.

### 7.2.3 Regulatory Reporting

The Investigator will assess the expectedness of each related SAE to the study treatment. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib.

The Investigator is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with FDA regulations (21 Code of Federal Regulations [CFR] 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form)
- Exelixis Drug Safety group (or designee) will process and evaluate all SAEs as the reports are received. For each SAE received, Exelixis will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.

- Institutions and Investigators shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The Investigator is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the Principal Investigator of a clinical trial.
- The Investigator shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the Principal Investigator to disseminate these updates to participating Investigators.
- Reporting of SAEs by the Investigator to his or her Institutional Review Board (IRB)/Ethics Committees (ECs) will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.
- In the case of blinded studies, the treatment blind will be broken by the Principal Investigator and/or other necessary personnel prior to reporting an SAE that meets the criteria for expediting reporting to the Regulatory Authorities and to some central ECs. All personnel that are not involved in the unblinding and submission processes will remain blinded to the treatment assignment.

### 7.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) consist of immune-mediated AEs associated with ICIs, cases of potential DILI, and suspected transmission of an infectious agent by the study treatment. AECIs must be recorded as Adverse Events using the Events of Clinical Interest electronic case report form in REDCap's clinical data management system (CTMS).

AESIs will be reported to the Principal Investigator or designee using the SAE reporting form irrespective of whether the event is serious or nonserious; all AESIs must be reported within one (1) business day using the SAE process as described in Section 7.2.2.

Guidance for management of immune-mediated AEs is provided in the protocol (Section 5.4.2 – 5.4.3) and can also be found in the local prescribing information for each IO agent.

**Adverse Events of Special Interest**

| Event |
|---|
| Cases of potential DILI that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: |
| Suspected transmission of an infectious agent by the study treatment, as defined below:<br><br>Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected. |
| Pneumonitis |
| Colitis |
| Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis |
| Hepatitis, including AST or ALT > 10x ULN |
| Systemic lupus erythematosus |
| Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis |
| Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation |
| Nephritis |
| Ocular toxicities (e.g., uveitis, retinitis) |
| Myositis |
| Myopathies, including rhabdomyolysis |
| ≥ Grade 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis) |
| Vasculitis |

### 7.3.1 General Information on Immune-Related Adverse Events

The immune-modulating properties of IO agents are able to undermine immunologic tolerance and generate a subset of AEs (called irAEs) with an autoimmmune inflammatory pathomechanism. Immune-related AEs may involve any organ or tissue[23]. Most irAEs occur within the first 12 weeks of exposure to IOs but some may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an IO and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with IOs are fatigue, fever, and chills. Organ-specific irAEs consist of dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively unspecific symptoms. The following additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), FT4 and TSH (pituitary-thyroid function), luteinizing hormone (LH) and follicle-stimulating hormone (FSH; pituitary-gonadal function), adrenocorticotropic hormone (ACTH) and cortisol (pituitary-adrenal function).

Additional organ-specific irAEs include hepatitis (AST/ALT increases, hepatomegaly, periportal edema, periportal lymphadenopathy, lymphocyte infiltration of periportal tissue and surrounding primary biliary ducts) and pneumonitis (acute interstitial pneumonia). Less frequent irAEs include neurologic syndromes (myasthenia gravis, Guillian-Barré syndrome, meningoencephalitis), ocular AEs (uveitis), renal AEs (interstitial nephritis), cardiac AEs (myocarditis), and pancreatic AEs (lipase increase).

### 7.4 Follow-up of Adverse Events

Nonserious AEs will be followed until 30 days after the date of the decision to discontinue study treatment. All SAEs and AESIs (regardless of seriousness) will be followed until 100 days after the date of decision to discontinue study treatment.

All AESIs (regardless of seriousness) and all related SAEs that are ongoing 100 days after the date of the decision to discontinue study, and AEs assessed as related that led to study treatment discontinuation that are ongoing 100 days after the date of the decision to discontinue study treatment, are to be followed until either:

- The AE has resolved.
- The AE has improved to Grade 2 or lower.
- The investigator determines that the event has become stable or irreversible.

## 7.5 Other Safety Considerations

### 7.5.1 Pregnancy/Lactation Exposure

Use of highly effective methods of contraception is very important during the study and must continue for 4 months after the last dose of cabozantinib and 3 months after the last dose of ipilimumab and 5 months after the last dose of nivolumab. If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy and the infant should have follow up for at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, the Investigator will ask the pregnant female to consent to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth. Furthermore, male subjects must refrain from donating sperm in order to avoid transmission of study treatment in semen for the duration of study treatment and through 5 months after their last dose of study treatment. Both male and female subjects should seek advice and consider fertility preservation before receiving study treatment.

The Investigator must inform Exelixis/BMS of the pregnancy. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis/BMS. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Females should not breastfeed while receiving study treatment and for up to 4 months from the last dose of cabozantinib and up to 5 months from the last dose of ipilimumab or nivolumab.

### 7.5.2 Medication Errors/Overdose

Medication error is defined as the administration of each study drug medication outside or above the established dosing regimens per the specific protocol. Any study medication overdose, misuse, abuse, or medication error (excluding missed doses) that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis and BMS.

In case of overdose, the Principal Investigator should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

Please refer to the cabozantinib Investigator Brochure for additional management recommendations regarding overdoses of cabozantinib.

## 8 STATISTICAL CONSIDERATIONS

**Data and Statistical plan:**

Recent clinical trials have demonstrated median PFS as high as 5 months with the combination of low dose ipilimumab (1 mg/kg IV every 3 weeks) with anti-PD-1 therapies in patients with anti-PD1 refractory cutaneous melanoma. In this clinical trial, we will use the 5 month mPFS as our benchmark. In order to show a 4 month improvement in mPFS over the 5 month historical data benchmark (with a power of 0.8 and a one-sided test given a type I error rate of 0.05), a total of 41 subjects would need to be enrolled.

This signal seeking pilot study will enroll 25 subjects at our site (single institution) in less than 2 years. If we find that this treatment combination results in a ***mPFS of at least 8 months or an ORR of 45% or higher***, we will review these results with BMS and Exelixis and propose protocol and budget amendments to add 1-2 additional sites to expedite to a total of at least 41 subjects to be enrolled in a rapid timeframe.

**Descriptive Statistics:**

Descriptive statistics will be provided for all baseline, efficacy, and safety variables, as appropriate. Frequency counts and percentages will be provided for categorical data. Mean (standard deviation), median (interquartile range) will be calculated for continuous variables.

**Statistical Analyses for Primary and Secondary Endpoints:**

**Primary endpoint**: The progression-free survival (PFS) analyses will be performed considering the risk of dying from any cause before experiencing progression related events using the competing risk regression method[24] . Cumulative incidence functions will be displayed and summarized for the median time to progression as well as percentage of patients without disease progression at 12, 18, and 24 months.

**Secondary endpoints**: ORR will be determined as the rate of the confirmed best overall response of either PR or CR per iRECIST. Using the efficacy evaluable analysis set, the Kaplan-Meier method will be used to estimate PFS, OS and DOR, and the summary statistics (e.g., 12-month survival and median

survival with 95% confidence intervals). DOR will be estimated only among responders (i.e. participants achieving at least once CR or PR). Data visualization tools such as waterfall plots (% change in tumor size) or swimmer plot (DOR) will be used to display the data.

Using the safety evaluable analysis set, the incidence of having Grade ≥ 3 AEs will be determined for study participants that received at least one dose of their assigned treatment. The point estimate and 95% confidence interval will be reported.

For correlative molecular profiling endpoint, paired t-test or Wilcoxon signed-rank test will be performed to evaluate tumor infiltrating immune cell profiling and gene expression changes between pre- and post-treatment.

## 9 DATA QUALITY ASSURANCE

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into REDCap clinical data management system (CTMS) via eCRFs. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's electronic medical records. All printed source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the Regional Research Quality Assurance Department and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked.

# 10 ETHICAL ASPECTS

## 10.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997) and remain consistent with the most recent version of the Declaration of Helsinki. 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."

## 10.2 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.

The investigator or the study designated staff will ensure all participants are provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedures. The participant must be offered/provided a copy of the

signed and dated consent document. The original signed copy of the consent document must be retained in the research file. Please see 21CFR, Part 50 for additional guidance.

### 10.3 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 and BMS(or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed by the Providence Health & Services IRB. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

## 11 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the Principal Investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis and BMS 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 (e.g., change in monitor or change of telephone number).

## 12 CONDITIONS FOR TERMINATING THE STUDY

At any time, the study may be terminated by the Principal Investigator, the Principal Investigator's institution, or by Exelixis or BMS. Should this be necessary, Exelixis, BMS and the Principal Investigator

will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis, BMS and the Principal Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the Principal Investigator and all Investigator(s) shall cease enrolling subjects into the study and shall discontinue conduct of the study as soon as is medically practicable.

# 13 STUDY DOCUMENTATION AND RECORD-KEEPING

## 13.1 Investigator's Files and Retention of Documents

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

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

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

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

### 13.2 Source Documents and Background Data

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

### 13.3 Audits and Inspections

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

### 13.4 Case Report Forms

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

Clinical data will be recorded on the study-specific electronic case report form (eCRF) in the REDCap clinical data management system (CTMS). For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted.

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

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

## 14 MONITORING THE STUDY

**Oversight and Monitoring Plan**

*Oversight of patient safety will include review of adverse events as well as study progress and outcomes. Patient updates, outcomes, and recruitment and retention of patients will be reviewed on a regular basis by the PI, research nurse, and data coordinator. Deviations will be reviewed during oversight meetings and/or through internal reporting procedures. Aggregate protocol deviations are monitored for trends to be reviewed by the Providence Cancer Institute Clinic and Research Quality Committee. In addition, a "first patient review" is conducted and documented for all clinical trials. This review includes treatment administration, deviations, and SAEs to ensure any compliance and/or safety issues are addressed prior to the enrollment of additional patients.*

*Study monitoring activities (Quality Control Reviews) are performed by clinical research staff members who have completed specialized training in study monitoring procedures and human subjects' protections. Individuals who perform study monitoring activities do not report to Principal Investigators or research scientists and may not monitor studies for which they have direct responsibility. Results of study monitoring activities will be reported to applicable study personnel, Clinical Trials Management and Quality Assurance. Study monitoring activities are conducted regularly and include (but are not limited to) review and verification of the following:*

- *Eligibility*
- *Informed Consent process*
- *Adherence to protocol treatment plan*
- *Case Report Forms (CRFs)*
- *Source Documentation*
- *Adverse Events*
- *Regulatory*

***Quality Assurance***

*Quality Assurance (QA) personnel will perform monitoring activities on a routine basis following the monitoring plan. If necessary, QA will determine follow-up actions to resolve significant findings. QA has the authority to request immediate corrective action if significant patient safety issues are identified. QA will track and trend results from routine monitoring activities as well as associated corrective and preventive actions. If necessary, a QA summary report will be provided to the IRB at the time of continuing review. QA personnel do not have a direct reporting relationship to the principal investigator and are not responsible for enrollment or coordination of care for study participants.*

## 15 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents, subjects should be identified by identification codes and not by their names. The Investigator should keep a subject enrollment log

showing codes, names, and addresses. The Investigator should maintain documents (e.g., subjects' written consent forms) in strict confidence.

## 16 PUBLICATIONS OF DATA AND PROTECTION OF TRADE SECRETS

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

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# 18 APPENDICES

## Appendix A

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

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

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory 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.

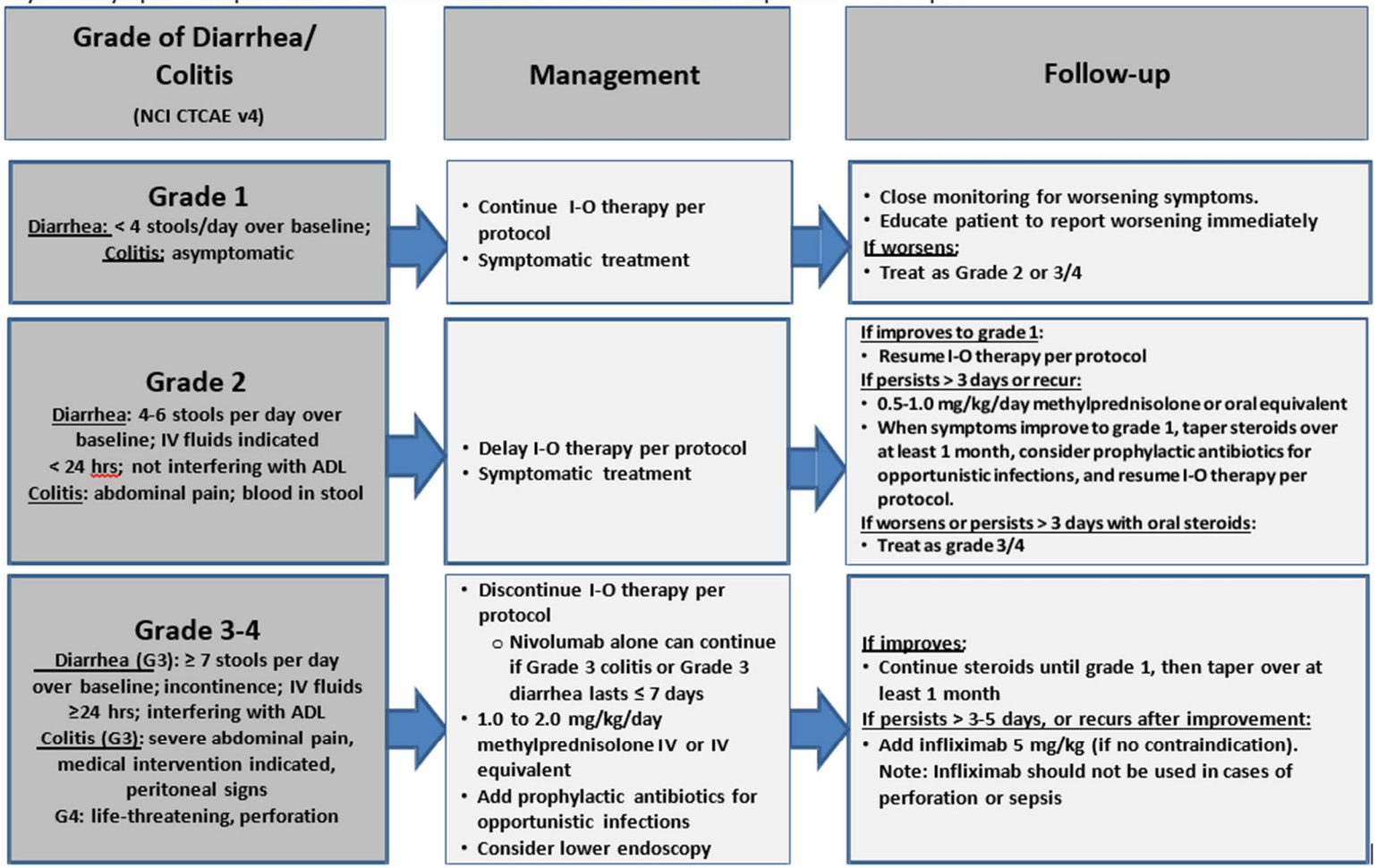
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

For recommendations on dose modifications of BOTH cabozantinib and IO treatment due to hepatocellular toxicity, see Section 5.4.3.

# GI Adverse Event Management Algorithm

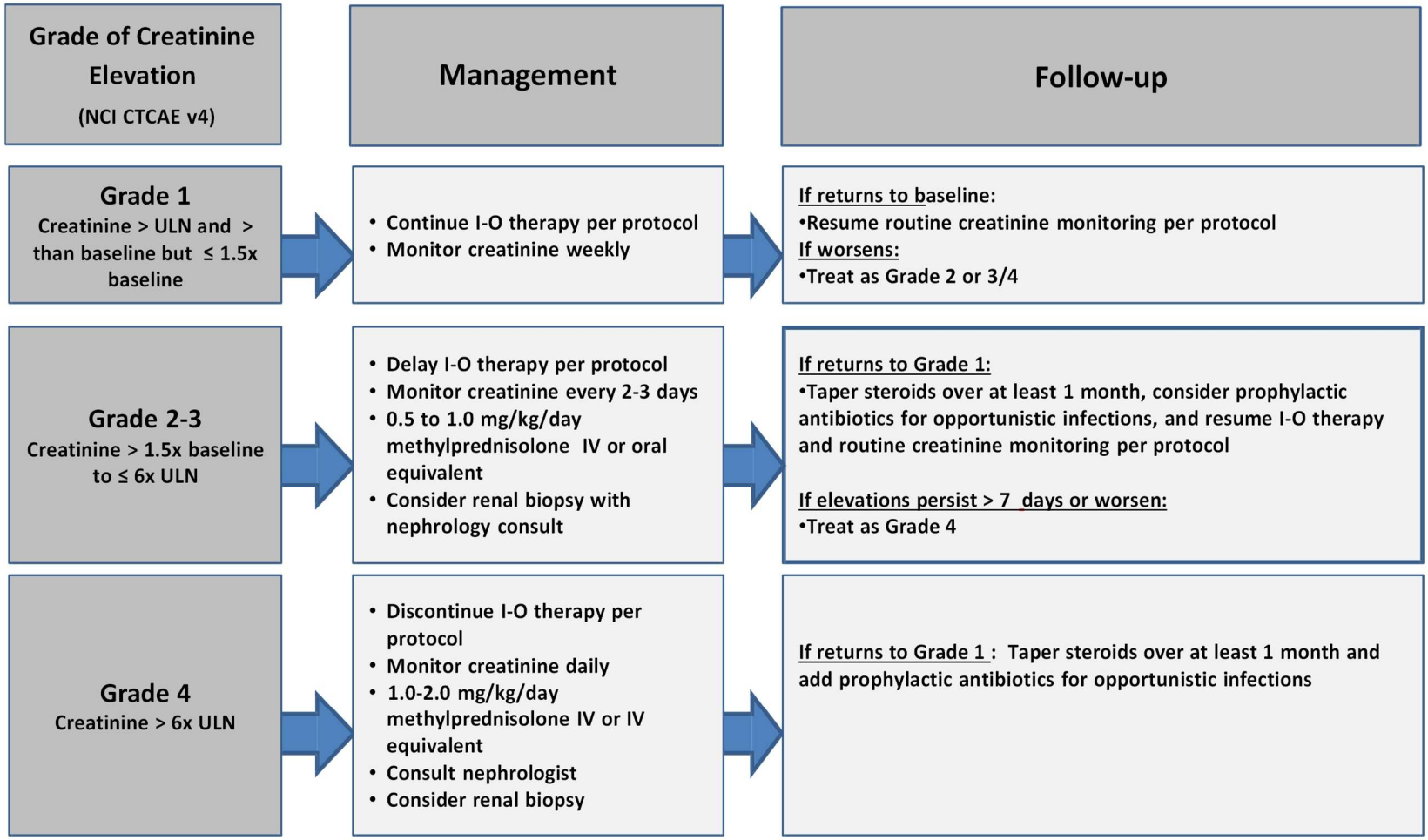
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




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

# Renal Adverse Event Management Algorithm

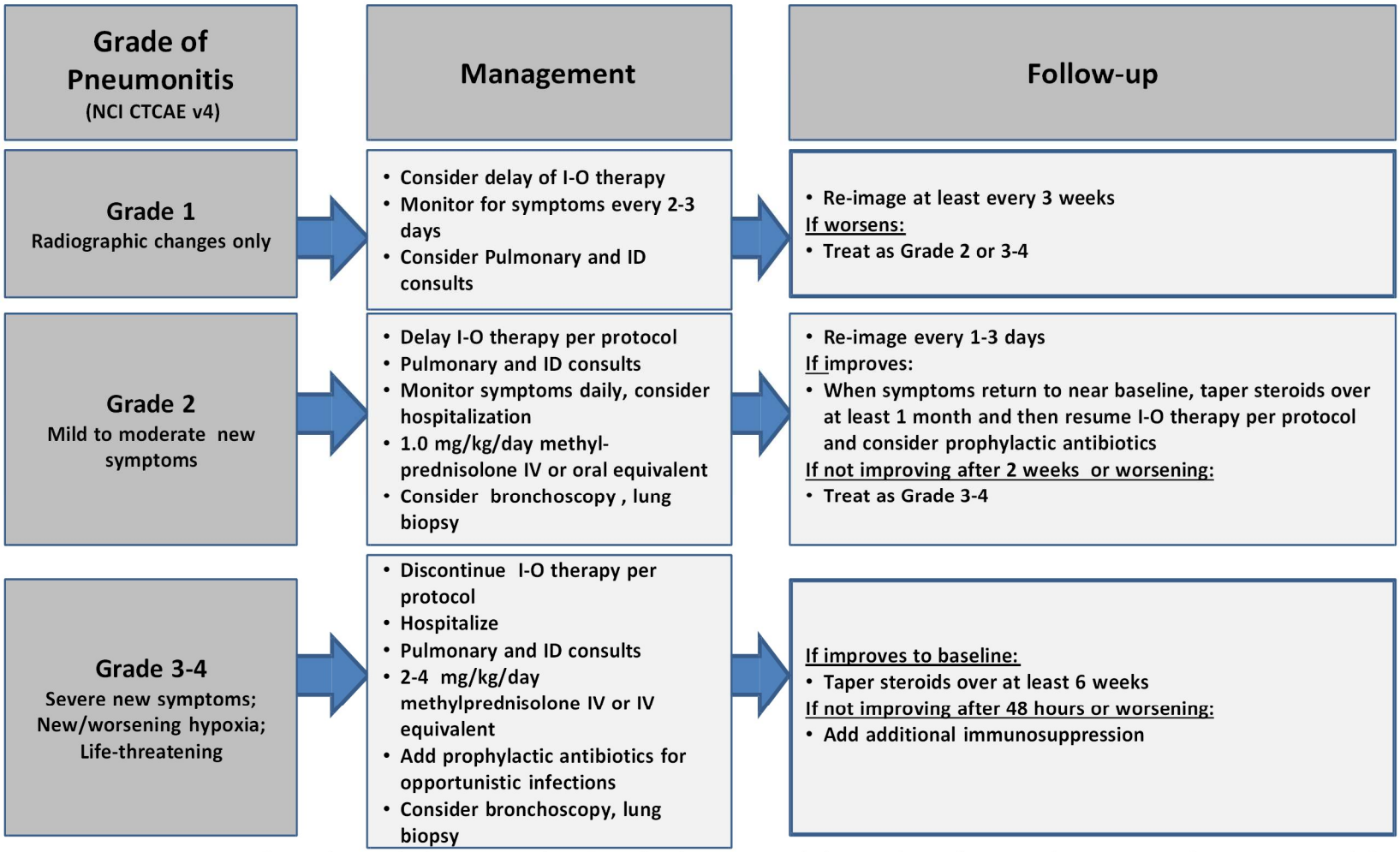
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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

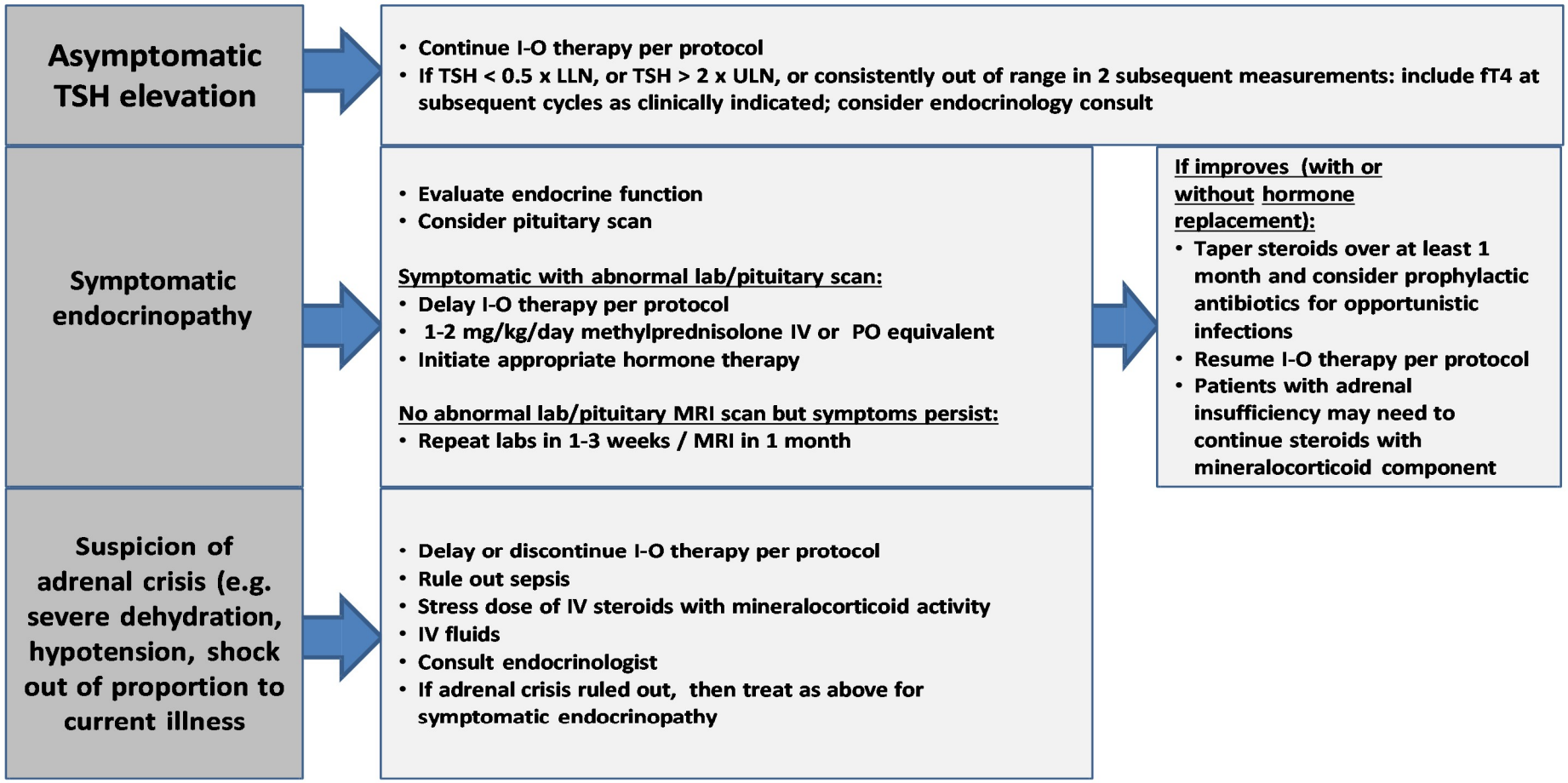
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




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 clini 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

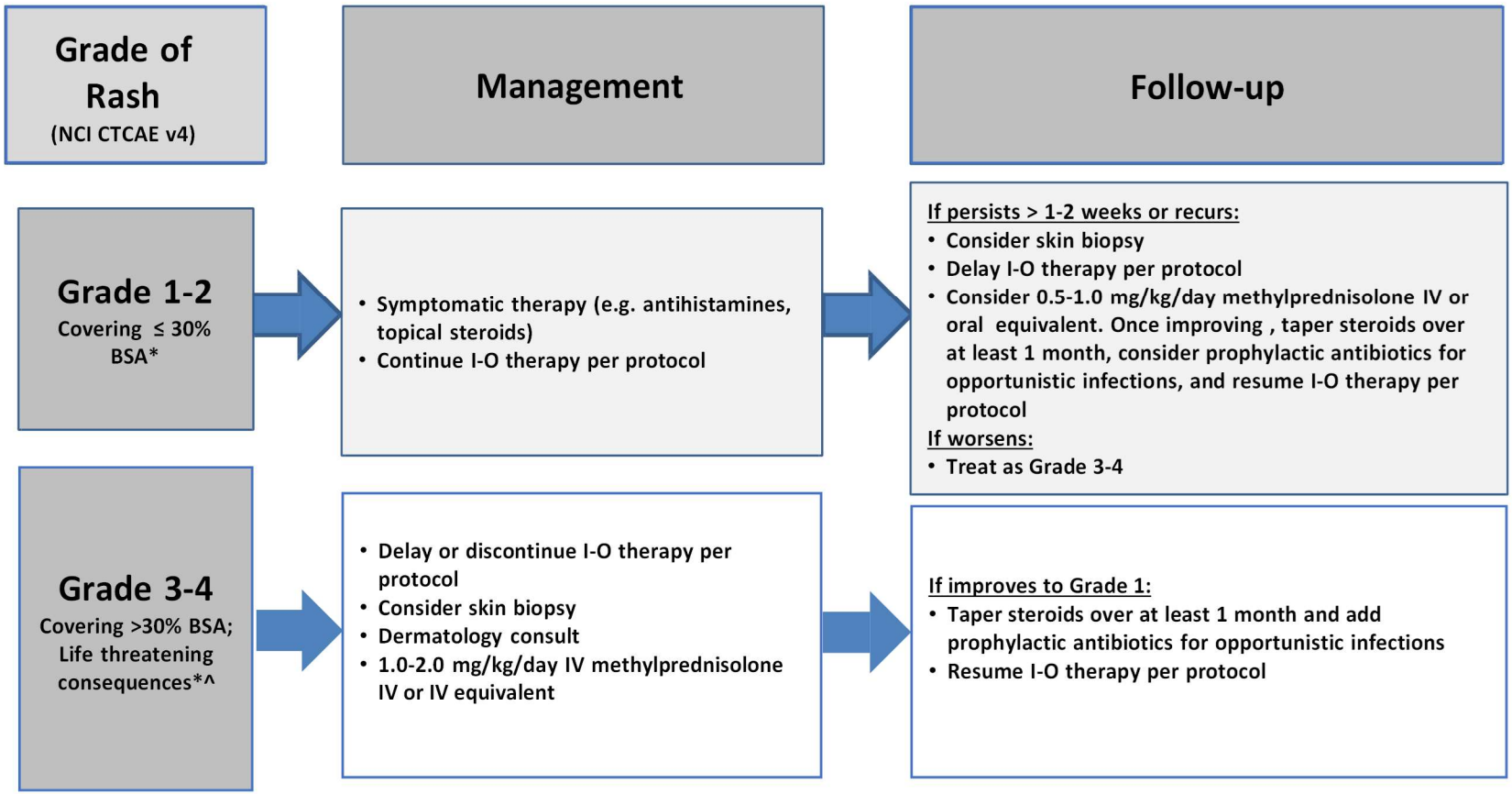
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testin endocrinology consultation, and imaging.




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



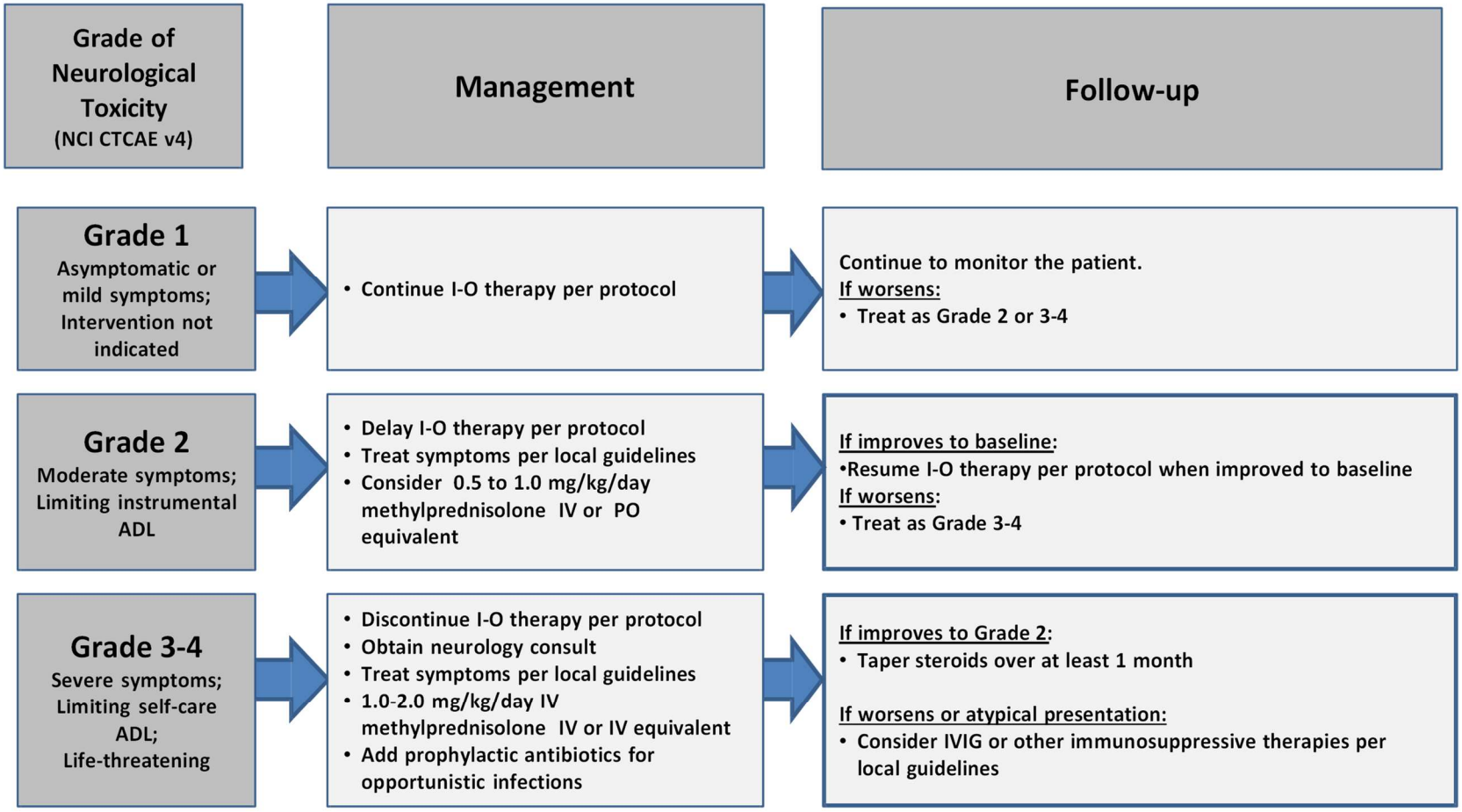

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

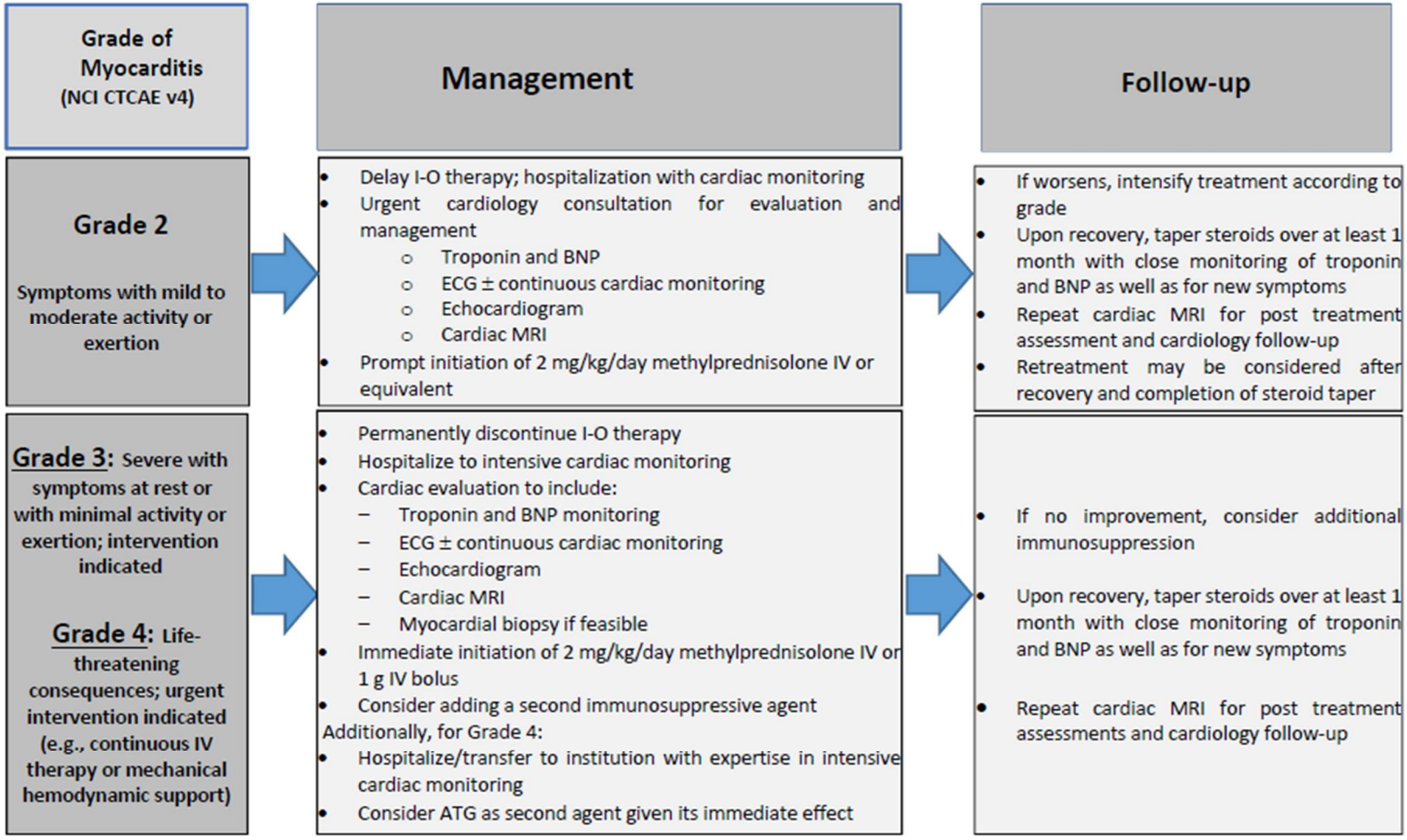
# Neurological Adverse Event Management Algorithm

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

**Infusion-related Reactions**

Infusion-related reactions (IRRs) are known to occur with the administration of monoclonal antibodies and have been reported with IO therapies. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 h of administration and are generally mild to moderate in severity.

Infusion reactions may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, back pain, or other allergic-like reactions. Regardless of whether the event is attributed to these study drugs, all Grade 3 or 4 infusion reactions should be reported within 24 hours to the Principal Investigator and reported as an SAE if it meets the criteria.

Subjects who experience an IRR with IO therapy may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

High-level treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

**Management of Infusion Reactions**

| Event | Management |
|---|---|
| Grade 1 | • Consider reducing the infusion rate.<br>• Monitor vital signs as clinically indicated.<br>• Consider premedication prior to the next infusion. |
| Grade 2 | • Interrupt infusion.<br>• Provide supportive therapy.<br>• Monitor vital signs as clinically indicated.<br>• Restart infusion at a lower rate if symptoms resolve.<br>• Premedicate prior to the next infusion. |
| Grade 3- 4 | • Interrupt infusion and permanently discontinue IO therapy.<br>• Provide supportive therapy.<br>• Monitor vital signs as clinically indicated.<br>• Hospitalize as indicated for clinical sequelae. |

**Cytokine Release Syndrome (CRS)**

Cytokine-release syndrome (CRS) is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction[25]. CRS has been well documented with chimeric antigen receptor T cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1[26,27].

Subjects who experience a CRS with IO therapy may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

| Event | Management |
|---|---|
| **Grade 1**[a]<br>Fever[b] with or without constitutional symptoms | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment[c], including maintenance of IV fluids for hydration.<br>• In case of rapid decline or prolonged CRS (> 2 days) or in subjects with significant symptoms and/or comorbidities, consider managing as per Grade 2.<br>• For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. |
| **Grade 2**[a]<br>Fever[b] with hypotension not requiring vasopressors and/or<br>Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment.[c]<br>• For hypotension, administer IV fluid bolus as needed.<br>• Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.<br>• Consider IV corticosteroids (suggest: methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy.[e]<br>• Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, i.e., hospitalize subject (monitoring in the ICU is recommended), permanently discontinue IO agent, and contact the Principal Investigator.<br>• If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of IO agent may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics and monitor closely for IRRs and/or CRS.<br>• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Principal Investigator. |

| | |
|---|---|
| **Grade 3**[a]<br>Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or<br>Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask | • Permanently discontinue IO agent and contact the Principal Investigator.<br>• Administer symptomatic treatment.[c]<br>• For hypotension, administer IV fluid bolus and vasopressor as needed.<br>• Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.<br>• Administer IV corticosteroids (suggest: methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy.[e]<br>• Hospitalize subject until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, i.e., admit subject to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for subjects who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Principal Investigator. |
| **Grade 4**[a]<br>Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or<br>Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) | • Permanently discontinue IO agent and contact the Principal Investigator.<br>• Administer symptomatic treatment.[c]<br>• Admit subject to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.<br>• Administer IV corticosteroids (suggest: methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy[e]. For subjects who are refractory to anticytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator and in consultation with the Principal Investigator.<br>• Hospitalize subject until complete resolution of symptoms. |

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bi-level positive airway pressure; CAR, chimeric antigen receptor; CPAP, continuous positive airway pressure; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; eCRF, electronic Case Report Form; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IRR, infusion-related reaction; MAS,macrophage activation syndrome; NCCN, National Cancer Comprehensive Network; NCI, National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature > 38°C not attributable to any other cause. In subjects who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors[26,27] but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Refer to Riegler et al (2019) for information on experimental treatments for CRS[28].

**Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome**

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Subjects with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A subject should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL) ($<$ 100 g/L [10 g/dL] for infants $<$ 4 weeks old)
  - Platelet count $<$ 100 $\times$ $10^9$/L (100,000/$\mu$L)
  - ANC $<$ 1.0 $\times$ $10^9$/L (1000/$\mu$L)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Subjects with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq$ 181 $\times$ $10^9$/L (181,000/$\mu$L)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)

- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines the table below.

**Management Guidelines for Suspected HLH or MAS**

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently discontinue IO therapy and contact Principal Investigator.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids and/or an immunosuppressive agent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |
| HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome | |

**Appendix B**

## FACT-M Non-Surgery (Version 4)

FACTMN001

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

## FACT-M Non-Surgery (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

## FACT-M Non-Surgery (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| M1 | I have pain at my melanoma site or surgical site | 0 | 1 | 2 | 3 | 4 |
| M2 | I have noticed new changes in my skin (lumps, bumps, color(colour)) | 0 | 1 | 2 | 3 | 4 |
| M3 | I worry about the appearance of surgical scars | 0 | 1 | 2 | 3 | 4 |
| B1 | I have been short of breath | 0 | 1 | 2 | 3 | 4 |
| ITU4 | I have to limit my physical activity because of my condition | 0 | 1 | 2 | 3 | 4 |
| An10 | I get headaches | 0 | 1 | 2 | 3 | 4 |
| Hep3 | I have had fevers (episodes of high body temperature) | 0 | 1 | 2 | 3 | 4 |
| C1 | I have swelling or cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| M5 | I have aches and pains in my bones | 0 | 1 | 2 | 3 | 4 |
| M6 | I have noticed blood in my stool | 0 | 1 | 2 | 3 | 4 |
| ITU3 | I have to limit my social activity because of my condition | 0 | 1 | 2 | 3 | 4 |
| MS8 | I feel overwhelmed by my condition | 0 | 1 | 2 | 3 | 4 |
| M8 | I isolate myself from others because of my condition | 0 | 1 | 2 | 3 | 4 |
| M9 | I have difficulty thinking clearly (remembering, concentrating) | 0 | 1 | 2 | 3 | 4 |
| HI7 | I feel fatigued | 0 | 1 | 2 | 3 | 4 |