Update #10

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A091902

A MULTICENTER PHASE II TRIAL OF PACLITAXEL WITH AND WITHOUT NIVOLUMAB IN TAXANE NAÏVE, AND NIVOLUMAB AND CABOZANTINIB IN TAXANE PRETREATED SUBJECTS WITH ANGIOSARCOMA

[X] **Update:**	[ ] **Status Change:**
[X] Editorial/Administrative changes	[ ] Activation
[ ] Eligibility changes	[ ] Closure
[ ] Therapy/Dose Modifications/Study Calendar changes	[ ] Suspension
[ ] Scientific/Statistical Considerations changes	[ ] Reactivation
[ ] Correlative Science/BioMS changes	
[X] Informed Consent changes	
[X] Other: Updated CAEPRs for Cabozantinib and Nivolumab	

The changes included in this update to A091902 have been made in response to Action Letters from Dr. Steve Gore (steve.gore@nih.gov) for Cabozantinib and Dr. Brian Ko (brian.ko@nih.gov) for Nivolumab. These Action Letters are posted on the A091902 study page on the CTSU website. The revised CAEPRs for Cabozantinib and Nivolumab with new risks have been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions.

No recommended level of IRB review is provided by the Alliance as the CIRB is the IRB of record for this trial. This amendment must be implemented within 30 days after posting.
The consent form addendum(s) will need to be signed by all patients currently receiving treatment or having treatment held with Cabozantinib and/or Nivolumab and those patients who have been consented but have not yet started treatment. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page
The Protocol Coordinator's contact information has been updated for accuracy per Alliance protocol template.

Study Resources

Donna Vattanakul has replaced Heidi Finnes as the Pharmacy Contact. All contact information has been updated accordingly.

Section 9.4.1 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib, NSC 761968)

This section has been revised to include the updated cabozantinib CAEPR (Version 2.6 ~~5~~, ~~August 29, 2024~~ May 20, 2025) provided by NCI CTEP. Changes from Version 2.5 to Version 2.6 include the following:

- Added New Risk:
  - Rare but Serious: Arterial thromboembolism
- Increase in Risk Attribution:
  - Changed to Rare but Serious from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Myocardial infarction; Wound dehiscence
- Deleted Risk:
  - Less Likely: Hair color changes
  - Also Reported on XL184 Trials But With Insufficient Evidence for Attribution: Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Nail changes; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema)
- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) Reporting Requirements:
  - Deleted: Hair color changes

Section 9.4.2 (Comprehensive Adverse Events and Potential Risks list (CAEPR) For BMS-936558 (Nivolumab, NSC 748726)

This section has been revised to include the updated nivolumab CAEPR (Version 2.6 ~~5~~, ~~June 10, 2023~~ May 14, 2025) provided by NCI CTEP. Changes from Version 2.5 to Version 2.6 include the following:

- Added New Risk:
  - Rare but Serious: Immune system disorders - Other (solid organ transplant rejection); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (eruptive keratoacanthoma); Renal and urinary disorders - Other (renal dysfunction)
  - Also Reported on Nivolumab Trials But With Insufficient Evidence for Attribution: Immune system disorders - Other (complications of allogeneic HSCT)
- Deleted Risk:
  - Rare but Serious: Autoimmune disorder
  - Also Reported on Nivolumab Trials But With Insufficient Evidence for Attribution: Chills; Flatulence; Flushing; Gastrointestinal disorders - Other (mouth sores); Hyperhidrosis; Hypophosphatemia; Investigations - Other (protein total decreased); Optic nerve disorder; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform

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UPDATES TO THE MODEL CONSENT FORM:

What risks can I expect from taking part in the treatment study?

- In Drug Risks, the table under the '**Possible Side Effects of Cabozantinib**,' has been updated with the following risk list changes:
- Added New Risk:

- Rare: Blood clot in artery which may cause swelling, pain, shortness of breath or change of color in extremity

Increase in Risk Attribution:

- Changed to Rare from Also Reported on XL184 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Heart attack

- Deleted Risk:
  - Occasional: Change in hair color

What risks can I expect from taking part in the treatment study?

- In Drug Risks, the table under the '**Possible Side Effects of Nivolumab**,' has been updated with the following risk list changes:
- Added New Risk:
  - Rare: Rejection of organ transplant; Low grade skin tumor that is skin-colored or red which may cause itching
- Provided Further Clarification:
  - Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage) and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received nivolumab therapy, since the risk and severity of transplant-associated complications may be increased (under Rare). is now reported as Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage) and can lead to death. If you are considering an allogeneic stem cell transplant after participating in this study, please tell your doctor that you have received nivolumab therapy, since the risk and severity of transplant-associated complications may be increased (under Rare).
  - A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss (under Rare) is now listed under the section "Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:" (under Rare).

A replacement protocol document and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091902

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Industry-supplied agents: Nivolumab (NSC #748726;) IND #[redacted]; IND holder: DCTD, NCI, and Cabozantinib (NSC #761968); IND #[redacted]; IND holder: DCTD, NCI
Commercial agent: Paclitaxel (NSC #673089)
ClinicalTrials.gov Identifier: NCT04339738

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Study Resources:

Expedited Adverse Event Reporting https://ctepcore.nci.nih.gov/ctepaers	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, and where applicable, Data Manager (cc Protocol Coordinator)
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	Please see the Correlative Science Manual (CSM)
Questions regarding drug supply	PMB
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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Eligibility Criteria (see Section 3.0)

Histologic documentation of cutaneous or visceral angiosarcoma

All local diagnostic slides AND 5 unstained slides for retrospective central pathology review (See §3.2.1)

Measurable disease (as defined in §3.2.2)

Not pregnant and not nursing (See §3.2.3)

Age ≥ 18

ECOG Performance Status 0-1

Prior Treatment (See §3.2.6)

Prior Surgery

No surgery (except the diagnostic biopsy) ≤ 28 days of study registration (See §3.2.7)

Comorbid conditions (See §3.2.9)

Concomitant medications (See §3.2.10)

Language (See §3.2.11)

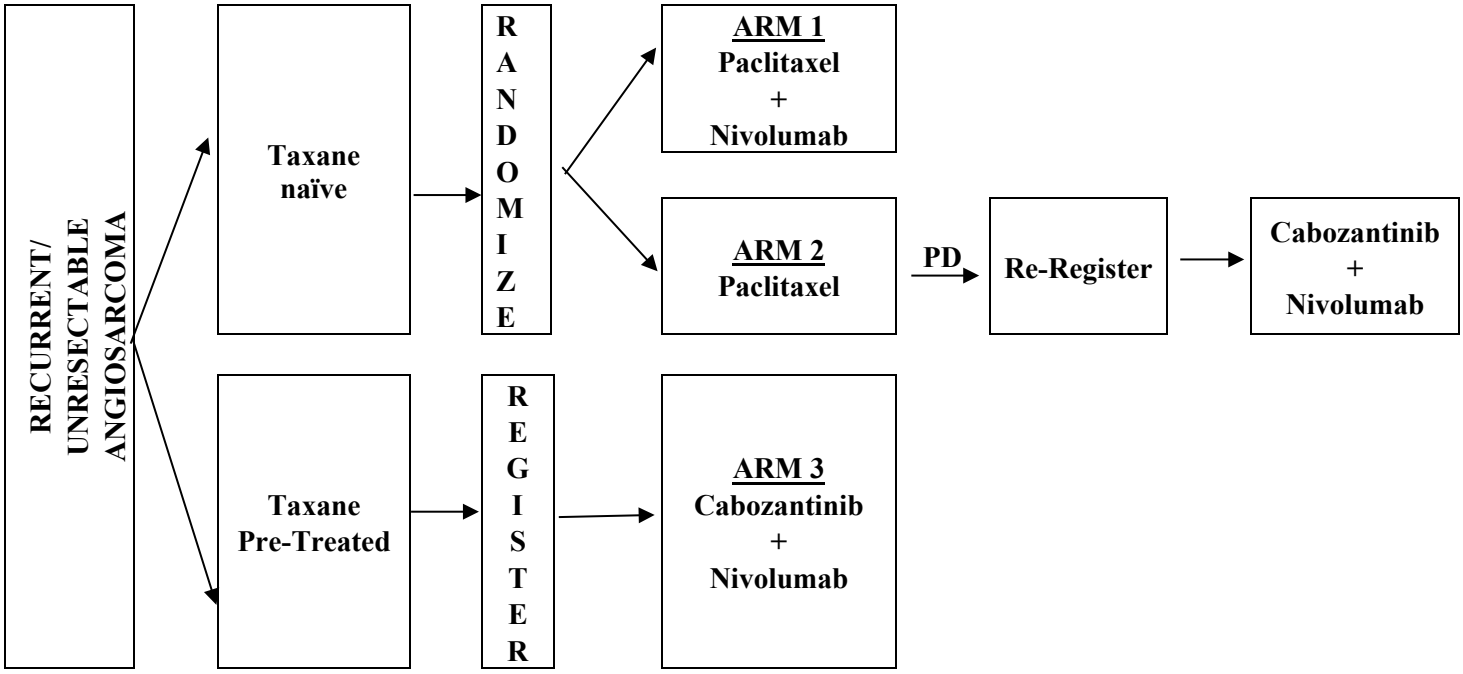
Required Initial Laboratory Values

Absolute neutrophil count (ANC): ≥ 1,500/mm^3
Platelet count: ≥ 100,000/mm^3
Hemoglobin ≥ 9.0 g/dL
Calc. creatinine clearance*: ≥ 30 mL/min*
Total bilirubin: ≤ 1.5 x ULN**
AST/ALT: ≤ 2.5 x ULN***
UPC Ratio < 1 or urine protein ≤ 1+ **(Only for Arm 3 Taxane pre-treated and crossover patients)**

* Per Cockcroft-Gault
** For patients with documented/suspected Gilbert's disease, bilirubin ≤3 × ULN
*** For patients with significant hepatic metastases, ALT and AST <5 × ULN

Schema

1 Cycle = 28 Days



Treatment is to continue until disease progression or unacceptable adverse event; and for a maximum period of 2 years for patients on immunotherapy). Patients will be followed for 3 years (after end of treatment) or until death, whichever comes first.

Note: Arm 3 was closed to new patient accrual effective 10/28/2021.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND

Angiosarcoma (AS) is a rare, heterogeneous malignant vascular tumor, which accounts for approximately 2% of all soft tissue sarcomas [1, 2]. It is often classified according to the primary site of the tumor into cutaneous angiosarcoma (CA), and visceral angiosarcoma. It is additionally classified based on the type into primary (*de novo*) and secondary (i.e. radiation induced) angiosarcoma, and the grade into low, moderate and high [3,4]. There is an emerging subset of angiosarcomas that is characterized by high mutational burden and UV signature mutations, while others have low mutational burden. Regardless of their clinical presentations, angiosarcomas share aggressive behavior with a high rate of locoregional recurrence [5]. Despite a multimodality approach of radical surgical excision with pre- or postoperative wide-field radiation therapy and/or chemotherapy patients have a short median survival (15 to 30 months) [6-14] with a five-year overall survival (OS) of 33.5% in meta-analysis [15], highlighting need for new therapies.

1.1 Chemotherapy for angiosarcoma

Evidence-based recommendations are missing for the treatment of angiosarcoma. It is known that angiosarcoma is particularly sensitive to taxanes, in contrast to virtually every other soft tissue sarcoma subtype, and paclitaxel monotherapy is often used in first or second line for recurrent/metastatic disease. In the Phase II ANGIOTAX trial, 30 patients with angiosarcoma demonstrated an overall response rate (ORR) of 19%, median progression free survival (mPFS) of 4 months and an OS of 8 months with weekly paclitaxel [12]. A second trial randomized patients to receive paclitaxel with or without bevacizumab [16]. The response rates were significantly higher (28% and 45%, respectively), perhaps due to the more stringent cardiovascular and performance status eligibility criteria. A previous retrospective study of the EORTC soft tissue and bone sarcoma group which included 32 patients with advanced angiosarcoma treated with paclitaxel either every week or every 3 weeks. The ORR in this study was 62% and the median PFS was 7.6 months [17]. In a small retrospective study of 9 patients treated with paclitaxel alone, the majority receiving paclitaxel every 3 weeks, the ORR was 89% and the median PFS was 5 months [18]. This objective response rate seemed to be superior to the results previously obtained with doxorubicin-based chemotherapy [18].

1.2 Angiogenesis in angiosarcoma

The varied presentations and limited rate and duration of responses to therapy highlight the need for combination therapeutic strategies. Most common molecular alterations in angiosarcoma are linked to angiogenesis. Behjati et al. identified recurrent mutations in two genes intimately linked to angiogenesis, PTPRB and PLCG1 [19]. The endothelial phosphatase PTPRB (receptor type B), a negative regulator of VEGF tyrosine kinases, harbored predominantly truncating mutations in 10 of 39 tumors (26%). PLCG1 (phospholipase C, gamma 1), a signal transducer of tyrosine kinases, encoded a recurrent, likely activating p.Arg707Gln missense variant in 3 of 34 cases (9%). Few other angiogenic driver mutations were identified for a total of 15/39 (38%) angiogenic signaling genes. Genomic heterogeneity of angiosarcoma is supported by data available on cBioPortal, a curated database for cancer genomics [20, 21].

1.3 Role of immune-oncology

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [22]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can

be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma [23, 24].

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [25, 26].

The structure of murine PD-1 has been resolved [27]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [26, 28, 29]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010].

1.3.1 Immunotherapy in Angiosarcoma

Preclinical data has demonstrated the overexpression of vascular endothelial growth factor (VEGF) and receptors in angiosarcoma [30, 31]. In other malignancies, VEGF inhibition has been shown to potentially exhibit immune modulatory effects by improving CD8+ T-cell migration [32], promoting T-cell priming and activation via dendritic cell maturation [33], normalization of the tumor vasculature for increased T-cell tumor infiltration, and by establishing an immune-permissive tumor microenvironment by decreasing myeloid derived suppressor cells (MDSCs) and Treg populations [34]. In angiosarcoma, therapies targeting VEGF signaling pathways (bevacizumab, sorafenib) produced similar modest responses both as monotherapy [3,35], and in combination with paclitaxel [16]. Cabozantinib is an oral VEGF and c-Met inhibitor currently under investigation for a variety of soft tissue sarcomas (NCT01755195) and has been previously combined with nivolumab [36] in other malignancies with encouraging success prompting phase III testing in metastatic renal cell carcinoma in the Checkmate-9ER study (NCT03141177).

PD-1 and programmed cell death ligand-1 (PD-L1) expression in angiosarcomas have been reported with the rates ranging from 12 to 58% [37-39]. *In vitro* experiments have shown that some cutaneous angiosarcoma cell lines constitutively express PD-L1 and can increase the expression in response to interferon gamma (IFNγ) stimulation [40]. In one study, PD-L1 tumor expression was identified in 5 (19%) specimens, PD-L1 tumor-infiltrating immune cell expression in 9 (33%) specimens, and PD-1 tumor-infiltrating immune cell expression 1 (4%) specimen [41]. Kim et al [42] reported that PD-1-positive tumor-infiltrating lymphocytes (TILs) and PD-L1 expression were significantly correlated with the progression and poor survival outcomes in soft tissue sarcomas. However, less than 5% of patients in the study had angiosarcoma. High expression levels of PD-L1 in cutaneous angiosarcoma were identified as a significant predictor for poor prognosis, especially in patients of the clinical stage I disease. As a result, inhibition of PD-L1 function could be a

novel therapeutic target for cutaneous angiosarcoma with high PD-L1 expression. The reason for the differing results could be due to the small heterogeneous cohort and the use of a differing PD-L1 assay in these studies. Fujii et al. confirmed high levels of CD8+ TILs could also be a significant biomarker for favorable outcome [43]. Our group has shown moderately high CD8+ TIL's by CD8 immunostain and adjacent inflammatory cells that stain for PD-L1 [44]. Other studies have reported the importance of tumor-infiltrating lymphocytes (TILs) in determining patient outcomes in angiosarcoma [35, 43, 45]. Fujii et al demonstrated that high levels of CD8+ TILs are closely correlated with an improved prognosis and a longer disease-free period of distant metastases in patients with cutaneous angiosarcoma (CA), suggesting that immunotherapy using TILs could be a novel treatment approach for angiosarcoma [43]. Some studies, however, provide contrasting data on the incidence of PD-L1 expression in angiosarcoma and its prognostic impact. Shimizu et al found that PD-L1 expression is inversely correlated with the prognosis of patients with CA [46] while the Honda study has demonstrated that PD-L1 expression at the tumor site, and the number of PD-1-positive infiltrating cells are positive prognostic markers of patients with CA [40]. Nonetheless, these two studies show that the immune system plays a role in the progression of CA, although the value of PD-L1 positivity as a prognostic marker remains unclear. Paoluzzi et al. reported that PD-1 and PD-L1 expression was correlated with higher tumor grade, advanced stage of disease, presence of metastasis, and poor clinical outcome [39] and Kawamura et al. showed that patients with PD-L1+ cells in cutaneous angiosarcoma lesions showed significantly worse prognosis compared to those that were PD-L1 [47]. Therefore, more studies on angiosarcomas are needed to determine if tumor PD-L1 expression plays a role in VEGF-related pathophysiology of this rare disease and to study the association between tumor PD-L1 expression and prognosis.

1.3.2 Combination of PD-1 Inhibitors and Chemotherapy

Combinations of PD-1 inhibitors and chemotherapy are currently being investigated in an effort to improve response rates. Several phase I/II/III studies are ongoing including a Merck-sponsored studies combining pembrolizumab with either cisplatin and pemetrexed or carboplatin and paclitaxel in non-small cell lung cancer (KEYNOTE-11; NCT01840579), and evaluating carboplatin plus paclitaxel/nab-paclitaxel with and without pembrolizumab as first-line therapy in patients with advanced squamous non-small cell lung cancer (KEYNOTE-407). Additionally, early results have been published in a Merck-sponsored phase I/II study evaluating the efficacy and safety of pembrolizumab in combination with either carboplatin AUC 6 with pemetrexed or paclitaxel plus bevacizumab for non-squamous histology or carboplatin AUC 6 with paclitaxel for any histology [48]. The early results show promising safety data, grade 3-4 treatment-related adverse events occurring in 36% of patients on maintenance pembrolizumab (cohort A), 46% of patients on maintenance pembrolizumab plus bevacizumab (cohort B) and 42% of patients on maintenance pembrolizumab and pemetrexed (cohort C). The most common treatment-related adverse events were febrile neutropenia, neutropenia, anemia and AST elevation, dependent on the cohort. The efficacy data is still considered immature.

1.4 Proposed Angiosarcoma Study

The immune system is critical in cancer control and progression, and appropriate modulation of the immune system may provide an effective therapeutic option for angiosarcoma [40-42]. Recent clinical trials targeting inhibitors of PD-1 or PD-L1 have exhibited a promising survival outcome in patients with a variety of solid tumors. Combinations of chemotherapy with checkpoint inhibitors, and combination of nivolumab (a PD-1 inhibitor) with paclitaxel, in particular, have previously been evaluated in clinical trials [49,53-55]. Other studies of other immune checkpoint inhibitors in combination with standard chemotherapy have also

demonstrated positive results in solid tumors [56-60]. Hamacher R, et al. tested tumor tissue of 130 angiosarcoma cases and observed several cases of cutaneous angiosarcoma that showed a significant expression of PD-L1 between 10-20% on tumor cells, and infiltration of immune cells with the presence of CD8+ cells [61]. One heavily pretreated patient with PD-L1-positive angiosarcoma of the scalp was treated with pembrolizumab resulting in an ongoing complete remission 6 months into treatment at the time of the publication [62]. Another case report similarly documents anti-PD-1 therapy success in cutaneous angiosarcoma [41]. One of three angiosarcoma patients enrolled in the combination arm of the A091401 study of nivolumab with or without ipilimumab in patients with metastatic sarcoma not amenable to surgery (NCT02500797), sustained a confirmed response. A phase II study to assess the efficacy of a combination immunotherapy is currently enrolling patients with advanced sarcoma in the United States (NCT02815995). Florou et al. performed a retrospective analysis of seven angiosarcoma patients treated with immune checkpoint inhibitors either as part of clinical trials or off label use [63]. Four patients received pembrolizumab monotherapy, two received CTLA-4 inhibitor (AGEN1884) monotherapy and one patient received a combination of pembrolizumab and axitinib. Five of the seven patients had cutaneous angiosarcoma. Twelve weeks post-initiation of treatment, 5/7 patients (71%) had a PR of their lesions as determined by either imaging or clinical exam; 2 patients (29%) had progressive disease. At the time of the publication of the report 6/7 patients were still alive (all cutaneous angiosarcoma subjects were still alive) and only 3/7 patients (43%) had progressed (median 3.4 months). Importantly, none of the patients experienced any ≥ grade 2 toxicities. The one subject who received AGEN1884 in this retrospective study, additionally had mononuclear cells isolated from the peripheral blood on the first day of the first 4 cycles and had correlative analysis performed. Peripheral B cells and CD8+ T cells increased from 35.8 to 47.5% and 37.8 to 43.8%, respectively, above baseline with treatment whereas, CD4+ T cells and natural killer (NK) cells decreased.

Based on these preclinical and clinical studies, combination treatment utilizing PD-L1-directed therapy may represent an improved treatment option for angiosarcomas given the frequency of PD-L1 expression and infiltration of immune cells. The goal of this two-arm, open label, multicenter phase II trial is to improve outcomes in patients with angiosarcoma not amenable to curative intent treatment, by treating them with nivolumab in combination with paclitaxel (taxane naïve) or cabozantinib (taxane-pretreated patients). Nivolumab will be studied in combination with paclitaxel, a standard of care chemotherapy for angiosarcoma, based on synergistic effects of chemo-immunotherapy combinations in a variety of solid tumors. Combining nivolumab with a more rapidly active agent also may help stabilize disease while providing time for checkpoint inhibition to take effect. In the taxane naïve arm, stratified randomization will be used to allocate patients to receive paclitaxel with or without nivolumab. Nivolumab will also be studied in combination with cabozantinib based on known high VEGF expression and ability to potentiate immunomodulatory effects, potentially offering patients a non-cytotoxic chemotherapy option. In the taxane pretreated population, patients will not undergo randomization. Patients receiving paclitaxel monotherapy in the taxane naïve arm may cross over to the cabozantinib-nivolumab taxane pretreated arm upon disease progression or intolerance resulting in paclitaxel pretreated status. More generally, all patients enrolled will continue therapy until disease progression or withdrawal for other reasons or for a maximum period of 2 years of immunotherapy. The primary objective is to determine clinical activity of the addition of nivolumab to paclitaxel by assessment of progression free survival and separately nivolumab to cabozantinib by assessment of response rate. Toxicity will be assessed during treatment via NCI CTCAE v5.0. Tissue will be collected at baseline for retrospective confirmation of the subject's diagnosis of angiosarcoma.

Note: Effective 10/28/2021, new patient accrual to Arm 3 (Cabozantinib and Nivolumab Taxane Pre-treated arm) was permanently closed due to accrual having been met.

2.0 OBJECTIVES

2.1 Co-primary Objectives

2.1.1 To determine the progression free survival (PFS) for paclitaxel with and without nivolumab in subjects with taxane naïve angiosarcoma.

2.1.2 To determine the overall response rate (ORR) of nivolumab in combination with cabozantinib in patients with taxane pre-treated angiosarcoma.

2.2 Secondary objectives

2.2.1 To determine the ORR of paclitaxel in combination with nivolumab.

2.2.2 To determine clinical activity of the addition of nivolumab to paclitaxel or cabozantinib in subjects with angiosarcoma by determination of overall survival (OS) for each combination.

2.2.3 To determine clinical activity of the addition of nivolumab to cabozantinib in subjects with taxane pre-treated angiosarcoma by determination of progression free survival (PFS) at 6 months by RECIST v1.1 criteria.

2.2.4 To assess toxicity of the concurrent nivolumab-paclitaxel and nivolumab-cabozantinib combinations in subjects with angiosarcoma based on NCI-CTCAE v.5.0.

2.2.5 To measure symptomatic adverse events (AE) for patients via PRO-CTCAE, FACT-G, and LASA.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a “currently active” malignancy if they have completed therapy and have no evidence of disease for ≥ 1 year. Stage 1-2 melanoma patients status-post resection are eligible to participate if they have not had adjuvant immunotherapy. Patients with prostate cancer who are only on androgen suppression are eligible to enroll.
- Patients who cannot swallow oral formulations of the agent (taxane pretreated and crossover patients only).

In addition:

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for 5 months after treatment is discontinued due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease:**

Histologic Documentation: Histologically confirmed cutaneous or visceral angiosarcoma, where curative treatment is either not possible or curative modality therapy is declined by the subject. Note: If a subject declines curative modality therapy, the reason must be documented (e.g. excessive morbidity to necessary surgery).

Note: Radiation induced angiosarcomas are permitted.

- All local diagnostic slides AND 5x 4-6micron unstained slides from diagnostic tumor tissue should be available for retrospective central pathology review (See Section 6.2.3).

___ **3.2.2 Must have measurable disease per RECIST v1.1 (see Section 11.0).** Per RECIST v1.1, clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers or ruler (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required. When lesions can be evaluated by both clinical exam and imagining, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. The same method of measurement should be used throughout the study, preferably performed by the same investigator. Areas previously radiated must have demonstrated disease progression at some point over the past 6 months and growth must be subsequent to the last line of anti-cancer directed therapy (e.g. chemotherapy, radiation therapy, surgery).

___ **3.2.3 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 3 days prior to registration is required.

___ **3.2.4 Age ≥ 18 years.**

___ **3.2.5 ECOG Performance Status 0-1.**

___ **3.2.6 Prior Treatment**

- Patient must have completed all prior cancer directed therapies (including investigational) ≥ 7 days prior to cycle 1 day 1.
  - Exception: prostate patients who are allowed to concurrently receive androgen suppression therapy.
  - Note: Radiation therapy must be completed ≥7 days of Day 1 of study treatment, and must not be expected to significantly impact blood count recovery.
- There is no limit to overall number of prior lines of therapy.
- No prior PD-1 inhibitor or PD-L1 inhibitor therapy is permitted.
- No prior administration of VEGF TKI therapy is permitted.
- Recovery to baseline or, ≤ grade 1 CTCAE version 5.0 from toxicity related to any prior treatment, unless adverse events are clinically nonsignificant and/or stable on supportive therapy, with the exception of fatigue (which should be ≤ grade 2) or alopecia. Note: Patients should be expected to have experienced any nadir and have adequate blood count recovery prior to cycle 1 day 1.

Taxane Naïve Patients Only:

- No prior exposure to taxane therapy of any duration for angiosarcoma.

Taxane Pre-treated Patients Only (Effective 10/28/2021, new patient accrual to Arm 3 was permanently closed)

- Prior taxane therapy is allowed at any point prior to registration as long as prior treatment eligibility criteria (Section 3.2.6) are met prior to cycle 1 day 1.

___ **3.2.7 Prior Surgery**

- No major surgery (except the diagnostic biopsy) ≤ 28 days of study registration. Procedures such as thoracentesis, paracentesis, percutaneous biopsy, Lasik eye surgery are **not** considered major surgery. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

___ **3.2.8 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm^3

Platelet Count ≥ 100,000/mm^3

Hemoglobin ≥9.0 g/dL

Calc. Creatinine Clearance ≥ 30 mL/min (per Cockcroft-Gault)

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)**

AST / ALT ≤ 2.5 x upper limit of normal (ULN)***

UPC Ratio < 1 or urine protein ≤ 1+ **(Only for Arm 3 Taxane pre-treated and crossover patients)**

** For patients with documented/suspected Gilbert's disease, bilirubin ≤3 × ULN

*** For patients with significant hepatic metastases, ALT and AST ≤5 × ULN. No clinically active or chronic liver disease resulting in moderate/severe hepatic impairment (Child-Pugh Class B or C), ascites, coagulopathy or bleeding due to liver dysfunction.

___ **3.2.9 Comorbid conditions**

- No uncontrolled CNS metastases. Patients with history of CNS metastasis will be allowed as long as the metastatic sites were adequately treated as demonstrated by clinical and radiographic improvement, and the patients has recovered from the intervention (no residual adverse events >CTCAE grade 1), and the patient has remained without recurrence of new or worsening CNS symptoms for a period of 28 days prior to registration. Treated CNS mets should have no ongoing requirement for steroids, and no evidence of hemorrhage after treatment for at least 28 days prior to registration.
- No uncontrolled intercurrent illness that would put the patient at undue risk by participation in the study, in the opinion of the investigator. (See taxane pretreated section for arm specific hypertension guidelines).
- No history of syncope of cardiovascular etiology, uncontrolled cardiac arrhythmia, History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place, myocardial ischemia or infarction, severe or unstable angina, New York Heart Association (NYHA) class II to IV heart failure, or stroke/transient ischemic attack (TIA) within the past 3 months.
- No thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 1 month before randomization. Subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with LMWH for at least 2 weeks before first dose. Iatrogenic arterial embolization procedures such as tumor arterial embolization or splenic artery embolization are allowed.

  Note: See additional details regarding taxane pre-treated patients at the end of Section 3.2.9.
- Patients with a requirement for steroid treatment or other immunosuppressive treatment: Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).
- Active autoimmune disease requiring systemic treatment (i.e. disease modifying agents, corticosteroids, or immunosuppressive drugs) within the past 2 years. These include but are not limited to patients with a history of immune-related neurologic

disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

Note: Patients are permitted to enroll if they have vitiligo; type I diabetes mellitus; hypothyroidism, pituitary or adrenal insufficiency requiring only hormone replacement; psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- No planned palliative procedures for alleviation of pain such as radiation therapy or surgery.
- No untreated or impending spinal cord compression or evidence of spinal metastases with a risk of impending fracture or spinal cord compression.
- No known or suspected contraindications or hypersensitivity to paclitaxel, cabozantinib or nivolumab or to any of the excipients.
- Disorders associated with a high risk of perforation or fistula formation: active inflammatory bowel disease, active diverticulitis, active cholecystitis, active symptomatic cholangitis or active appendicitis, active acute pancreatitis or active acute obstruction of the pancreatic or biliary duct, or active gastric outlet obstruction; abdominal fistula, gastrointestinal perforation, bowel obstruction, or intra-abdominal abscess within 6 months before randomization. Note: Complete healing of an intra-abdominal abscess must be confirmed before randomization.
- No clinically significant hematuria, hematemesis, or hemoptysis, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before randomization.
- No lesions invading major pulmonary blood vessels.
- No other clinically significant disorders: uncompensated/symptomatic hypothyroidism; requirements for hemodialysis or peritoneal dialysis; history of solid organ transplantation.
- Serious non-healing wounds unrelated to cancer are excluded.

  Note: Wounds that are cutaneous angiosarcoma are allowed.
- Chronic concomitant treatment with strong inhibitors and inducers of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors and inducers must discontinue the drug 7 days and 14 days, respectively prior to registration on the study. See Section 8.1.8 for more information.

Taxane Naïve Patients Only:

- No clinically significant neuropathy (grade ≥2 per NCI CTCAE v5.0).

Taxane Pre-treated only (Effective 10/28/2021, new patient accrual to Arm 3 was permanently closed):

- Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose. Subjects with a diagnosis of DVT within 6 months are allowed if stable and treated with LMWH for at least 2 weeks before first dose.
- No history of clinically significant coagulopathy.
- No uncontrolled hypertension, defined as systolic blood pressure of >140 mmHg or diastolic pressure >90 mmHg on anti-hypertensive medications.
- No known or suspected gastrointestinal disorder affecting absorption of oral medications (for patients getting cabozantinib).

___ **3.2.10 Concomitant medications**

- No clinical, laboratory or radiographic evidence of an active bacterial, fungal, or viral infection requiring treatment at the time of registration. No concurrent use of parenteral (IV) antibiotics is permitted. Oral antibiotics administered for a defined course with expectation of resolution of infection are permitted at the discretion of the investigator.
- No use of ongoing systemic steroid therapy within 7 days prior to study registration. Dose equivalence of prednisone 10mg daily or less is permitted.

Taxane Pre-treated only (Effective 10/28/2021, new patient accrual to Arm 3 was permanently closed):

- No current use of aspirin (>81 mg/day), or any other antiplatelet agents.
- Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin inhibitors, and factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel) is not permitted. Low-dose (prophylactic) low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects with **no** known brain metastases, **no** clinically significant hemorrhage, or **no** complications from a thromboembolic event on the anticoagulation regimen, and who have been on a stable dose of LMWH for at least 2 weeks before first dose. See Section 8.1.8 for more information.

___ **3.2.11 Language:** Patients must be able to speak and comprehend English or Spanish in order to complete the mandatory patient-completed measures.

3.3 Re-Registration Eligibility Criteria (upon progression on Arm 2 only)

___ **3.3.1 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 3 days prior to re-registration is required.

___ **3.3.2 Age ≥ 18 years.**

___ **3.3.3 ECOG Performance Status 0-1.**

___ **3.3.4 Prior Treatment**

- Patient must have completed all prior treatments (including investigational Arm 2 paclitaxel) ≥ 7 days prior to cycle 1 day 1.
  - Exception: prostate patients who are allowed to concurrently receive androgen suppression therapy.

  Note: Re-registration is only permitted after progression on Arm 2.
- No prior PD-1 inhibitor or PD-L1 inhibitor therapy is permitted.
- Recovery to baseline or, ≤ grade 1 CTCAE version 5.0 from toxicity related to any prior treatment, unless adverse events are clinically nonsignificant and/or stable on supportive therapy, with the exception of fatigue (which should be ≤ grade 2) or alopecia. Note: Patients should be expected to have experienced any nadir and have adequate blood count recovery prior to cycle 1 day 1.

___ **3.3.5 Prior Surgery**

- No major surgery (except the diagnostic biopsy) ≤ 28 days of study re-registration. Procedures such as thoracentesis, paracentesis, percutaneous biopsy, Lasik eye surgery are **not** considered major surgery. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

___ **3.3.6 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm^3

Platelet Count ≥ 100,000/mm^3

Hemoglobin ≥9.0 g/dL

Calc. Creatinine Clearance ≥ 30 mL/min (per Cockcroft-Gault)

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)**

AST / ALT ≤ 2.5 x upper limit of normal (ULN)***

UPC Ratio < 1 or urine protein ≤ 1+

** For patients with documented/suspected Gilbert's disease, bilirubin ≤3 × ULN

*** For patients with significant hepatic metastases, ALT and AST ≤5 × ULN. No clinically active or chronic liver disease resulting in moderate/severe hepatic impairment (Child-Pugh Class B or C), ascites, coagulopathy or bleeding due to liver dysfunction.

___ **3.3.7 Comorbid conditions**

- No uncontrolled CNS metastases. Patients with history of CNS metastasis will be allowed as long as the metastatic sites were adequately treated as demonstrated by clinical and radiographic improvement, and the patients has recovered from the intervention (no residual adverse events >CTCAE grade 1), and the patient has remained without recurrence of new or worsening CNS symptoms for a period of 28 days prior to registration. Treated CNS mets should have no ongoing requirement for

steroids, and no evidence of hemorrhage after treatment for at least 28 days prior to registration.

- No uncontrolled intercurrent illness that would put the patient at undue risk by participation in the study, in the opinion of the investigator. (See taxane pretreated section for arm specific hypertension guidelines).
- No history of syncope of cardiovascular etiology, uncontrolled cardiac arrhythmia, History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place, myocardial ischemia or infarction, severe or unstable angina, New York Heart Association (NYHA) class II to IV heart failure, or stroke/transient ischemic attack (TIA) within the past 3 months.
- No thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 1 month before randomization. Subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with LMWH for at least 2 weeks before first dose. Iatrogenic arterial embolization procedures such as tumor arterial embolization or splenic artery embolization are allowed.
- Patients with a requirement for steroid treatment or other immunosuppressive treatment: Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Active autoimmune disease requiring systemic treatment (i.e. disease modifying agents, corticosteroids, or immunosuppressive drugs) within the past 2 years. These include but are not limited to patients with a history of immune-related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

  Note: Patients are permitted to enroll if they have vitiligo; type I diabetes mellitus; hypothyroidism, pituitary or adrenal insufficiency requiring only hormone replacement; psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).
- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- No planned palliative procedures for alleviation of pain such as radiation therapy or surgery.
- No untreated or impending spinal cord compression or evidence of spinal metastases with a risk of impending fracture or spinal cord compression.

- No known or suspected contraindications or hypersensitivity to cabozantinib or nivolumab or to any of the excipients.
- Disorders associated with a high risk of perforation or fistula formation: active inflammatory bowel disease, active diverticulitis, active cholecystitis, active symptomatic cholangitis or active appendicitis, active acute pancreatitis or active acute obstruction of the pancreatic or biliary duct, or active gastric outlet obstruction; abdominal fistula, gastrointestinal perforation, bowel obstruction, or intra-abdominal abscess within 6 months before initiation of therapy. Note: Complete healing of an intra-abdominal abscess must be confirmed before initiation of therapy.
- No clinically significant hematuria, hematemesis, or hemoptysis, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 3 months before randomization.
- No lesions invading major pulmonary blood vessels.
- No other clinically significant disorders: uncompensated/symptomatic hypothyroidism; requirements for hemodialysis or peritoneal dialysis; history of solid organ transplantation.
- Serious non-healing wounds unrelated to cancer are excluded.

  Note: Wounds that are cutaneous angiosarcoma are allowed.
- Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose. Subjects with a diagnosis of DVT within 6 months are allowed if stable and treated with LMWH for at least 2 weeks before first dose.
- No history of clinically significant coagulopathy.
- No uncontrolled hypertension, defined as systolic blood pressure of >140 mmHg or diastolic pressure >90 mmHg on anti-hypertensive medications.
- No known or suspected gastrointestinal disorder affecting absorption of oral medications (for patients getting cabozantinib).

___ **3.3.8 Concomitant medications**

- No clinical, laboratory or radiographic evidence of an active bacterial, fungal, or viral infection requiring treatment at the time of registration. No concurrent use of parenteral (IV) antibiotics is permitted. Oral antibiotics administered for a defined course with expectation of resolution of infection are permitted at the discretion of the investigator.
- No use of ongoing systemic steroid therapy within 7 days prior to study re-registration. Dose equivalence of prednisone 10mg daily or less is permitted.
- No current use of aspirin (>81 mg/day), or any other antiplatelet agents.
- Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin inhibitors, and factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel) is not permitted. Low-dose (prophylactic) low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects with no known brain metastases, no clinically significant hemorrhage, or no complications from a thromboembolic event on the anticoagulation regimen, and who

have been on a stable dose of LMWH for at least 2 weeks before first dose. See Section 8.1.8 for more information.

- Chronic concomitant treatment with strong inhibitors and inducers of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1.8 for more information.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- **Investigator (IVR)** — MD, DO, or international equivalent;
- **Non-Physician Investigator (NPIVR)** — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **Associate Plus (AP)** — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- **Associate (A)** — other clinical site staff involved in the conduct of NCI-sponsored trials;

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, licensure, and certification.	✓	✓	✓	
GCP Training Certificated (mandatory file upload)	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional file upload)	✓	✓	✓	

In addition. IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the **NCI RCR** page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 CTSU Site Registration Procedures

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;

- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A091802.*
- Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.4 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at https://dtl.ctsu.org. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re- sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Registration/Randomization Requirements

Note: Taxane naïve patients will be randomized to either Arm 1 or Arm 2; taxane pre-treated patients will be registered to Arm 3.

Note: Arm 3 was closed to new patient accrual effective 10/28/2021.

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.3.2 Patient-reported outcomes

This study includes the use of the mandatory patient completed measures. The measures are available in English and Spanish. Participation in Alliance A091902 is restricted to patients who are able to speak, understand and read English or Spanish.

Electronic patient reported outcomes (ePRO): This study includes the use of ePRO, (electronic patient-reported outcomes). After the patient is registered to the trial, the CRP will complete a second registration to the Patient Cloud. The CRP will create a unique patient registration code by accessing the Patient Cloud through iMedidata Rave. Patients (with assistance from CRPs) will need to download the Patient Cloud ePRO app on their own device and use the unique registration code given by the CRP to create an account. Once completed, the patient will be able to complete the submission of patient reported outcomes electronically.

Prior to registration, the patient should be asked about the availability of an electronic device and willingness to complete the patient-reported questionnaires on the device. For

those patients unable or unwilling to use ePRO, the patient may complete the questionnaires using paper booklets. However, the patient should be informed that the same method of completion, ePRO or paper booklets, must be used by the patient throughout the duration of the study for all time points, as much as possible. See for further instructions on setting up ePRO.

Patient questionnaire booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A091902 CTSU web site) and submitting the form through the CTSU regulatory portal. A sample of the booklet is found in which is to be used for reference and IRB submission only. They are not to be used for patient completion.

Booklets should be offered only to those patients who are not willing and/or are unable to use an electronic device for completion of questionnaires.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

4.5 Re-Registration at the Time of Progression (Step 2, if applicable)

Upon progression on paclitaxel, patients may elect to crossover to cabozantinib + nivolumab.

Re-registration procedures: Only for patients originally assigned to paclitaxel:

For a patient on paclitaxel, once they are deemed by their local physician to have progressive disease as per Section 11.3, they may cross-over to receive cabozantinib + nivolumab.

Recovery to baseline or, ≤ grade 1 CTCAE version 5.0 from toxicity related to any prior treatment, unless adverse events are clinically nonsignificant and/or stable on supportive therapy, with the exception of fatigue (which should be ≤ grade 2) or alopecia. Note: Patients should be expected to have experienced any nadir and have adequate blood count recovery prior to cycle 1 day 1.

See Section 3.3 for additional re-registration criteria.

Follow OPEN enrollment procedures as detailed in Section 4.4 to register patient to crossover.

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

4.6 Stratification and Grouping Factors

Grouping Factors:

Taxane Naïve vs. Taxane Pre-treated

Permuted Block: Patients that are registered as taxane pretreated will be assigned to the nivolumab + cabozantinib arm. Patients that are registered as taxane naïve will be randomized to one of two treatment arms (paclitaxel vs. paclitaxel + nivolumab) in a 1:1 ratio utilizing a permuted block schedule [37]. The goal of the algorithm is to maintain arm balance with respect to the following important stratification factor:

Stratification Factor:

Cutaneous vs. Other

Note: Cutaneous lesions specifically refer to head and neck cutaneous angiosarcomas.

5.0 STUDY CALENDAR

Pre-Study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 28 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

To be completed ≤ 28 DAYS before registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

Study Calendar Key:

"*", "**", "†", etc., are used for additional information relating to the column headers.

"(1)", "(2)", "(3)", are added to the X's for further explanation.

"X"'s are replaced with "A" "B" "C", for tests that vary from the schedule named in the column header.

Taxane Naïve Arm 1 (paclitaxel + nivolumab) and Arm 2 (paclitaxel):

	Prior to Registration*	Day 1 and 15 of cycles 1 & 2 and Day 1 of each subsequent cycle*	Day 8 and Day 15 of every cycle**	Post treatment follow up***	After PD or withdrawal or removal from treatment***
Tests & Observations					
H&P, weight, ****	X	X		X	X
Height	X				
Pulse, Blood Pressure***	X	X	X	X	
O2 sat	X				
ECG	X(4)				
ECHO	X(4)				
AE Assessment (CTCAE)		X			
Adverse Event Assessment (PRO-CTCAE-Appendix IV)		X(1)			
FACT-G (Appendix IV)		X(1)			
Global QOL/LASA (See Appendix IV)		X(1)			
ECOG PS	X(2)	X		X	
Laboratory Studies					

	Prior to Registration*	Day 1 and 15 of cycles 1 & 2 and Day 1 of each subsequent cycle*	Day 8 and Day 15 of every cycle**	Post treatment follow up***	After PD or withdrawal or removal from treatment***
Complete Blood Count, Differential, Platelets	X	X	X		
Creatinine, Na, K	X	X	X		
Albumin, glucose	X	X	X		
AST, ALT, Alk. Phos., Total Bili	X	X	X		
Serum or Urine HCG	X(3)				
TSH with Reflex Free T4†		X (4)			
Troponin	X(4)				
Staging					
Cutaneous Tumor Measurement	X	X(A)		X	
Imaging††	X(5)	B, C		B, C	

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 3 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** If paclitaxel is discontinued and patient remains on nivolumab monotherapy, then day 8 and 15 of subsequent cycles (i.e. physical exam, vital signs, and laboratory studies) are not required.

*** Physical examination and vital signs are required 4 weeks +/- 3 days after the end of treatment; thereafter, survival information is required every 3 months until 3 years after the end of treatment . See also Section 12.0. For patients on Arm 1 or 3 only, if there is evidence of progression during the first 12 weeks of therapy, patient is allowed to continue treatment (see Section 7.4 and footnote B and C).

****Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

† Required only for subjects receiving nivolumab (Arm 1). Free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

†† Image regions and modality selected as appropriate per the patient's standard of care. The same type of imaging should be followed throughout the study (for example, if CT scan was done for baseline, please follow with CT scans as much as possible).

1 PRO-CTCAE, FACT-G and Global Quality of Life/LASA are to be completed after registration and ≤7 days prior to treatment, C1 D15, C2 D1, C2 D15, and then once every 4 weeks starting with C3D1 while the patient is on active treatment (patients will be requested to complete assessments in clinic at each of the timepoints).

2 To be completed after registration and ≤7 days prior to treatment.

3 For women of childbearing potential (see Section 3.2.3). Must be done ≤ 3 days prior to registration and then as clinically indicated during study treatment.

4 As clinically indicated.

5 Scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan, and the CT acquired with 5 mm or less slice thickness.

A ≤ 2 days prior to every cycle treatment if accessible to physical examination.

B At the completion of every 3rd cycle, prior to beginning each subsequent cycle until evidence of progression or relapse. Required for cutaneous only if disease is visible on baseline imaging. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 8 weeks following documentation of objective response. For those that complete all protocol specified treatment without progression or patients who ended treatment early for any reason (without

progression), physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression, or up to 3 years if no progression, unless consent is withdrawn for clinical follow up (see Section 11.1).

C If there is evidence of progression before the first 3 cycles, treatment is allowed to be continued. The patient's baseline assessment is now the 1st assessment showing progression (not the pre-study disease assessment) and is used for the remainder of the patient's initial treatment assignment (not crossover). Contact the Data Manager or Study Chair for questions. If this occurs, an additional scan is to be scheduled 4 weeks after evidence of disease progression for confirmation.

Taxane Pre-Treated Arm 3 (Cabozantinib + Nivolumab) and Crossover Patients:

	Prior to Registration*	Days 1 and 15 of cycles 1 & 2 and then Day 1 of each subsequent cycle*	Post treatment follow up**	At PD, withdrawal, or removal**
Tests & Observations				
H&P, weight	X	X	X	X
Height	X			
Pulse, Blood Pressure**	X	X	X	
O2 sat	X			
ECG	X			
ECHO	X(5)			
Adverse Event Assessment (CTCAE)		X		
Adverse Event Assessment (PRO-CTCAE-Appendix IV)		X(1)		
FACT-G (See Appendix IV)		X (1)		
Global QOL/LASA (See Appendix IV)		X (1)		
Patient Medication Diary		X(2)		
ECOG PS	X	X		
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	X		
Creatinine, Na, K	X	X		
Albumin, glucose	X	X		
AST, ALT, Alk. Phos., Total Bili	X	X		
Serum or Urine HCG	X(3)			
UPC ratio/urine protein	X	A		
TSH with Reflex Free T4†		X(4)		
Troponin	X(5)			
Staging				
Cutaneous Tumor Measurement	X	X(B)	X	
Imaging††	X(5)	C, D	C, D	

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 3 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** Physical examination and vital signs are required 4 weeks +/- 3 days after the end of treatment; thereafter, survival information is required every 3 months until 3 years after the end of treatment. See also Section 12.0. For patients on Arm 1 or 3 only, if there is evidence of progression during the first 12 weeks of therapy, patient is allowed to continue treatment (see Section 7.4 and footnote C and D).

† Free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

†† Image regions and modality selected as appropriate per the patient's standard of care. The same type of imaging should be followed throughout the study.

1 PRO-CTCAE, FACT-G, and Global Quality of Life/LASA are to be completed after registration and ≤7 days prior to treatment, C1 D15, C2 D1 , C2 D15, and then once every 4 weeks starting with C3D1 while the patient is on active treatment (patients will be requested to complete assessments in clinic at each of the timepoints).

2 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team. Please refer to Appendix V for the patient diary.

3 For women of childbearing potential (see Section 3.2.3). Must be done ≤ 3 days prior to registration.

4 TSH with free T4 will be obtained prior to treatment on day 1 cycle 1 and then as clinically indicated.

5 When clinically indicated.

A. All patients receiving cabozantinib will have a urinalysis or urine protein performed ≤ 72 hours prior to every even cycle; if urine protein is ≥ 2+, 24-hour urine collection or UPC ratio will be required (see Section 8.1.2).

B. ≤ 2 days prior to every cycle treatment if accessible to physical examination.

C. Scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan, and the CT acquired with 5 mm or less slice thickness. At the completion of every 3rd cycle, prior to beginning each subsequent cycle until evidence of progression or relapse until evidence of progression or relapse. Required for cutaneous only if disease is visible on baseline imaging. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 8 weeks following documentation of objective response. For those that complete all protocol specified treatment without progression or patients who ended treatment early for any reason (without progression), physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression, or up to 3 years, if no progression, unless consent is withdrawn for clinical follow up (see Section 11.1).

D. If there is evidence of progression before the first 3 cycles, treatment is allowed to be continued. The patient's baseline assessment is now the 1st assessment showing progression (not the pre-study disease assessment) and is used for the remainder of the patient's initial treatment assignment (not crossover). Contact the Data Manager or Study Chair for questions. If this occurs, an additional scan is to be scheduled 4 weeks after evidence of disease progression for confirmation.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation

instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

ePRO:

The data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response and progression. Supporting documentation will include pathology clinical notes (including labs and imaging). These must be submitted at the following time points:

- Pathology reports from diagnosis should be submitted 10 days prior to registration or at progression if applicable.
- Radiology reports will be required at each measurement (baseline, during treatment, and during event monitoring, per Section 5.0). Supporting documentation is to be submitted via Rave.

6.2 Specimen collection and submission

6.2.1 A091902-Biobanking

All participating institutions must ask patients for their consent to participate in the biobanking planned for Alliance A091902, although patient participation is optional. For patients who consent to participate (model consent question, "I agree that my samples and related health information may be kept in a biobank for use in future health research." Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0.

6.2.2 Correlative Science Manual (CSM)

The Alliance A091902 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS, CTSU, and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For all patients registered to Alliance A091902: the submission of all local diagnostic slides and five 4-6 micron unstained slides from diagnostic tumor tissue for retrospective central pathology review to confirm local diagnosis is required for all patients registered to this study. Please see CSM for more details.

For patients who consent to biobanking: All participating institutions must ask patients for their consent to participate in the banking of their specimens for future correlative studies, although patient participation is optional. For patients who consent to participate, tissue and blood will be collected at the following time points for banking. **Please also see the study CSM for more instructions regarding specimen collection and submission**.

6.2.3 Overview of Specimen Requirements

	Baseline (≤14 days after registration)	**Cycle 4 Day1**	**Cycle 4 or first restaging**	**Progression**
Mandatory for all patients registered to A091902:				
All local diagnostic slides AND 5x 4-6micron unstained slides from diagnostic tumor tissue for retrospective central pathology review	X			
For patients registered to A091902 biobanking, submit the following:				
Research biopsy tissue	A		A	
Archival tissue	X			
Plasma from peripheral whole blood collected in EDTA tubes (kits provided)	1x10ml	1x10ml		1x10ml
Whole blood in STRECK tubes (kits provided)	2x8.5ml	2x8.5ml		2x8.5ml

Whole blood in ACD tubes (kits provided)	3x10ml	3x10ml		3x10ml

A For cutaneous angiosarcoma patients only.

6.3 Submission of Patient Completed Measures

It is strongly recommended that patients are offered the option of completing the measures using ePRO. Paper booklets should be offered only to those patients who are not willing and/or are unable to use an electronic device for completion of questionnaires.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3.2). Samples of questionnaire booklets are available in Appendix IV for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person and site staff will enter patient responses into Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

Submission of Completed Booklets: The data from the booklets are to be entered into Medidata Rave by site staff.

Submission of measures completed in the patient cloud app: The data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation. See Appendix II.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

For all cycles, day 8 and 15 dosing is permitted to be +/- 1 day, but no less than 6 days between doses of paclitaxel.

Treatment will continue for a maximum of 2 years (24 months) for patients who achieve a CR/PR or SD on immunotherapy/nivolumab (Arm 1 and Arm 3), or until disease progression, or unacceptable adverse event for all patients.

Patients who have not previously received a taxane for any duration of time for treatment of their angiosarcoma will be randomized to 1 of 2 arms: Arm 1 (paclitaxel + nivolumab) and Arm 2 (paclitaxel). Patients who have previously received a taxane for any duration of time for treatment of their angiosarcoma will be placed on Arm 3 (cabozantinib + nivolumab). Patients who progress on Arm 2 may crossover to Arm 3 if they meet eligibility criteria for Arm 3.

In Arms 1 and 2, intermittent use of dexamethasone as premedication for paclitaxel is permitted. Every attempt should be made to use minimum necessary steroid dose. When possible, other antiemetic therapies (other than dexamethasone) should be selected. Recommended premedication prior to paclitaxel is: Dexamethasone 12 mg prior to cycle 1, day 1. Dexamethasone 8 mg prior to cycle 1, day 8 and thereafter (including day 1 of future cycles).

7.1 Arm 1 (paclitaxel + nivolumab)

Taxane naïve patients randomized to Arm 1 will be treated with nivolumab 480mg followed by paclitaxel 80 mg/m^2 until disease progression or unacceptable toxicity.

Recommended premedication prior to paclitaxel is: Dexamethasone 12 mg prior to cycle 1, day 1. Dexamethasone 8 mg prior to cycle 1, day 8 and thereafter (including day 1 of future cycles).

Treatment will continue until disease progression or unacceptable adverse event for a maximum period of 2 years.

Agent	Dose	Route	Day	Treatment
Nivolumab	480 mg	IV	Day 1	every 4 weeks
Paclitaxel	80 mg/m^2	IV	Day 1, 8, 15	every 4 weeks

7.2 Arm 2 (paclitaxel)

Taxane naïve patients randomized to Arm 2 will receive paclitaxel monotherapy until disease progression or unacceptable toxicity.

Treatment will continue until disease progression or unacceptable adverse event for a maximum period of 2 years. If your treating doctor feels you will benefit from additional treatment you may receive treatment beyond two years.

Agent	Dose	Route	Day	Treatment
Paclitaxel	80 mg/m^2	IV	Day 1, 8, 15	every 4 weeks

7.3 Arm 3 (cabozantinib + nivolumab)/Crossover

Note: Arm 3 was closed to new patient accrual effective 10/28/2021

Patients previously treated with a taxane will receive cabozantinib 40 mg by mouth daily on an empty stomach (do not eat **2 hours** before and **1 hour** after taking cabozantinib) in combination with nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity.

Treatment will continue until disease progression or unacceptable adverse event for a maximum period of 2 years. If your treating doctor feels you will benefit from additional treatment you may receive treatment beyond two years.

Agent	Dose	Route	Day	Treatment
Cabozantinib	40 mg	PO	Daily	Continuous, cycle = 4 weeks
Nivolumab	480 mg	IV	Day 1	every 4 weeks

7.4 Treatment Decisions within the First Twelve Weeks of Therapy

Note: This section is applicable to patients receiving nivolumab (Arms 1 and 3).

Patients who progress by imaging (See Section 11.3) during the first 12 weeks of therapy may continue treatment, at the discretion of the patient and treating investigator. These patients must meet all of the following in order to be eligible to continue therapy:

- No more than 4 new lesions. The sum of the longest diameter (SHORT diameter for LN) of target lesions and the new lesions are less than 40% increase from the baseline.
- Patients must be clinically stable with no change in performance status due to disease progression
- No indication for immediate alternative treatment
- Patient [assessed by the investigator] is showing clinical benefit and tolerates study drug. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.
- The time of progression is noted from the first assessment that exceeds standard criteria

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

If the decision is made to continue treatment after progressive disease is identified within the initial 12 weeks (and criteria above are met), then the patient may continue therapy for a maximum of 4 weeks. **Note:** At this time, the baseline scan to use for further assessments of disease status is reset to this assessment. After 4 weeks a scan is to be repeated. If the scan shows progression compared to the scan 4 weeks prior, they should be removed from protocol therapy. If the scan shows stable disease or response, compared to the scan 4 weeks prior, they can remain on protocol therapy should they choose to, and the suspected initial progression date and assessment is considered the baseline scan to use for until further PD is evident. See Section 11.3 for more information for determining objective status and Section 12.1 for information regarding duration of therapy. Scan schedule will resume routine schedule, as per Section 5.0 footnote C or D.

Patients who have progression AFTER the initial 12-week period will be removed from protocol therapy in arm 2 (arm 2 patients may elect to cross over to dual agent therapy with progression after a minimum of 10 weeks of single agent paclitaxel).

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

There is potential for interaction of study drugs with other drugs. All other drugs should be recorded on the CRFs, including over the counter and alternative therapies.

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm. Androgen suppression is allowed for patients with prostate cancer.

8.1.2 Patients should receive full supportive care while on this study.

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

the medical records. No concurrent use of parenteral antibiotics is permitted. Oral antibiotics administered for a defined course with expectation of resolution of infection are permitted at the discretion of the investigator.

Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values.

Taxane Pre-treated Arm and Crossover Patients Only

No current use of aspirin >81 mg/day, or any other antiplatelet agent is permitted. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin inhibitors, and factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel) is not permitted. Low-dose (prophylactic) low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects with no known brain metastases, no clinically significant hemorrhage, or no complications from a thromboembolic event on the anticoagulation regimen, and who have been on a stable dose of LMWH for at least 2 weeks before first dose.

Chronic concomitant treatment with strong inhibitors and inducers of CYP3A4 is not allowed.

For adverse events that could be possibly, probably, or definitely related to more than one of the study agents, e.g., diarrhea, fatigue, amylase/lipase elevations, skin toxicity and thrombocytopenia, decisions regarding which agent(s) should be held or dose adjusted will be per investigator discretion. Generally, if one drug is to be held for any AE that could be attributable to more than one study agent, all study agents will be held. If toxicity attribution can be distinguished, the other agent(s) may be restarted per discretion of the investigator.

8.1.3 Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see https://crediblemeds.org/). These agents should be used with caution at the discretion of the investigator.
- Treatment with CYP3A4 inhibitors (which may increase cabozantinib drug levels).
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status e.g., severe or prolonged diarrhea.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (e.g., after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator.

8.1.4 Treatment with hormones or other chemotherapeutic agents

Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given in physiologic dosing for adrenal failure (≤10 mg/day prednisone equivalents); hormones administered for non-disease-related conditions (e.g., insulin for diabetes); GnRH agonists for treatment of non-metastatic prostate cancer. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted. Intermittent use of dexamethasone as premedication for paclitaxel is permitted (see Section 7.1). Every attempt should be made to use minimum necessary steroid dose.

8.1.5 Palliative radiation therapy

Palliative radiation therapy may not be administered. Palliative radiation therapy may not be administered except for whole-brain irradiation given for documented CNS disease. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.6 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

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

The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is prohibited OR permitted at the discretion of the treating physician.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF)

White Blood Cell Growth Factors (Includes: filgrastim (G-CSF), pegfilgrastim) and other FDA approved white blood cell growth factor biologics)

1. White blood cell growth factor treatment for patients on protocols that do not specify their use is discouraged.

2. White blood cell growth factor may not be used:
    a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported. (e.g. on CRFs per protocol requirements).
    c. If White blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.1.7 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to paclitaxel and nivolumab as per institutional standards.

8.1.8 CYP3A4 Inhibitors and Inducers

Chronic concomitant treatment with strong inhibitors and inducers of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors and inducers must discontinue the drug 7 days and 14 days, respectively prior to registration on the study. See Sections 8.1.9 and 8.1.10 for more information.

CYP3A4 Inhibitors

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

- Indinavir
- Clarithromycin
- Ketoconazole
- Grapefruit/grapefruit juice

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment for patients being treated with cabozantinib, and for patients being treated with paclitaxel:

- Rifampin

- Carbamazepine
- St. John's Wort

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.9 Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Study Chair. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, Study Chair, and the patient.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than those for this trial
- Radiation therapy

8.1.10 Immune related toxicity

Nivolumab can lead to a variety of immune manifestations. The following supportive care guidelines are given for specific toxicities:

- **Colitis:** Typical symptoms of immune-mediated enterocolitis are diarrhea, abdominal pain, mucus or blood in stool, with or without fever. Consider evaluation to ensure that there is not an infectious etiology. Consider treatment with anti-diarrheals or corticosteroids at the discretion of the treating physician. Evaluation by GI should be considered. Treating physicians should consider the risk of perforation with colitis and utilize anti-diarrheals with this in mind. Recommend evaluation for all patients for additional causes including C. diff, acute

and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.

- **Pneumonitis:** Patients with suspected pneumonitis should undergo full evaluation, which may include CT scan, PFTs, O2 saturation, bronchoscopy. Treatment may involve steroids (any grade pneumonitis) and possibly empiric antibiotics, at the discretion of the treating physician. Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Consider that new lung nodules may represent sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine, as per the bullet below ("vaccinations").
- **Nephritis:** For suspected nephritis, the patient should be evaluated by nephrology and considered for renal biopsy.
- **Hepatitis**: For hepatitis, close monitoring with serial LFTs should be instituted. Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including gallbladder inflammation/pancreatitis.
- **Endocrinopathy:** At the discretion of the treating physician consider endocrine consult, draw all appropriate labs (such as cortisol, ACTH, and T4), perform any appropriate imaging (such as pituitary MRI), and supplement any deficiency. It is recommended to perform any clinically indicated laboratory evaluation of pituitary function before beginning steroid therapy or replacement therapy of any kind.
- **Gastritis:** In patient with nausea or vomiting consider evaluation for upper GI inflammation and other immune related events.
- **Rash:** Consider dermatology consult and skin biopsy, at the discretion of the treating physician. Patient with purpuric or bullous lesions may be evaluated for vasculitis, Stevens-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically. Please be aware of the possibility that additional autoimmune events may occur shortly after the appearance of skin rashes or pruritus and during the steroids withdrawal period.
- **Neuropathy:** Consider neurology consult for any grade 3 or 4 neuropathy, at the discretion of the treating physician.
- **Pancreatitis:** Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur with other immune mediated events including colitis, hepatitis, and gallbladder infection.
- **Myocarditis and other cardiac conditions:** For suspected myocarditis, evaluate for signs and symptoms and consider admission to hospital, with troponin, EKG, cardiac echo**.**

Cardiac*	Management/Next Dose for BMS-936558 (Nivolumab) Toxicities
Less than grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off protocol treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

- **Immunosuppressive agents:** Steroids are recommended as first line intervention for the immune related toxicity of these drugs. Steroids should be started prior to obtaining results of any testing, based on clinical indications for steroid initiation. Specifically: Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing , per NCCN guidelines, including cortisol, ACTH, TSH and T4 should be obtained to document baseline pituitary function which may be suppressed on treatment. Steroids should be tapered over 1 month if clinically appropriate, while monitoring for any return of toxicity. Potential second line agents are mycophenolate, cyclophosphamide, infliximab, IVIG etc., at the discretion of the treating physician.
- **Vaccination:** Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated

vaccines, and are not allowed. Pneumococcal vaccine, and any other relevant vaccines are recommended PRIOR to initiation of protocol therapy, at the discretion of the treating physician.

8.2 Dose Modifications

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Doses and dose level adjustments are described in the tables below. Patients who are unable to tolerate paclitaxel or cabozantinib may dose reduce to the next lower dose level, independent of nivolumab. Patients unable to tolerate paclitaxel or cabozantinib at dose level -2 will discontinue the agent. Continuation of nivolumab may be considered if, in the opinion of the investigator, the toxicity is not attributed to nivolumab. Nivolumab will not be dose reduced. If nivolumab requires discontinuation due to toxicity, paclitaxel or cabozantinib may be continued if in the opinion of the investigator, the toxicity is not attributed to that agent.

If more than one of these apply, use the most stringent (i.e., the greatest dose reduction).

AERS reporting may be required for some adverse events (See Section 9.0).

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

Dose reductions for paclitaxel are just recommendations and should be performed per investigator discretion after consultation with the package insert.

8.2.1 Dose Modifications: Paclitaxel (Arm 2)

The following table should be used when reducing paclitaxel doses for toxicity. There will be no dose reduction below dose level –2. Patients experiencing toxicities but with a response at this dose level may be discussed with the Study Chair regarding further treatment.

Dose Level	Paclitaxel
0*	80 mg/m2 days 1, 8, 15 q4 wks
-1	65 mg/m2 days 1, 8, 15 q4 wks
-2	50mg/m2 days 1, 8, 15 q4 wks

* Dose 0 refers to the starting dose.

Hematologic Toxicity

The ANC must be ≥ 1500 and platelet count must be ≥ 100,000 on day 1 of each cycle for treatment to continue. Treatment with paclitaxel may be delayed for up to 2 weeks for neutropenia and/or thrombocytopenia. If counts do not return to these levels within 3 weeks patients should dose reduce or discontinue therapy with paclitaxel.

Patients developing febrile neutropenia of any duration must be dose reduced by one dose level for the subsequent cycles.

Nephrotoxicity

There are no dose modifications for paclitaxel for renal toxicity.

Neurotoxicity (Peripheral)

Paclitaxel doses should be modified for neurologic toxicity. Serum magnesium and calcium levels should be checked; folate and vitamin B12 levels may need to be evaluated especially in older patients.

Grade 1: Give paclitaxel at full dose.

Grade ≥2: Hold paclitaxel until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel.

Hepatic Toxicity

Give the following doses for paclitaxel only:

SGOT		Bilirubin	Paclitaxel
≤2.5 x ULN	**And**	< 1.5 mg/dl	Same dose level
2.5-5.0 x ULN	**And**	< 1.5 mg/dl	Decrease 1 dose level
>5.0 x ULN	**Or**	≥ 1.5 mg/dl	Hold*

* Hold paclitaxel until AST ≤ 5 x ULN and bilirubin < 1.5 mg/dl, then resume treatment at one dose level lower. If paclitaxel is held for ≥21 days, discontinue paclitaxel therapy.

Cardiac Toxicity

If a patient develops chest pain, hypotension or cardiac arrhythmia, the paclitaxel infusion should be stopped. Any arrhythmia should be managed according to standard practice. Patients who experience chest pain during paclitaxel infusion should not restart the drug until a cardiac ischemic event has been ruled out. The patient should not receive further paclitaxel in the cases of symptomatic arrhythmias, AV block (except 1st degree), or heart block. For asymptomatic sinus bradycardia or 1st degree AV block, the patient can continue to receive paclitaxel but should be followed carefully at the discretion of the treating physician.

Hypersensitivity to Paclitaxel

Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.

Grade 2: Stop the infusion. Administer H1 and/or H2 blockers ± dexamethasone according to physician discretion/institutional guidelines. Restart when symptoms resolve and pretreat before all subsequent doses.

Grade 3 or 4: Discontinue therapy with paclitaxel.

Other non-hematologic toxicities

For any grade 3 or 4 toxicity (except alopecia, nausea, vomiting, fatigue and anorexia), treatment with paclitaxel should be held for a maximum of 21 days until the toxicity recovers to grade ≤1. Subsequent paclitaxel therapy should be administered at a decrease of 1 dose level.

8.2.2 Dose Modifications: Nivolumab/Paclitaxel (Arm 1)

For the combined paclitaxel and nivolumab treatment there are dose reductions for paclitaxel but none for nivolumab. See Section 8.2.1 for toxicity monitoring related to paclitaxel. Clinicians may choose to treat patients at the nivolumab alternative dose of 240 mg IV every 2 weeks if they believe it will help with toxicities.

If nivolumab requires discontinuation due to toxicity, paclitaxel may be continued if in the opinion of the investigator, the toxicity is not attributed to that agent.

If paclitaxel requires discontinuation due to toxicity, continuation of nivolumab may be considered if, in the opinion of the investigator, the toxicity is not attributed to nivolumab.

Hematologic Toxicity

The ANC must be ≥ 1500 and platelet count must be ≥ 100,000 on day 1 of each cycle for treatment to continue. Treatment with paclitaxel may be delayed for up to 2 weeks for neutropenia and/or thrombocytopenia. If counts do not return to these levels within 3 weeks patients should dose reduce or discontinue therapy with paclitaxel.

Patients developing febrile neutropenia of any duration must be dose reduced by one dose level for the subsequent cycles.

Dose Level	Nivolumab	Paclitaxel
Cycle Length = 28 days		
0*	480mg IV q4 wks	80 mg/m2 days 1, 8, 15 q4 wks
-1	480mg IV q4 wks	65 mg/m2 days 1, 8, 15 q4 wks
-2	480mg IV q4 wks	50mg/m2 days 1, 8, 15 q4 wks

* Dose 0 refers to the starting dose.

8.2.3 Dose Modifications Nivolumab/Cabozantinib (Arm 3 & Crossover)

For the combined cabozantinib and nivolumab treatment there are dose reductions for cabozantinib but none for nivolumab. However, clinicians may choose to treat patients at the nivolumab alternative dose of 240 mg IV every 2 weeks if they believe it will help with toxicities.

If nivolumab requires discontinuation due to toxicity, cabozantinib may be continued if in the opinion of the investigator, the toxicity is not attributed to that agent.

If cabozantinib requires discontinuation due to toxicity, continuation of nivolumab may be considered if, in the opinion of the investigator, the toxicity is not attributed to nivolumab

Dose Level	Nivolumab**	Cabozantinib
Cycle Length = 28 days		
0*	480mg IV q4 wks	40 mg PO daily
-1	480mg IV q4 wks	20 mg PO daily
-2	480mg IV q4 wks	20 mg PO every other day

*Dose level 0 refers to the starting dose.

**Clinicians may choose to treat patients at the nivolumab alternative dose of 240 mg IV every 2 weeks if they believe it will help with toxicities.

Table 1: General guidelines for the management of non-hematologic and hematologic toxicities for cabozantinib

CTCAE Version 5.0 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Interrupt cabozantinib treatment or dose reduction. Add supportive care as indicated. • If cabozantinib dosing is interrupted, then upon resolution of the AE to baseline or Grade ≤ 1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt cabozantinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes, liver or pancreatic enzyme elevation) with resolution to baseline or Grade ≤1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction. If patient is at the lowest dose level, may continue on same dose level.
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.	

Hematologic toxicity	**Nivolumab**	**Cabozantinib**
≤ Grade 1	No change in dose *	No change in dose
Grade 2	No change in dose *	No change in dose
Grade 3 neutropenia w/infection, Grade 3 neutropenia ≥ 5 days, or Grade 4 neutropenia	No change in dose *	Hold cabozantinib until toxicity resolves, ANC ≤grade 1 and temperature ≤38.0°C. Then resume cabozantinib at one dose level reduction
Grade 3 thrombocytopenia w/bleed or Grade 4 thrombocytopenia	No change in dose *	Hold cabozantinib until ≤ Grade 1, then restart at 1 dose level reduction
Grade 3 febrile neutropenia	No change in dose *	Hold cabozantinib until toxicity resolves, ANC ≤grade 1 and temperature ≤38.0°C and resume cabozantinib at one dose level reduction
Grade 4 febrile neutropenia	No change in dose *	Discontinue protocol therapy

*Hold nivolumab for demonstrable grade 2-4 autoimmune induced hematologic toxicity. Resume nivolumab once recovered. Discontinue nivolumab permanently for autoimmune hemolytic anemia (AHA), immune thrombocytopenia (ITP), and for prolonged immune mediated neutropenia or associated with prolonged pancytopenia with bone marrow failure.

Proteinuria **Urine Protein/ Creatinine Ratio (UPCR)**	**Nivolumab**	**Cabozantinib**
≤ 1 mg/mg (≤ 113.1 mg/mmol)	No change in dose.	No change in cabozantinib treatment or monitoring.

Proteinuria **Urine Protein/ Creatinine Ratio (UPCR)**	**Nivolumab**	**Cabozantinib**
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	No change in dose.	• Confirming with a repeat UPCR or 24-hour protein assessment within 7 days. • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 hours on 24-hour urine collection. • Interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 hours on 24-hour urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	Hold until resolved. Resume Nivolumab.	• Hold cabozantinib treatment pending repeat UPCR within 7 days and/or 24-hour urine protein. • 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	Hold until resolved. Resume Nivolumab.	• Discontinue all study treatment.

Proteinuria Urine Protein/ Creatinine Ratio (UPCR)	**Nivolumab**	**Cabozantinib**
Given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib.		

Renal (not nephrosis/proteinuria): Nephritis, hematuria, increased Cr	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Continue therapy. Evaluation with urinalysis, urine protein/creatinine, sediment evaluation, consider nephrology consult	Continue therapy. Evaluation with urinalysis, urine protein/creatinine, sediment evaluation, consider nephrology consult.
Grade 2	If concern for immune-mediated nephritis: recommend nephrology consult and renal biopsy/steroid treatment. Hold until ≤ Grade 1. Resume at same dose.	Evaluation with urinalysis, urine protein/creatinine, sediment evaluation, consider nephrology consult. Hold cabozantinib for 1 week, re-evaluate urine studies. If improved, may be cabozantinib-related and not immune related. Resume at one dose level reduction when ≤ grade 1
Grade 3	If concern for immune-mediated nephritis: recommend nephrology consult and renal biopsy. Steroid treatments and other immunosuppressive treatments as needed. Hold until ≤ Grade 1. Resume at same dose.	Evaluation with urinalysis, urine protein/creatinine, sediment evaluation, consider nephrology consult. Hold cabozantinib for 1 week, re-evaluate urine studies. If improved, may be cabozantinib-related and not immune related. Resume at one dose level reduction when ≤ grade 1.
Grade 4	Discontinue treatment	Discontinue treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever		

Cardiac toxicity (non-immune mediated):

For asymptomatic QTcF interval > 500 msecs attributable to cabozantinib, check calcium, potassium, and magnesium levels and correct any abnormalities; interrupt cabozantinib. If possible, stop any medications that may prolong the QTcF interval. Once QTcF returns to ≤ 500 msecs, electrolyte abnormalities have been corrected, and any symptoms have resolved, resume cabozantinib with one dose level reduction and nivolumab at the previous dose for all subsequent cycles.

Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation Cabozantinib.

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

Fistula, perforations, bowel obstruction or wound dehiscence

Risk factors for fistula, perforations, bowel obstruction or wound dehiscence events may include (but may not be limited to) the following:

- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis .
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

For any grade perforation of any organ, GI leak, or any fistula, discontinue cabozantinib, hold nivolumab. When symptoms resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose.

For any grade bowel obstruction requiring medical intervention, interrupt cabozantinib until obstruction resolves completely, then resume cabozantinib at the previous dose. For obstruction requiring surgery interrupt cabozantinib until full recovery from surgery, then resume cabozantinib at the previous dose. If cabozantinib is interrupted for > 21 days for bowel obstruction, discontinue cabozantinib. When symptoms resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 weeks, patients should discontinue protocol therapy.

For wound dehiscence requiring medical or surgical intervention discontinue cabozantinib and hold nivolumab. When wound dehiscence has resolved and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 weeks, patients should discontinue protocol therapy.

For planned surgical procedures that are compatible with the rest of the protocol, stop cabozantinib at least 28 days before surgery and to resume after wound has completely healed.

Non-GI fistula:

Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs Non GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non GI perforation/fistula.

Wound Healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 28 days prior to major surgery. Cabozantinib may be resumed after complete would healing has occurred.

If clinically possible, treatment with cabozantinib should be held for at least 28 days prior to a dental procedure and resumed after complete wound healing occurred 1-2 weeks and/or dental clearance is recommended.

Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have cabozantinib study treatment discontinued. Continuation of nivolumab is permitted at the discretion of the investigator. Venous filters (e.g. vena cava filters) are not recommended due to the high incidence of complications associated with their use. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Arterial thrombotic events (e.g., transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

For grade 2 or 3 venous thrombosis requiring anticoagulation, interrupt cabozantinib. If the planned duration of full dose anticoagulation is ≤ 2 weeks, omit cabozantinib until anticoagulation is completed. If the planned duration of full dose anticoagulation is > 2 weeks, cabozantinib may be restarted during anticoagulation if all of the following are met:

The patient must be on a stable dose of LMWH prior to restarting cabozantinib. Warfarin may not be used for anticoagulation.

The patient must not have any pathological condition that carries a high risk of bleeding.

The patient must not have had any hemorrhagic events while on study.

When symptoms resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 weeks, patients should discontinue protocol therapy.

For recurrent/worsening venous thromboembolic events after resumption of cabozantinib, discontinue cabozantinib.

For grade 4 venous thromboembolic events, discontinue cabozantinib and hold nivolumab. When symptoms resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 weeks, patients should discontinue protocol therapy.

For arterial thromboembolic events including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue cabozantinib and hold nivolumab. When symptoms

resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 weeks, patients should discontinue protocol therapy.

Hemorrhage

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and 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 lesions which invade major blood vessels. The anatomic location and characteristics of primary tumors or metastases as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib. Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel while on study treatment must be discontinued from cabozantinib treatment.

Recent or concurrent radiation to the thoracic cavity.

Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases.

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.

For grade 2 CNS or pulmonary hemorrhage, discontinue cabozantinib, hold nivolumab. When symptoms resolve to ≤ grade 1, nivolumab may be resumed at the prior dose.

For any grade 3 or 4 hemorrhage, discontinue cabozantinib, hold nivolumab. When symptoms resolve to ≤ grade 1, nivolumab may be resumed at the prior dose.

Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold 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. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be taken in accordance with best clinical practice.

Caution should be taken to avoid adding antihypertensive medications that are strong inducers or inhibitors of CYP3A4.

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications). • Maintain dose of cabozantinib. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Interrupt treatment with cabozantinib. (nivolumab may be continued) Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications). • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib at the same dose level. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
Hypertensive emergency or hypertensive encephalopathy	Discontinue all study treatment.
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria	

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

For signs and symptoms suggestive of RPLS (e.g., confusion, headache, seizures, cortical blindness) interrupt cabozantinib. Suspected RPLS should be investigated with MRI. If RPLS is confirmed, discontinue cabozantinib.

If RPLS is ruled out via MRI, the decision to resume cabozantinib should be based on the signs and symptoms: for grade 4 events considered at least possibly related to cabozantinib, discontinue it.

For grade 3 events, cabozantinib may be resumed if events improve to ≤ grade 1 with one dose level reduction.

When symptoms resolve to ≤ grade 1 and patient is clinically stable, nivolumab may be resumed at prior dose. If nivolumab is held for more than 8 week, patients should discontinue protocol therapy.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. A dental consultation is recommended prior to initiation of cabozantinib in patients receiving bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 1 week prior to a dental procedure and resumed after complete wound healing occurred 1-2 weeks and/or dental clearance.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by the Sponsor on a case by case basis. Advise patient to keep good oral hygiene. Must discuss with investigator or/and study team before scheduling dental procedures.

To minimize the risk of osteonecrosis of the jaw, it is recommended that cabozantinib be stopped at least 28 days prior to dental procedures such as tooth extraction, implants and major jaw surgery whenever possible. Following dental procedures, withhold cabozantinib until complete resolution/healing. Cabozantinib need not be held for held for routine dental fillings and cleanings.

Skin Rash

Palmar-plantar erythrodysesthesia syndrome (PPE; 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 in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures include the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. 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. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented below.

In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Oral Lesions/Dental

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.

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.

Skin Rash, Oral and Dental Lesions	**Nivolumab**	**Cabozantinib**
≤ Grade 1	No change in dose *	No change in dose if tolerable, reduce 1 level if intolerable. Maximize supportive care.
Grade 2	Hold* until 1≤ Grade resolved (#). Consider dermatology evaluation. Resume at same dose.	Reduce 1 level and/or interrupt dosing. If interrupted restart at 1 dose level reduction upon resolution to ≤ Grade 1. Maximize supportive care.
Grade 3	Hold* until ≤ Grade 1. Recommend dermatology evaluation. Resume at same dose at investigator discretion	Hold until ≤ Grade 1, then restart at 1 dose level reduction. Maximize supportive care.
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy.
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.		
Recommended management: AE management guidelines		

Hepatitis: Elevated AST/ALT/Bilirubin	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Hold nivolumab at investigator's discretion until ULN or baseline then resume at same dose.	Continue cabozantinib. More frequent monitoring is recommended.

Hepatitis: Elevated AST/ALT/Bilirubin	**Nivolumab**	**Cabozantinib**
Grade 2	Hold until grade 1 or baseline. Resume at investigator discretion. Note: if LFTs improve with holding cabozantinib alone, nivolumab should be restarted at the same dose.	Hold therapy for 3-5 days, re-evaluate LFTs, if improving off of cabozantinib, then likely not immune-mediated. Once LFTs ≤ grade 2 or baseline, restart cabozantinib at one dose level reduction.
Grade 3	Hold until grade 1 or baseline. Resume nivolumab at investigator discretion with return to grade 1 or baseline without steroids. If persistent and deemed to be autoimmune related or steroids are required, off protocol therapy.	Hold therapy for 3-5 days, re-evaluate LFTs, if improving off of cabozantinib, then likely not immune-mediated. Once LFTs ≤ grade 2, restart cabozantinib at one dose level reduction. Continue with at least weekly LFTs until resolution to Grade ≤ 1. If grade ≥ 3 transaminase elevation recurs discontinue cabozantinib.
Grade 4	Discontinue nivolumab if deemed to be immune-mediated. Consider hepatobiliary/GI evaluation. Steroid therapy and consider other immunosuppressive therapies as needed.	Hold therapy for 3-5 days, re-evaluate LFTs, if improving off of cabozantinib, then likely not immune-mediated. For Grade 4 hepatitis that is due to cabozantinib, discontinue cabozantinib.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended.		
LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.		
Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g., International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 x ULN, total bilirubin < 1.5 x ULN, aminotransferases ≤ baseline grade).		
Recommended management: see Hepatic AE management algorithm.		

Diarrhea/Colitis

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. In addition, general supportive measures should be implemented including but not limited to: continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Diarrhea/ Colitis	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Hold until baseline. No change in dose.	Consider holding therapy for 3-5 days, re-evaluate diarrhea. If improving off of cabozantinib, then likely not immune-mediated and more likely due to cabozantinib.
Grade 2	Hold nivolumab and consider steroid treatment if concern for immune- mediated colitis. If diarrhea improves with holding cabozantinib alone, nivolumab may be restarted at same dose.	Hold therapy for 3-5 days, re-evaluate diarrhea. If improving off of cabozantinib, then likely not immune- mediated and more likely due to cabozantinib. Once diarrhea ≤ grade 1, restart cabozantinib at one dose level reduction.
Grade 3	Hold nivolumab. If deemed to be immune-mediated, resume at same dose at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If deemed to be immune mediated and persistent or steroids are required, discontinue protocol therapy. Discontinue nivolumab if deemed to be immune-mediated. Consider GI evaluation for sigmoidoscopy/colonoscopy. Steroid therapy as needed.	Hold therapy for 3-5 days, re-evaluate diarrhea, if improving off of cabozantinib, then likely not immune- mediated. Once diarrhea ≤ grade 1, restart cabozantinib at one dose level reduction.
Grade 4	Discontinue nivolumab if deemed to be immune-mediated. Consider GI evaluation for sigmoidoscopy/colonoscopy. Steroid therapy and other immunosuppressive therapies as needed.	Hold therapy for 3-5 days, re-evaluate diarrhea, if improving off of cabozantinib, then likely not immune- mediated. For Grade 4 colitis that is due to cabozantinib, discontinue cabozantinib.
See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids for immune-mediated grade 3 or grade 4 colitis should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.		
Recommended management: see GI AE management Algorithm		

Pancreatitis Amylase/Lipase	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Continue at same dose if asymptomatic at investigator discretion.	Continue therapy.
Grade 2	Continue at same dose if asymptomatic at investigator discretion. If symptomatic, hold and resume at same dose when resolved.	Continue therapy. More frequent monitoring is recommended.
Grade 3	Continue at same dose if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should hold therapy until patients are on a stable regimen for their diabetes mellitus. If treated with steroids, patients must be stable off steroids for 2 weeks. Patients may resume at same dose at investigator discretion if on a stable regimen for their diabetes.	Hold until ≤ Grade 2 or baseline. Cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤2 or baseline and retreatment must be at a reduced dose.

Pancreatitis Amylase/Lipase	**Nivolumab**	**Cabozantinib**
Grade 4	Hold until grade 2. Resume at same dose if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis should be taken off treatment. Patients who develop diabetes mellitus should hold therapy until patients are on a stable regimen for their diabetes mellitus. If treated with steroids, patients must be stable off steroids for 2 weeks. Patients may resume at same dose at investigator discretion if on a stable regimen for their diabetes. Consider endocrine evaluation.	• Interrupt treatment. • Monitor lipase and amylase twice weekly. • Upon resolution to Grade ≤2 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose if the patient was asymptomatic per treating physician discretion. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤2 or baseline and retreatment must be at a reduced dose.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm.		

Pneumonitis	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Consider evaluation by pulmonary and/or ID to exclude lymphocytic pneumonitis.	Continue therapy with same dose
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Discontinue treatment if steroids are required. ^	Continue therapy with same dose

Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Discontinue treatment if steroids are required	Hold treatment until ≤ grade 1, then resume with one level dose reduction.
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.		
Recommended management: See Pulmonary Adverse Event Management Algorithm		

Nausea and vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in the table below should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure and/or decrease efficacy of nivolumab.

Other GI, Nausea/Vomiting	**Nivolumab**	**Cabozantinib**
≤ Grade 1	No change in dose.	No change in dose
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose after resolution to ≤ Grade 1.	No change in dose
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy	Hold treatment until ≤ grade 1, then resume with one level dose reduction.
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.		

Fatigue	**Nivolumab**	**Cabozantinib**
≤ Grade 1	No change in dose.	No change in dose
Grade 2	No change in dose	No change in dose

Grade 3	Hold until ≤ Grade 2. Resume at same dose level	Hold treatment until ≤ grade 1, then resume with one level dose reduction.
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.		

Neurologic events	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.	No change in dose
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated cranial nerve VII (Bell's palsy).	No change in dose
Grade 3	Discontinue nivolumab therapy	Hold treatment until ≤ grade 1, then resume with one level dose reduction. Consider MRI workup for reversible posterior leukoencephalopathy syndrome. Discontinue cabozantinib if diagnosis of RPLS is made.
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy. Consider MRI workup for reversible posterior leukoencephalopathy syndrome.
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.		
Recommended management: See Neurologic Adverse Event Management Algorithm		

Endocrine: Hypothyroidism	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Asymptomatic TSH elevation may continue treatment while evaluating the need for thyroid replacement.	No change in dose

Grade 2	If deemed immune-mediated thyroiditis and/or hypothyroidism: Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose.	Hold cabozantinib for 1 week and recheck thyroid profile (including TSH and free T4/free T3). If thyroid profile corrects into normal range, likely not immune-mediated. Restart cabozantinib at one dose level reduction.
Grade 3	If deemed immune-mediated thyroiditis and/or hypothyroidism: Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.	Hold cabozantinib for 1 week and recheck thyroid profile (including TSH and free T4/free T3). If thyroid profile corrects into normal range, likely not immune-mediated. Restart cabozantinib at one dose level reduction.
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.		
Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.		
Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.		
Recommended management: See Endocrine Management Algorithm		

Endocrine: Hypophysitis Adrenal Insufficiency	**Nivolumab**	**Cabozantinib**
≤ Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis.	No change in dose

Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.	No change in dose
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.	Discontinue protocol therapy
Grade 4	Discontinue protocol therapy	Discontinue protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.		
Recommended management: See Endocrine Management Algorithm		

Cardiac*	**Management/Next Dose for Nivolumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off protocol treatment.

Cardiac*	**Management/Next Dose for Nivolumab Cardiac Toxicities**
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

Infusion reaction	**Nivolumab**	**Cabozantinib**
Grade 1	Continue therapy.	Continue therapy.
Grade 2	Symptomatic management. Hold until ≤ Grade 1. Resume at same dose.	Continue therapy.
Grade 3	Symptomatic management. Hold until ≤ Grade 1. Resume at same dose.	Continue therapy.
Grade 4	Discontinue treatment	Continue treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.		

Fever	**Nivolumab**	**Cabozantinib**
≤ Grade 1	Evaluate and continue at same dose level.	Continue treatment.
Grade 2	Symptomatic management. Hold until ≤ Grade 1. Resume at same dose level.	Continue treatment.
Grade 3	Symptomatic management. Hold until ≤ Grade 1. Resume at same dose level.	Continue treatment.
Grade 4	Discontinue treatment.	Continue treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever		
See Section 8.1.7 infusion reactions		

ALL OTHER EVENTS	**Nivolumab**	**Cabozantinib**
≤ Grade 1	No change in dose.	No change in dose.

Grade 2	Hold until ≤ Grade 1 OR baseline(exceptions as noted below).	Hold treatment and re-evaluate in 3-5 days. If improved after holding cabozantinib and attributed to cabozantinib, hold treatment until symptoms or lab findings resolve to ≤ Grade 1 OR baseline, then restart at one dose level reduction.
Grade 3	Discontinue nivolumab therapy (see exceptions noted below).	Hold treatment and re-evaluate in 3-5 days. If improved after holding cabozantinib and attributed to cabozantinib, hold treatment until symptoms or lab findings resolve to ≤ Grade 1 OR baseline, then restart at one dose level reduction.
Grade 4	Discontinue nivolumab therapy.	Hold cabozantinib and permanently discontinue unless it is determined that patient is unequivocally deriving clinical benefit. In this case, upon recovery of symptoms or laboratory findings to ≤ Grade 1, the patient may be re-treated at one dose level reduction after discussion with the Study Chair.
Recommended management: As clinically indicated		

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.
- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment d**oes not** require discontinuation.
- Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events.
- Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.
- Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.
- Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

- Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment.
- Patients requiring > two dose delays for the same event should go off protocol therapy.
- Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.
- Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.
- Patients may be dose-delayed for evaluation and restarted depending on results.
- Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendix IV. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: Protocols > Documents> Protocol Related Documents> Adverse Event Reporting; and
- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

9.1.2 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE v1.0 Term
Alopecia	Skin and subcutaneous tissue disorders	Alopecia (amount) 1 item
Anemia	Blood and lymphatic system disorders	
Constipation	Gastrointestinal disorders	Constipation (severity question) (1 item)
Cough	Respiratory, thoracic and mediastinal disorders	Cough (severity and interference) (2 items)
Anorexia	Metabolism and nutrition disorders	Decreased Appetite (2 items)
Diarrhea	Gastrointestinal disorders	Diarrhea (frequency question) (1 item)

Dyspnea	Respiratory, thoracic and mediastinal disorders	Shortness of breath (severity and interference) (2 items)
Fatigue	General disorders and administration site conditions	Fatigue (severity and interference questions) (2 items)
Hypertension	Vascular disorders	
Myalgia	Musculoskeletal and connective tissue disorders	Muscle Pain (frequency, severity, interference) (3 items)
Nausea	Gastrointestinal Disorders	Nausea (frequency and severity questions) (2 items)
Febrile Neutropenia	Blood and lymphatic system disorders	
Palmar-plantar erythrodysesthesia syndrome	Skin and subcutaneous tissue disorders	Hand-Foot Syndrome (1 item)
Peripheral motor neuropathy	Nervous system disorders	
Peripheral sensory neuropathy	Nervous system disorders	Numbness or tingling in your hands or feet (severity and interference questions) (2 items)
Pruritus	Skin and subcutaneous tissue disorders	Itching (1 item)
Fever	General disorders and administration site conditions	
Rash maculo-papular	Skin and subcutaneous tissue disorders	Rash (1 item)
Vomiting	Gastrointestinal Disorders	Vomiting (frequency and severity questions) (2 items)

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	A	a, b	a, b	a, b
Probable	a	A	a, b	a, b	a, b
Definite	a	A	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Study Chair, and their

Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE Within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

9.3.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A091902 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

All other grade 1-5 adverse events that result in ≥24 hours of hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS unless above the grade specified in SPEER.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib, NSC 761968)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 3219 patients. Below is the CAEPR for XL184 (Cabozantinib).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Myocardial infarction	
ENDOCRINE DISORDERS			
		Endocrine disorders - Other (thyroid dysfunction)	
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2] Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
		Wound dehiscence	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia Hypophosphatemia		

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
	Voice alteration		***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Hyperthyroidism; Hypopituitarism

EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); Portal vein thrombosis

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wrist fracture

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; Skin ulceration

VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) For BMS-936558 (Nivolumab, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for Nivolumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, May 14, 2025[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3] Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever Injection site reaction		***Fever (Gr 2)*** ***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]	
		Immune system disorders - Other (solid organ transplant rejection)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (eruptive keratoacanthoma)	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-related nephritis)	
		Renal and urinary disorders - Other (renal dysfunction)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia and systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving nivolumab. These complications may occur despite intervening therapy between receiving nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis)
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders – Other (complications of allogeneic HSCT); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 CTEP Agent Ordering, Accountability, Inventory, IB Availability, and Contacts

10.1.1 NCI Supplied Agents

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order supplies once a patient has been enrolled to the trial.

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Shortages

Specific guidance on how to address agent shortages for patients already enrolled on a clinical study as well as how to manage potential enrollment of new patients is provided at https://ctep.cancer.gov/branches/pmb/drug_shortages.htm.

Treatment plan modifications being made to avoid immediate hazard to patients is permissible under the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). In accordance with HHS regulations, local investigators must promptly inform the IRB of record of this unanticipated problem and the management plan for the trial.

Material Safety Data Sheets

The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

10.1.2 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a complete accountability of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

10.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

10.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB AURORA application: https://ctepcore.nci.nih.gov/aurora
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

10.2 Cabozantinib (Cabozantinib, XL184, NSC# 761968, IND # [redacted], IND holder: DCTD, NCI)

Description

Chemical Name: N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Other Names: Cabozantinib s-malate, EXEL-7184, EXEL-02977184, Cabometyx®

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: C28H24FN3O5.C4H6O5 M.W.: 635.6

Mode of Action:

Cabozantinib inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are VEGFR3, RET, AXL, KIT, TIE-2, FLT-3, ROS1, and RON.

Procurement
Exelixis supplies and the PMB, CTEP, DCTD, NCI distributes cabozantinib. At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation
The 20 mg tablets are round (5.6 mm) and yellow film-coated that are packaged as 30 tablets per HDPE bottle.

Preparation, Storage and Stability
Store intact bottles at controlled room temperature 20°C to 25°C (68°F to 77°F); temperature excursions are permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

If a storage temperature excursion outside of 15°C and 30°C (59°F to 86°F) is identified, promptly return XL184 (Cabozantinib) to 20° to 25°C (68° to 77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature

monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability testing is on-going.
Refer to the drug label for expiration date. Cabozantinib must be dispensed in original bottles.

If dispensing the exact quantity of cabozantinib tablets is an institutional guideline:

- Removing the extra tablets from the original bottle is allowed, and it must be used within 30 days of the preparation date. Document the extra tablets as waste in Oral DARF.
- Adding additional cabozantinib tablets into the original bottle in which the original bottle is exceeding its 30 Count bottle, is **Not Allowed**.

Repackaging XL184 (Cabozantinib) for a short period of time is acceptable and limited to:

- Up to 24 hours when dispensed in an open container such as a pill cup.
- Up to 7 days when dispensed in a closed container (e.g., a pharmacy dispensing bottle).

Administration
Cabozantinib is taken orally on an empty stomach. Fasting is required for at least 2 hours before and at least 1 hour after each dose of cabozantinib. Patients should swallow tablets whole with a full glass (at least 8 ounces) of water. Do not crush or chew. Do not take a missed dose within 12 hours of the next dose. Cabozantinib should not be taken with grapefruit/grapefruit juice or Seville oranges.

Potential Drug Interactions
Cabozantinib is a substrate of CYP3A4. Coadministration of cabozantinib with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days), to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC) by 77%. Examples of strong CYP3A4 inducers are carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampentin, rifampin, and St. John's Wort. Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days), to healthy subjects increased single-dose plasma cabozantinib exposure (AUC) by 38%. Strong CYP3A4 inhibitors are boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole. Avoid grapefruit/grapefruit juice and Seville oranges while participating in this trial.

Coadministration of gastric pH modifying drugs such as proton pump inhibitors (PPIs), H2-blockers, or antacids has no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers; thus, concomitant use of these drugs with cabozantinib is allowed.

Cabozantinib is highly protein bound, 99.9%. Use caution when coadministering cabozantinib with medications that are highly protein-bound (e.g. diazepam, furosemide, dicloxacillin, and propranolol). Administration of warfarin with cabozantinib is not allowed as warfarin is highly protein-bound and has a very narrow therapeutic index.

Drugs that prolong the QTc interval should be avoided or replaced if possible, as cabozantinib can prolong the QTC interval. Patients who receive potential QTc-prolonging medications should be monitored closely.

P-glycoprotein (P-gp) substrates (e.g. fexofenadine, aliskiren, ambrisentan digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.) should be used with caution during treatment with cabozantinib as coadministration can cause increased P-gp substrate levels.

MRP2 inhibitors (e.g. cyclosporine, delavirine, efavirenz, emtricitabine, etc.) should be used with caution during treatment with cabozantinib as coadministration can cause increased cabozantinib plasma concentrations.

Pharmacokinetics

Distribution: Vd: ~319 L

Protein Binding: ≥ 99.7% to plasma proteins

Metabolism: Hepatic via CYP3A4

Half-life Elimination: ~99 hours

Time to Peak: ~3-5 hours

Excretion: Feces (54%); urine (27%)

Adverse Events

See CAEPR in Section 9.4.1

Nursing Guidelines

- Instruct patients to take on an empty stomach. They should be fasting 2 hours prior and 1 hour after taking agent.
- Instruct patients to not to crush, or chew tablets.
- Do not take agent with grapefruit/grapefruit juice or Seville oranges.
- Agent has many drug to drug interactions. Assess patient's medication list including OTC and herbal products. Instruct patient to report any new medications to the study team immediately.
- Surgery (including dental work)should be avoided within 28 days of last dose of agent, if at all possible.
- Patients may experience hypertension. Monitor BP as required per protocol and instruct patients to make sure they continue any prescribed antihypertensives.
- Warn patients of possible changes to hair color.
- Monitor electrolytes closely, especially calcium as hypocalcemia is common.
- Patients may experience GI side effects including but not limited to abdominal pain, constipation, anorexia, dysgeusia, and nausea/vomiting. Treat symptomatically and monitor for effectiveness.
- Monitor CBC w/diff as cytopenias are common. Instruct patient's to report any signs or symptoms of infection and/or bruising/bleeding to study team immediately.
- Monitor LFT's
- Warn of possible hand-foot syndrome (PPE). Instruct patient to report pain, skin changes, etc. to study team.
- Rarely pulmonary embolism and other arterial thromboembolism has been reported.

10.3 Nivolumab (BMS-936558, MDX-1106, NSC# 748726, IND #[redacted], IND holder: DCTD, NCI)

Procurement

Nivolumab is an investigational agent supplied by the National Cancer Institute (NCI). Bristol-Myer-Squibb (BMS) will supply nivolumab to the DCTD/NCI and will be distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

Formulation
Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween 80®), pH 6.0. Nivolumab injection is supplied as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL Type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Storage and Stability
Vials of Nivolumab injection must be stored at 2°- 8°C (36°- 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours. If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. Shelf-life surveillance of the intact vials is ongoing.

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

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

Preparation
Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Administration
Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection. Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Potential Drug Interactions
The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential

for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Pharmacokinetics
Distribution: The mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses.

Half-life elimination: The mean terminal half-life of a single dose of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. The mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg.

Adverse Events
See CAEPR in Section 9.4.2

Nursing Guidelines

- Nivolumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids. Additionally, combination therapy (with ipilimumab) tends to have a higher rate of immune mediated side effects.
- Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per Section 8.0 and monitor for effectiveness.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, new onset diabetes and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating, headache and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.
- Patients who are started on steroid therapy for any side effects of nivolumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
- Monitor renal function as patients may experience acute interstitial nephritis. Report any increase of levels to the study team.

- Patients who have previously undergone a solid organ or tissue transplant and subsequently undergo therapy with nivolumab are at increased risk of organ/tissue rejection. Instruct patients that it is crucial that they stay in touch with their transplant team during treatment.
- Patients who have undergone allogeneic BMT are at higher risk of GVHD and death when receiving nivolumab. Monitor patients closely for GVHD symptoms and instruct patients to report these symptoms to the study team immediately.

10.4 Paclitaxel (Taxol) (NSC #673089)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 6 mg/mL (5 mL, 16.7 mL, 25 mL, and 50 mL) (contains alcohol and purified Cremophor EL {polyoxyethylated castor oil}).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature (20° to 25°C or 68° to 77°F) and protect from light. Dilute per institutional standard in 250-1000 mL D5W or 0.9% NaCl to a concentration of 0.3 – 1.2 mg/mL. Solutions in D5W and 0.9% NaCl are stable for up to 3 days at room temperature. Chemotherapy dispensing devices (e.g., Chemo Dispensing Pin) should not be used to withdraw paclitaxel from the vial.

Paclitaxel should be dispensed in either glass or non-PVC containers (e.g., Excel/PAB). Use nonpolyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching.

Administration

Infuse IV over 1hour (or per institutional standard). Infuse through a 0.22 micron in-line filter and polyethylene-lined administration set.

Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP2C8, CYP3A4; **Induces** CYP3A4 (weak).

Increased Effect/Toxicity: CYP2C8 inhibitors may increase the levels/effects of paclitaxel. Refer to the package insert or LexiComp1 for example inhibitors.

Decreased Effect: CYP2C8 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp1 for example inducers.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid valerian, St John's wort (may decrease paclitaxel levels), kava, gotu kola (may increase CNS depression).

Pharmacokinetics

Distribution: Vd: Widely distributed into body fluids and tissues; affected by dose and duration of infusion

Vdss: 1- to 6-hour infusion: 67.1 L/m2

Protein binding: 89-98%

Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel).

Half-life elimination: 1- to 6-hour infusion: Mean (beta): 6.4 hours,

3-hour infusion: Mean (terminal): 13-20 hours

Excretion: Feces (~71%, 5% as unchanged drug); Urine (14%)

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy. U.S. Boxed Warning: Bone marrow suppression (primarily neutropenia; may be severe or result in infection) may occur. Monitor blood counts frequently. Do not administer if baseline neutrophil count is (ANC) is <1500 cells/mm3 (1000 cells/mm3 for patients with AIDS-related KS); reduce future doses by 20% for severe neutropenia. U.S. Boxed Warning: Severe hypersensitivity reactions have been reported.

Common known potential toxicities, > 10%:

Cardiovascular: Flushing, ECG abnormal, edema, hypotension.

Central nervous system: Peripheral neuropathy

Dermatologic: Alopecia, skin rash.

Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis, abdominal pain (with intraperitoneal administration))

Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, hemorrhage.

Hepatic: Alkaline phosphatase increased, AST increased.

Hypersensitivity: Hypersensitivity reaction

Infection: Infection

Local: Injection site reaction (Erythema, tenderness, skin discoloration, swelling, tenderness).

Neuromuscular & skeletal: Arthralgia, myalgia, weakness.

Renal: Creatinine increased.

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Bradycardia, tachycardia, hypertension, cardiac arrhythmia, syncope, venous thrombosis.

Dermatologic: Nail changes.

Hematologic: Febrile neutropenia.

Hepatic: Bilirubin increased.

Respiratory: Dyspnea.

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, brain disease (neurological), cardiac conduction disturbance, cardiac failure, cellulitis, chills, conjunctivitis, dehydration, desquamation, enterocolitis, exacerbation of scleroderma, fibrosis at injection site, hepatic encephalopathy, hepatic necrosis, increased lacrimation, induration, intestinal obstruction, intestinal perforation, interstitial pneumonitis, ischemic colitis, ischemic heart disease, maculopapular rash, malaise, MI, neutropenic enterocolitis, ototoxicity, pancreatitis, paralytic

ileus, phlebitis, pneumonitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall phenomenon, radiation pneumonitis, renal insufficiency, seizure, skin edema, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, typhlitis (neutropenic) ventricular tachycardia (asymptomatic), visual disturbances.

Nursing Guidelines

Premedicate with steroids, antihistamines, and H2 blockers as per institutional guidelines.

Mix the infusion bag well. Thorough admixture of this drug often prevents a hypersensitivity reaction. An inline filter of <0.22 micron must be used distal to the infusion pump. Filter may need to be changed if infusion is to be prolonged >12 hours. Inspect solution for excessive particulate matter, if present do not use.

Caution patients that the alcohol contained in the infusion may cause impairment in operating heavy equipment or in driving a vehicle and to assess their ability before trying either. Advise avoidance of any alcohol or depressants such as sedatives and opiates if not necessary.

Assess the patient frequently for the first 30 minutes. Taxol® hypersensitivity reactions, which may include chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm and/or urticarial, usually occur early in the infusion. Have the anaphylaxis tray available.

If a reaction occurs, stop the infusion immediately. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per MD's order.

Approximately 60% of patients experience peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss). Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses >170 mg/m2/day and with cumulative doses over multiple courses of therapy. The nerve damage may take months to resolve. Nonsteroidal anti-inflammatory agents and opiates have not been effective in treating neuropathic pain. Consult MD about trying tricyclic antidepressants or possibly Neurontin.

Increased risk of cardiotoxicity when given in combination with doxorubicin, with a sharp increase in risk of CHF once cumulative dose of doxorubicin is > 380 mg/m2. At this point taxol should be continued as a single agent only. Monitor for sign/symptoms of CHF. Instruct patient to report any swelling in the hands, arms, feet, or legs, and any chest pain.

Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1 quart boiled water) or try OTC oral Lysine or Vitamin E.

Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.

There is an increased risk of neutropenia and stomatitis when given prior to doxorubicin. Therefore Taxol should always be given after doxorubicin administration.

Monitor IV site closely and establish patency before administration. Paclitaxel is an irritant, however rarely rash, radiation recall, and ulceration have occurred with infiltration of drug.

Monitor liver function tests.

Inform patient about total alopecia.

If given on the same day as a platinum agent, paclitaxel should be administered first to limit myelosuppression and enhance efficacy of agent.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using RECIST 1.1 with modifications (as discussed below).

11.1 Schedule for Assessment of Disease

Baseline imaging should include a CT or MRI of the chest/abdomen/pelvis or PET for all patients to adequately evaluate for distant metastatic disease if clinically appropriate (chest/abdomen/pelvis baseline imaging is required for noncutaneous angiosarcoma at baseline). The patient should also undergo appropriate imaging for the primary site of their cutaneous angiosarcoma as applicable. CT scans should be done with IV and oral contrast (if clinically indicated) unless allergy prevents administration. If MRI is chosen as imaging modality for following target/non-target lesions then MRI should be used for evaluation of response during the study.

Repeat imaging to evaluate for response will be done after each third cycle, for example before every 4th cycle and will be used to determine whether every 4th cycle is given to the patient. This schedule will continue until progression of disease or completion of all protocol specified treatment.

For those that complete all protocol specified treatment without progression or patients who ended treatment early for any reason (without progression), physical examination and staging scans are required 12 weeks (+/- 7 days) after the end of treatment, then every 12 weeks (+/- 7 days) until disease progression, or up to 3 years, if no progression, unless consent is withdrawn for clinical follow up. These schedules apply to all arms (i.e. paclitaxel plus nivolumab, paclitaxel monotherapy, or cabozantinib plus nivolumab).

11.2 Assessment of Disease

11.2.1 Definitions

Measurable Lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least 10 mm on CT or MRI scan (or >20mm by X-ray). Cystic lesions thought to represent cystic metastasis can be considered as measurable lesions.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in the short axis when assessed by CT scan.

Cutaneous Lesions: Cutaneous lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers or ruler (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required. When lesions can be evaluated by both clinical exam and imagining, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. The same method of measurement should be used throughout the study, preferably performed by the same investigator.

Non-measurable Lesions: All other lesions < 10 mm or lymph nodes <15mm in the short axis by CT scan.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and up to 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of

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

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

11.3. Evaluation of Disease Response Determination Will be Defined Based on RECIST 1.1

Table 1. Definition of Response in Target Lesions.

Response	Definition
Complete Response (CR)	Disappearance of all target lesions. Each target lymph node must have reduction in short axis to <1.0 cm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions compared to the nadir (smallest) sum of target lesions, or any new lesions
Stable Disease (SD)	Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

Per RECIST 1.1, response should be confirmed by a repeat imaging. The scan for confirmation of response may be performed at the earliest 4 weeks after imaging that showed response (if clinically indicated) or at the next scheduled scan.

Lesions that can be measured clinically on physical exam (skin lesions or palpable lymph nodes) will be measured by the investigator with the longest axis recorded. These measurements can be used to guide clinical decision making, for example prompting an earlier CT scan to evaluate disease. However, only measurements based on radiology will be used to determine response.

Table 2. Assessment of Non-Target Lesions Response

Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions. Each target lymph node must have reduction in short axis to <1.0 cm.
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesion
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence.

Table 3. Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	PR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Given the observed pattern of response with immune checkpoint inhibitors (anti-PD-1 mAb, antiPD-L1 mAb, and Anti-CTLA4 mAb) where some patients develop evidence of progressive disease by RECIST 1.1, with significant increase in size of target lesions and/or new lesions, followed by regression of disease to SD or PR/CR, all imaging showing progressive disease by RECIST 1.1, in the absence of significant clinic deterioration of the patient will be confirmed with repeat imaging or cutaneous measurement at least 4 weeks from the initial imaging showing progression. Clinically stable patients will continue treatment in the interim before this scan. If progressive disease is confirmed on subsequent imaging, the patient will be defined as having progressive disease and will be taken off of the study. Progressive disease by RECIST 1.1 with clinical deterioration by the patient will be counted as progressive disease, and study treatment will be discontinued without confirmation of progressive disease with repeat scan.

Determination of clinical deterioration is at the discretion of the treating physician as defined by progression of disease at critical sites requiring urgent intervention (for example cord compression), or development of signs and symptoms of disease progression and/or significant decline in ECOG performance status.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue for a maximum of 2 years (24 months) patients who achieve a CR/PR or SD on immunotherapy/nivolumab, or until disease progression (for all patients). If one of the study medications is not tolerated, the patient may elect to remain on study and continue the other study medication in Arm 1 and Arm 3. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.1.1 Disease Progression:

Any patient with disease progression must be removed from protocol therapy, with the exception of management as per Section 7.4. In the 1st 12 weeks (3 cycles) of therapy, patients are allowed to continue therapy in the face of progression, as long as they meet all required bullets as per Section 7.4. Note that this is applicable to Arms 1 and 3 receiving nivolumab, but not Arm 2.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

Completion of therapy (maximum of 2 years)

Disease progression (if applicable)

Intercurrent illness that prevents further administration of treatment

Unacceptable adverse event(s)

Patient decides to withdraw from the study

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Clinical progression

Patient non-compliance

Pregnancy (if applicable)

All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

Termination of the study by sponsor.

The drug manufacturer can no longer provide the study agent.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.2.1 Criteria for Crossover

The following are criteria for eligibility for protocol therapy crossover from taxane naïve arms (Arms 2) to the taxane pre-treated arm (Arm 3):

Please see the eligibility Section 3.2 for the full re-registration eligibility criteria for patients who crossover.

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients should be followed for three years (after the end of treatment) for progression, survival, or until death, whichever occurs first.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

Follow up for patients who stop due to toxicity

Patients should complete the 4 week EOT visit with imaging (see Section 5.0), then be followed until resolution of toxicity or until determination that the toxicity will not resolve. Patients should also be followed per standard of care for at least three years (after the end of treatment) for progression and survival after completion of study therapy or until death, whichever occurs first.

Follow up for patients who receive non-protocol therapy

Patients should be followed per standard of care for at least three years (after the end of treatment) for progression and/or survival after completion of study therapy or until death, whichever occurs first.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

Document the reason(s) for discontinuation of therapy on data forms.

Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This phase II trial has 2 primary objectives, both with regard to patients with angiosarcoma.

13.1.1 PFS in taxane naïve patients with angiosarcoma

The first primary objective is to determine if there is a PFS benefit by addition of nivolumab to paclitaxel, compared to paclitaxel alone. This primary endpoint will utilize a randomized design and is available to patients with angiosarcoma who are taxane naïve. Once a patient progresses in the paclitaxel only arm, they are eligible to crossover to the arm described in 13.1.2 (as they will then no longer be taxane naïve).

13.1.2 Overall response rate in angiosarcoma patients who have had prior taxane

Patients with angiosarcoma who have had prior taxane can participate in the study on this arm which combines nivolumab with cabozantinib. The success, or failure, of this arm will be determined by comparing the overall response rate (ORR) to historical control. Patients that cross over from the paclitaxel only arm (described in Section 13.1.1) are not included in calculation of the primary endpoint.

13.2 Statistical Design and Analysis for the first Primary Endpoint (PFS, taxane naïve)

13.2.1 PFS in taxane naïve patients with angiosarcoma:

We are comparing the progression free survival (PFS) in taxane naïve angiosarcoma patients receiving either (1) paclitaxel + nivolumab compared to (2) paclitaxel alone. A patient is considered an event for this endpoint at the time of first evidence of disease progression, or death (without evidence of progression) and their PFS time is defined as the time from registration (randomization) to either progression or death (without progression). For patients receiving nivolumab, who have evidence of progressive disease in the first 12 weeks, a confirmation scan will be performed 4 weeks after the first evidence. If the progression is not confirmed, then the patient is allowed to continue treatment, however they will be considered to have progressed at the time of the unconfirmed progression for the purposes of the primary endpoint. See Section 7.4 for more information. For patients that are not considered an event for this endpoint, the PFS time will be censored at their last evaluation for progression. All randomized patients meeting the eligibility criteria who receive any quantity of their randomized care will be part of the analysis group for this primary endpoint.

13.2.2 Statistical Design and analysis plan:

The chosen trial design is built with the assumption that the paclitaxel only arm will have a median PFS time of approximately 4 months (Penel et al.). The aim is to improve upon this to 7 months with the addition of nivolumab. The chosen design requires 59 progression events and approximately 66 patients (33 per arm). The design has a power of 85.3% and a significance level of 0.148. If, after the 59th event is observed, the hazard ratio is less than 0.772, then the null hypothesis will be rejected in favor of the alternate (that the combination arm is superior in terms of PFS) and further study may be warranted.

13.2.3 Interim Analysis:

The chosen trial design also contains one interim look for futility based on a Wieand rule. If, after 30 events (i.e. roughly half of those required for the full analysis), the HR is greater than 1.006, then this part of the trial will stop accrual for futility.

13.3 Statistical Design and Analysis for the second Primary Endpoint (ORR, prior taxanes)

13.3.1 ORR in angiosarcoma patients with prior taxanes:

For the second primary endpoint we are comparing the overall response rate (ORR) of nivolumab + cabozantinib in patients with angiosarcoma who have had prior taxanes to historical control of VEGF inhibitors alone. For patients who have evidence of progressive disease in the first 12 weeks, a confirmation scan will be performed 4 weeks after the first evidence. If the progression is not confirmed, then the patient is not considered to have progressed. See Section 7.4 for more information.

13.3.2 Statistical Design and analysis plan:

The chosen trial design for this primary endpoint is a two-stage Simon design with the assumption that cabozantinib alone leads to an ORR similar to other VEGF inhibitors (approximately 10%, based on Ray-Coquard et al. and Agulnik et al.). In the first stage, 9 patients will be enrolled. If there are no patients with a confirmed response (out of 9 evaluable patients), then this portion of the study will stop accrual for futility. Otherwise and additional 9 patients will be enrolled. The study will be declared promising if there are 4 or more patients (out of 18 total evaluable patients) with a confirmed response. This study design has a power of 91.4% and a significance rate of 0.095. Accrual will not stop while awaiting follow up data for the first stage patients. All patients initially registered to this arm, that meet the eligibility criteria, who receive any quantity of study drug will be part of the analysis group for this primary endpoint.

13.4 Sample Size, Accrual time, and Study Duration

13.4.1 Sample Size:

Up to 66 evaluable patients are required for the PFS endpoint (in order to attain 55 events) and up to 18 evaluable patients are required for the ORR endpoint for a total of 84 evaluable patients. In addition to these 84 patients, we will plan to accrue 4 additional patients into the PFS arms and 2 additional patients into the ORR arm to account for any non-evaluable patients. This brings the overall maximum accrual to 90 patients.

13.4.2 Accrual Rate and Study Duration:

It is expected that accrual will occur at approximately 2 patients per month for both endpoints. Since the PFS endpoint requires more patients, the study duration will be based on that endpoint. The 2 PFS endpoint arms will require approximately 33 months to fully enroll. Under the alternate hypothesis (i.e. a PFS advantage for the combination arm), the primary endpoint will be evaluable at approximately 38 months post study opening.

13.5 Supplementary Analysis Plans

13.5.1 Secondary Endpoints

ORR in the nivolumab + paclitaxel: The overall response rate will be estimated by dividing the number of evaluable patients that achieve a confirmed response by the total number of evaluable patients in the nivolumab + paclitaxel combination arm. Additionally, a 95% confidence interval will be constructed utilizing properties of the binomial distribution.

Overall Survival in each of the 2 combination arms: Overall survival (OS) will be evaluated using the Kaplan-Meier method in order to determine the median survival rate. This median survival rate will be calculated for each of the 2 combination arms (i.e. nivolumab + paclitaxel and nivolumab + cabozantinib). A patient's survival time will is defined as the number of days from study enrollment until death due to any cause. A patient that is still alive at the time of the analysis will have this time censored at the time they were last known to be alive.

Progression Free Survival at 6 months (PFS6 rate) in nivolumab + cabozantinib: A patient will be declared an event for this endpoint if they had documented progression (or death) prior to, or at, their 6 month evaluation. This endpoint will be applied to the patients on the nivolumab + cabozantinib combination arm.

Safety/Toxicity: Maximum grade adverse events will be summarized by treatment arm in a tabular setting. This will be done both with and without regard to the assigned attribution of each adverse event.

Patient-reported outcomes (PRO) via PRO-CTCAE. In order to evaluate this endpoint we will calculate the proportion of patients that report a grade 3+ event along with a 95% confidence interval based on the properties of the binomial distribution. Any other analyses with these data will be done in an exploratory and hypothesis generating manner.

13.6 Adverse Event Stopping Rule:

The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the study statistician. Additionally, in order to ascertain if the study treatments are safe for patients, the following adverse event stopping rules will be employed. The following rules will be applied to each arm separately. If any rule is crossed then accrual will be suspended while the study team evaluates the data, develops a plan, and receives approval for re-opening from the DSMB.

- If at any point during the first 10 patients at least 3 patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment, or…
- If at any point after the first 10 patients at least 30% of all patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment.

13.7 Study Reporting

13.7.1 Alliance DSMB

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.7.2 Data Mapping Utility (DMU)

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (http://ctep.cancer.gov/reporting/dmu.html).

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

13.7.3 Result Reporting on ClinicalTrials.Gov

At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.8 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, sex, or ethnic origin. There is no information currently available regarding differential effects of study treatment in subsets defined by race, sex, or ethnicity. Although there is insufficient power to detect small or moderate effects, we will, as always, report the results by sex and ethnicity in exploratory analyses.

There is no reason to believe that there will be a sex difference in this disease and the study team expects there to be approximately 5% racial minorities.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	1	0	0	1	2
White	42	42	1	0	85
More Than One Race	0	0	0	0	0
Total	44	44	1	1	90

14.0 BIOBANKING FOR FUTURE CORRELATIVE SCIENCE

Alliance protocol A091902 has both mandatory tumor testing for retrospective central pathology review and optional testing for future correlative studies. The optional tissue and blood collection for future studies must be offered to all patients enrolled on Alliance A091902 (although patients may opt to not participate). This tissue collection does not require separate IRB approval. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

15.0 MONITORING PLAN

Use standard Alliance monitoring procedures.

15.1 Early Study Closure at Sites

Before completing the early study closure process please confirm this study does not appear on the list of trials terminated by the Alliance or on a study-specific termination memo (located on the "Study Terminations of Patient Follow-up" page of the Alliance website or on the study specific page of the CTSU website).

Institutions may not close this trial without discussion and approval by the Alliance Regulatory team (regulatory@alliancenctn.org). Sites will submit the CTSU Request for LPO Approval of Early Closure Form with page 2 completed to the Alliance Regulatory team. The CTSU Request Form can be found on the CTSU website under Resources > CTSU Operations Information > CTSU Forms. If the site has enrolled any patients they will need to include a screenshot of the Rave database listing of all patient IDs and that no queries are open and no data are outstanding.

16.0 REFERENCES

1 Holden, C. A., et al. “Angiosarcoma of the Face and Scalp, Prognosis and Treatment.” Cancer, vol. 59, no. 5, Mar. 1987, pp. 1046–57, http://www.ncbi.nlm.nih.gov/pubmed/3815265.

2 Coindre, J. M., et al. “Predictive Value of Grade for Metastasis Development in the Main Histologic Types of Adult Soft Tissue Sarcomas: A Study of 1240 Patients from the French Federation of Cancer Centers Sarcoma Group.” Cancer, vol. 91, no. 10, May 2001, pp. 1914–26, http://www.ncbi.nlm.nih.gov/pubmed/11346874.

3 Young, Robin J., et al. “Angiosarcoma.” The Lancet Oncology, vol. 11, no. 10, Oct. 2010, pp. 983–91, doi:10.1016/S1470-2045(10)70023-1.

4 Costigan, Danielle C., and Leona A. Doyle. “Advances in the Clinicopathological and Molecular Classification of Cutaneous Mesenchymal Neoplasms.” Histopathology, vol. 68, no. 6, May 2016, pp. 776–95, doi:10.1111/his.12930.

5 Choi, Jun Ho, et al. “Surgical Treatment and Prognosis of Angiosarcoma of the Scalp: A Retrospective Analysis of 14 Patients in a Single Institution.” BioMed Research International, vol. 2015, Hindawi, Dec. 2015, pp. 1–8, doi:10.1155/2015/321896.

6 Pawlik, Timothy M., et al. “Cutaneous Angiosarcoma of the Scalp.” Cancer, vol. 98, no. 8, Oct. 2003, pp. 1716–26, doi:10.1002/cncr.11667.

7 Morrison, W. H., et al. “Cutaneous Angiosarcoma of the Head and Neck. A Therapeutic Dilemma.” Cancer, vol. 76, no. 2, July 1995, pp. 319–27, http://www.ncbi.nlm.nih.gov/pubmed/8625109.

8 Abraham, John A., et al. “Treatment and Outcome of 82 Patients with Angiosarcoma.” Annals of Surgical Oncology, vol. 14, no. 6, May 2007, pp. 1953–67, doi:10.1245/s10434-006-9335-y.

9 Lahat, G., et al. “Outcome of Locally Recurrent and Metastatic Angiosarcoma.” Annals of Surgical Oncology, vol. 16, no. 9, Sept. 2009, pp. 2502–09, doi:10.1245/s10434-009-0569-3.

10 Bernstein, Jonathan M., et al. “Survival Outcomes for Cutaneous Angiosarcoma of the Scalp versus Face.” Head & Neck, vol. 39, no. 6, June 2017, pp. 1205–11, doi:10.1002/hed.24747.

11 Ogawa, K., et al. “Treatment and Prognosis of Angiosarcoma of the Scalp and Face: A Retrospective Analysis of 48 Patients.” The British Journal of Radiology, vol. 85, no. 1019, Nov. 2012, pp. e1127–33, doi:10.1259/bjr/31655219.

12 Penel, Nicolas, et al. “Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study.” Journal of Clinical Oncology, vol. 26, no. 32, Nov. 2008, pp. 5269–74, doi:10.1200/JCO.2008.17.3146.

13 Linch, Mark, et al. “Systemic Treatment of Soft-Tissue Sarcoma—Gold Standard and Novel Therapies.” Nature Reviews Clinical Oncology, vol. 11, no. 4, Apr. 2014, pp. 187–202, doi:10.1038/nrclinonc.2014.26.

14 Mendenhall, William M., et al. “Cutaneous Angiosarcoma.” American Journal of Clinical Oncology, vol. 29, no. 5, Oct. 2006, pp. 524–28, doi:10.1097/01.coc.0000227544.01779.52.

15 Shin, Jin Yong, et al. “Predisposing Factors for Poor Prognosis of Angiosarcoma of the Scalp and Face: Systematic Review and Meta-Analysis.” Head & Neck, edited by David W. Eisele, vol. 39, no. 2, Feb. 2017, pp. 380–86, doi:10.1002/hed.24554.

16 Ray-Coquard, Isabelle L., et al. “Paclitaxel Given Once Per Week With or Without Bevacizumab in Patients With Advanced Angiosarcoma: A Randomized Phase II Trial.” Journal of Clinical Oncology, vol. 33, no. 25, 2015, pp. 2797–802, doi:10.1200/JCO.2015.60.8505.

17 Schlemmer, M., et al. “Paclitaxel in Patients with Advanced Angiosarcomas of Soft Tissue: A Retrospective Study of the EORTC Soft Tissue and Bone Sarcoma Group.” European Journal of Cancer, vol. 44, no. 16, Nov. 2008, pp. 2433–36, doi:10.1016/j.ejca.2008.07.037.

18 Fata, F., et al. “Paclitaxel in the Treatment of Patients with Angiosarcoma of the Scalp or Face.” Cancer, vol. 86, no. 10, Nov. 1999, pp. 2034–37, http://www.ncbi.nlm.nih.gov/pubmed/10570428.

19 Behjati, Sam, et al. “Recurrent PTPRB and PLCG1 Mutations in Angiosarcoma.” Nature Genetics, vol. 46, no. 4, Apr. 2014, pp. 376–79, doi:10.1038/ng.2921.

20 Gao, J., et al. “Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the CBioPortal.” Science Signaling, vol. 6, no. 269, Apr. 2013, pp. pl1-pl1, doi:10.1126/scisignal.2004088.
21 Cerami, Ethan, et al. “The CBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data: Figure 1.” Cancer Discovery, vol. 2, no. 5, May 2012, pp. 401–04, doi:10.1158/2159-8290.CD-12-0095.
22 Disis, M.L. “Immune regulation of cancer.” J Clin Oncol, 2010. 28(29): p. 4531-8.
23 Dudley, M.E., et al. “Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma.” J Clin Oncol, 2005. 23(10): p. 2346-57.
24 Hunder, N.N., et al. “Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1.” N Engl J Med, 2008. 358(25): p. 2698-703.
25 Greenwald, R.J., G.J. Freeman, and A.H. Sharpe. “The B7 family revisited.” Annu Rev Immunol, 2005. 23:
26 Okazaki, T., et al. “PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine.” Proc Natl Acad Sci U S A, 2001. 98(24): p. 13866-71.
27 Zhang, X., et al. “Structural and functional analysis of the costimulatory receptor programmed death-1.” Immunity, 2004. 20(3): p. 337-47.
28 Chemnitz, J.M., et al. “SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation.” J Immunol, 2004. 173(2): p. 945-54.
29 Sheppard, K.A., et al. “PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta.” FEBS Lett, 2004. 574(1-3): p. 37-41.
30 Padró, T., et al. “Overexpression of Vascular Endothelial Growth Factor (VEGF) and Its Cellular Receptor KDR (VEGFR-2) in the Bone Marrow of Patients with Acute Myeloid Leukemia.” Leukemia, vol. 16, no. 7, July 2002, pp. 1302–10, doi:10.1038/sj.leu.2402534.
31 Wagner, Michael J., et al. “Endothelial Cell Malignancies: New Insights from the Laboratory and Clinic.” Npj Precision Oncology, vol. 1, no. 1, Nature Publishing Group, Dec. 2017, p. 11, doi:10.1038/s41698-017-0013-2.
32 Wallin, Jeffrey J., et al. “Atezolizumab in Combination with Bevacizumab Enhances Antigen-Specific T-Cell Migration in Metastatic Renal Cell Carcinoma.” Nature Communications, vol. 7, Nature Publishing Group, Aug. 2016, p. 12624, doi:10.1038/ncomms12624.
33 Gabrilovich, D. I., et al. “Production of Vascular Endothelial Growth Factor by Human Tumors Inhibits the Functional Maturation of Dendritic Cells.” Nature Medicine, vol. 2, no. 10, Oct. 1996, pp. 1096–103, http://www.ncbi.nlm.nih.gov/pubmed/8837607.
34 Socinski, Mark A., et al. “Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC.” The New England Journal of Medicine, vol. 378, no. 24, June 2018, pp. 2288–301, doi:10.1056/NEJMoa1716948.
35 Zietz, Christian, et al. “MDM-2 Oncoprotein Overexpression, P53 Gene Mutation, and VEGF Up-Regulation in Angiosarcomas.” The American Journal of Pathology, vol. 153, no. 5, Nov. 1998, pp. 1425–33, doi:10.1016/S0002-9440(10)65729.
36 Nadal et al. “Results of phase I plus expansion cohorts of cabozantinib (Cabo) plus nivolumab (Nivo) and CaboNivo plus ipilimumab (Ipi) in patients (pts) with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies.” Journal of Clinical Oncology 36, no. 6_suppl (February 20 2018) 515-515.
37 D’Angelo, Sandra P., et al. “Prevalence of Tumor-Infiltrating Lymphocytes and PD-L1 Expression in the Soft Tissue Sarcoma Microenvironment.” Human Pathology, vol. 46, no. 3, Mar. 2015, pp. 357–65, doi:10.1016/j.humpath.2014.11.001.

38 Kim, Chan, et al. “Prognostic Implications of PD-L1 Expression in Patients with Soft Tissue Sarcoma.” BMC Cancer, vol. 16, no. 1, Dec. 2016, p. 434, doi:10.1186/s12885-016-2451-6.

39 Paoluzzi, Luca, et al. “Anti-PD1 Therapy with Nivolumab in Sarcoma.” Journal of Clinical Oncology, vol. 34, no. 15_suppl, 2016, p. 11047, doi:10.1200/JCO.2016.34.15_suppl.11047.

40 Honda, Yuki, et al. “Infiltration of PD-1-Positive Cells in Combination with Tumor Site PD-L1 Expression Is a Positive Prognostic Factor in Cutaneous Angiosarcoma.” OncoImmunology, vol. 6, no. 1, Jan. 2017, p. e1253657, doi:10.1080/2162402X.2016.1253657.

41 Sindhu, Simran, et al. “Angiosarcoma Treated Successfully with Anti-PD-1 Therapy - a Case Report.” Journal for Immunotherapy of Cancer, vol. 5, no. 1, BioMed Central, 2017, p. 58, doi:10.1186/s40425-017-0263-0.

42 Kim, Jung Ryul, et al. “Tumor Infiltrating PD1-Positive Lymphocytes and the Expression of PD-L1 Predict Poor Prognosis of Soft Tissue Sarcomas.” PLoS ONE, edited by Ju-Seog Lee, vol. 8, no. 12, Dec. 2013, p. e82870, doi:10.1371/journal.pone.0082870.

43 Fujii, Hiroko, et al. “CD8 + Tumor-Infiltrating Lymphocytes at Primary Sites as a Possible Prognostic Factor of Cutaneous Angiosarcoma.” International Journal of Cancer, vol. 134, no. 10, May 2014, pp. 2393–402, doi:10.1002/ijc.28581.

44 Wu S, Googe PB. “PD-L1 and LAG 3 in advanced cutaneous squamous cell carcinoma.” American Society of Dermatopathology 55th Annual Meeting, November 8 – 11, 2018, Chicago.

45 Maddox, J. C., and H. L. Evans. “Angiosarcoma of Skin and Soft Tissue: A Study of Forty-Four Cases.” Cancer, vol. 48, no. 8, Oct. 1981, pp. 1907–21, http://www.ncbi.nlm.nih.gov/pubmed/7197190.

46 Shimizu, Akira, et al. “Positive PD-L1 Expression Predicts Worse Outcome in Cutaneous Angiosarcoma.” Journal of Global Oncology, vol. 3, no. 4, American Society of Clinical Oncology, Aug. 2017, pp. 360–69, doi:10.1200/JGO.2016.005843.

47 Kawamura, A., Kawamura, T., Riddell, M., Hikita, T., Yanagi, T., Umemura, H., & Nakayama, M. (2019). Regulation of programmed cell death ligand 1 expression by atypical protein kinase C lambda/iota in cutaneous angiosarcoma. Cancer science, 110(5), 1780–1789. doi:10.1111/cas.13981.

48 Somasundaram, A., & Burns, T. F. (2017). Pembrolizumab in the treatment of metastatic non-small-cell lung cancer: patient selection and perspectives. Lung Cancer (Auckland, N.Z.), 8, 1–11. doi:10.2147/LCTT.S105678.

49 Rizvi, Naiyer A., et al. “Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer.” Journal of Clinical Oncology, vol. 34, no. 25, Sept. 2016, pp. 2969–79, doi:10.1200/JCO.2016.66.9861.

50 Penn, I. “Kaposi’s Sarcoma in Transplant Recipients.” Transplantation, vol. 64, no. 5, Sept. 1997, pp. 669–73, http://www.ncbi.nlm.nih.gov/pubmed/9311700.

51 Penn, I. “Sarcomas in Organ Allograft Recipients.” Transplantation, vol. 60, no. 12, Dec. 1995, pp. 1485–91, http://www.ncbi.nlm.nih.gov/pubmed/8545879.

52 Merchant, M. S., et al. “Adjuvant Immunotherapy to Improve Outcome in High-Risk Pediatric Sarcomas.” Clinical Cancer Research, vol. 22, no. 13, July 2016, pp. 3182–91, doi:10.1158/1078-0432.CCR-15-2550.

53 Govindan, Ramaswamy, et al. “Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer.” Journal of Clinical Oncology, vol. 35, no. 30, Oct. 2017, pp. 3449–57, doi:10.1200/JCO.2016.71.7629.

54 Kanda, S., et al. “Safety and Efficacy of Nivolumab and Standard Chemotherapy Drug Combination in Patients with Advanced Non-Small-Cell Lung Cancer: A Four Arms Phase Ib Study.” Annals of Oncology, vol. 27, no. 12, Oxford University Press, Dec. 2016, pp. 2242–50, doi:10.1093/annonc/mdw416.

55 George, Ben, et al. “P1.46: Phase I Study of Nivolumab + Nab-Paclitaxel in Solid Tumors: Preliminary Analysis of the Non-Small Cell Lung Cancer Cohort.” Journal of Thoracic Oncology, vol. 11, no. 10, Oct. 2016, pp. S211–12, doi:10.1016/j.jtho.2016.08.068.

56 Reck, M., et al. “134PD Primary PFS and Safety Analyses of a Randomized Phase III Study of Carboplatin + Paclitaxel +/− Bevacizumab, with or without Atezolizumab in 1L Non-Squamous Metastatic NSCLC (IMpower150).” Journal of Thoracic Oncology, vol. 13, no. 4, Elsevier, Apr. 2018, pp. S77–78, doi:10.1016/S1556-0864(18)30409-X.
57 Hellmann, Matthew D., et al. “Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden.” New England Journal of Medicine, vol. 378, no. 22, May 2018, pp. 2093–104, doi:10.1056/NEJMoa1801946.
58 Nanda, Rita, et al. “Pembrolizumab plus Standard Neoadjuvant Therapy for High-Risk Breast Cancer (BC): Results from I-SPY 2.” Journal of Clinical Oncology, vol. 35, no. 15_suppl, 2017, p. 506, doi:10.1200/JCO.2017.35.15_suppl.506.
59 Motzer, Robert J., et al. “IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma (MRCC).” Journal of Clinical Oncology, vol. 36, no. 6_suppl, 2018, p. 578, doi:10.1200/JCO.2018.36.6_suppl.578.
60 Reardon, David A., et al. “Safety of Pembrolizumab in Combination with Bevacizumab in Recurrent Glioblastoma (RGBM).” Journal of Clinical Oncology, vol. 34, no. 15_suppl, 2016, p. 2010, doi:10.1200/JCO.2016.34.15_suppl.2010.48
61 Hamacher R, Kämpfe D, Reuter-Jessen K, Pöttgen C, Podleska LE, Farzaliyev F, Steinau H-U, Schuler M, Schildhaus H-U, Bauer S. “Dramatic response of a PD-L1–positive advanced Angiosarcoma of the scalp to Pembrolizumab.” JCO Precis Oncol. 2018;2:1–7.
62 Hofer S, Zeidler K, Schipf A, Kempf W, Zimmermann D, Aebi S. “Angiosarcoma of the scalp responding to nivolumabL A case report.” Br J Dermatol. 2018 Aug;179(2):530-531. doi: 10.1111/bjd.16698. Epub 2018 Jun 13.
63 Florou V, Rosenberg AE, Wieder E, Komanduri KV, Kolonias D, Uduman M, Castle JC, Buell JS, Trent JC, Wilky BA. “Angiosarcoma patients treated with immune checkpoint inhibitors: A case series of seven patients from a single institution.” J Immunother Cancer. 2019 Aug 8;7(1):213. doi: 10.1186/s40425-019-0689-7.
64 Sindhu, Simran, et al. “Angiosarcoma Treated Successfully with Anti-PD-1 Therapy - a Case Report.” Journal for Immunotherapy of Cancer, vol. 5, no. 1, BioMed Central, 2017, p. 58, doi:10.1186/s40425-017-0263-0.

APPENDIX I CRADA

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).-Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX II TOXICITY ALGORITHMS

Adverse Event Algorithms for GI, Renal, Pulmonary, Hepatic, Endocrine, Skin, Neurologic, and Myocarditis

Version 21

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

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

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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or 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.

Endocrinopathy Adverse Event Management Algorithm

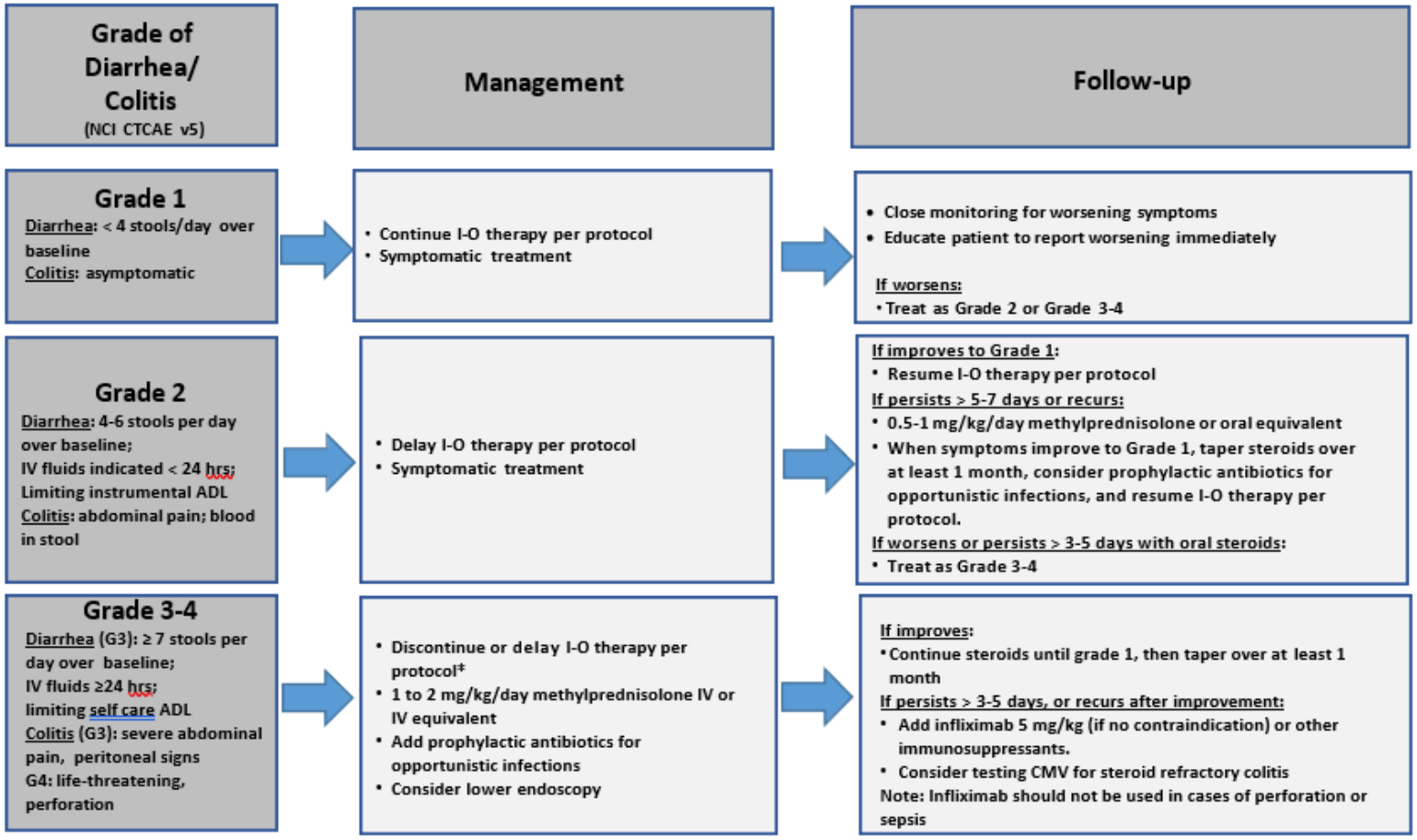
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

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.

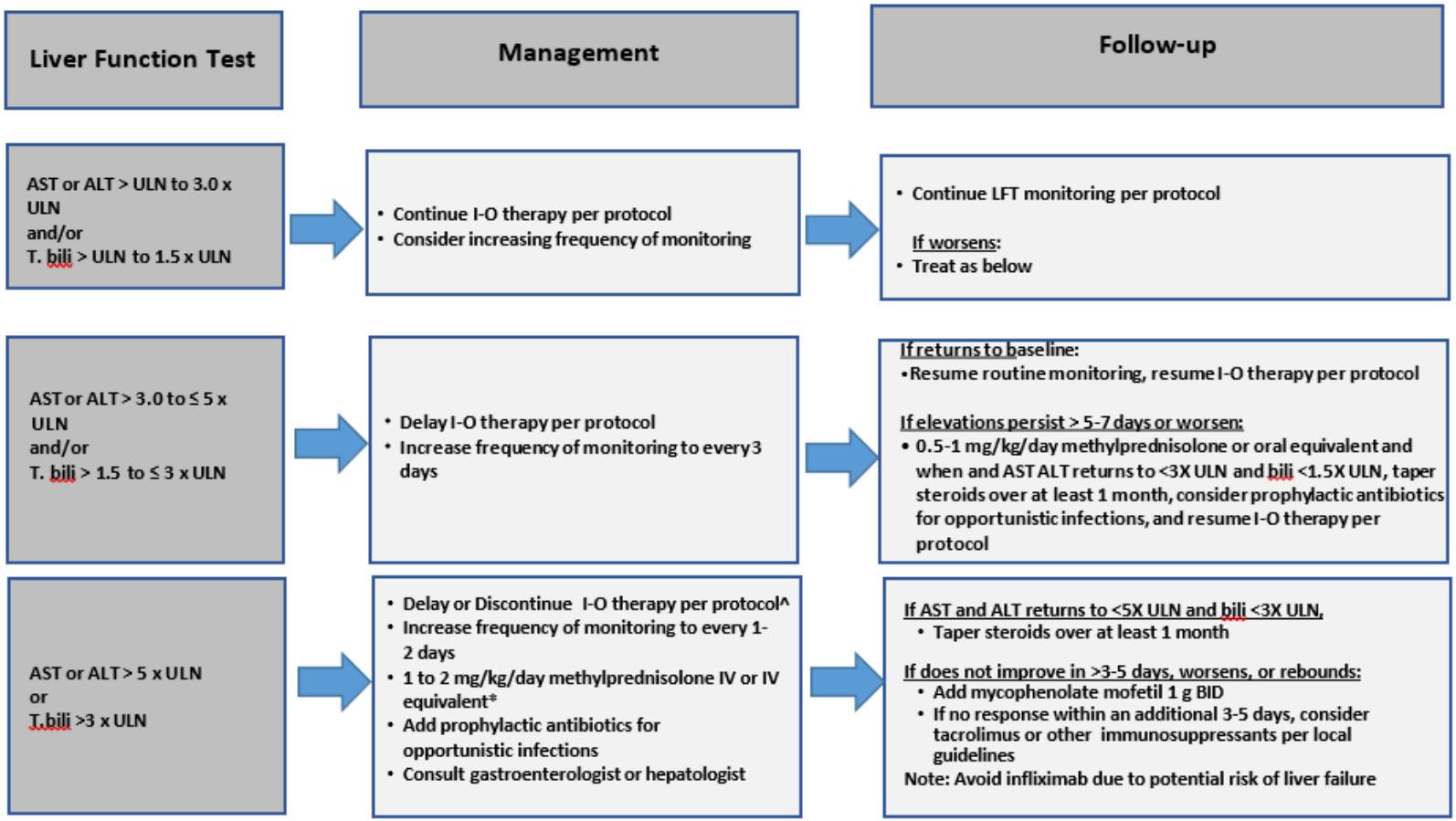


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Hepatic Adverse Event Management Algorithm

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



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

^ Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

For subjects with HCC, please refer to the protocol for specific details.

Neurological Adverse Event Management Algorithm

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

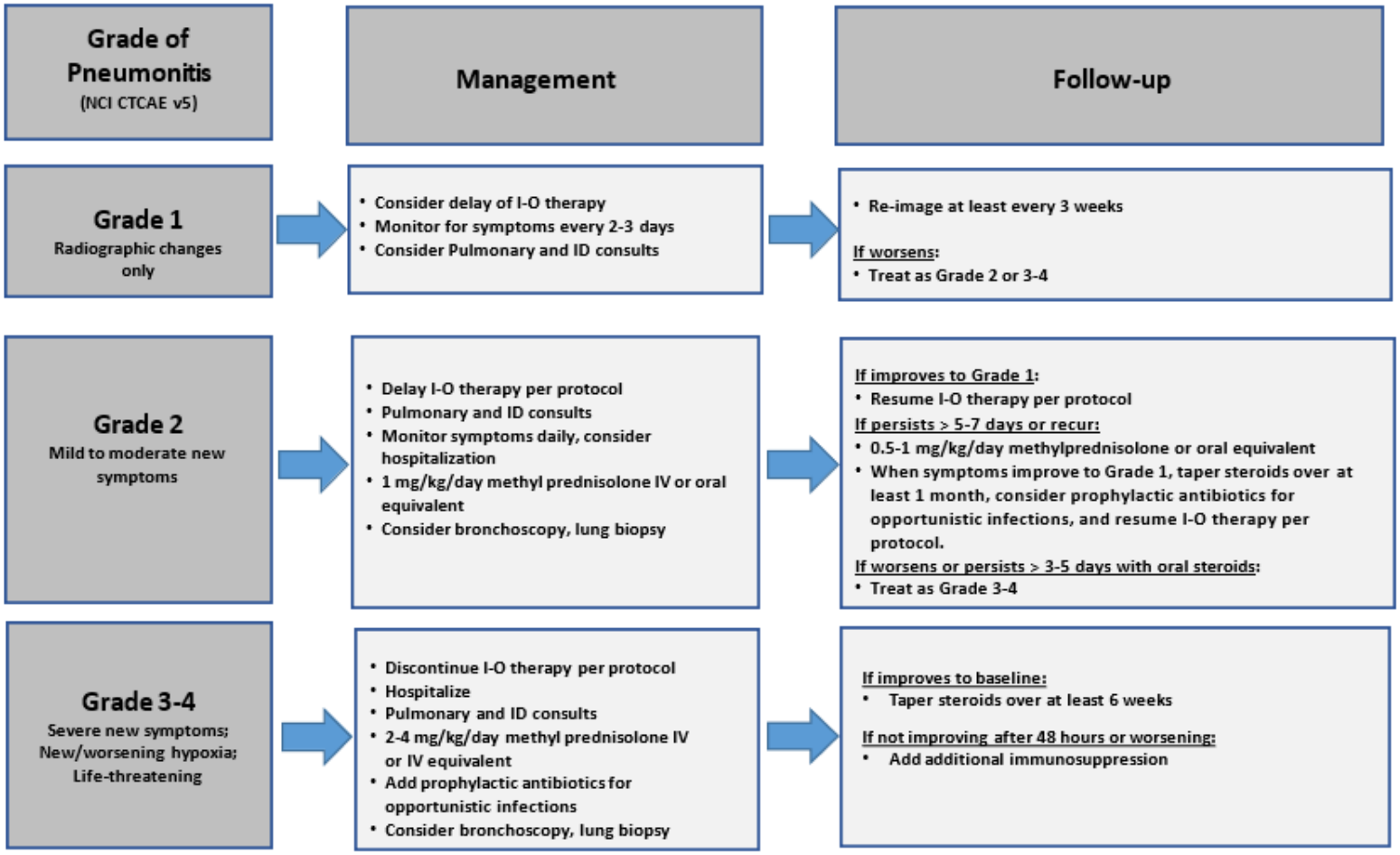
Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Pulmonary Adverse Event Management Algorithm

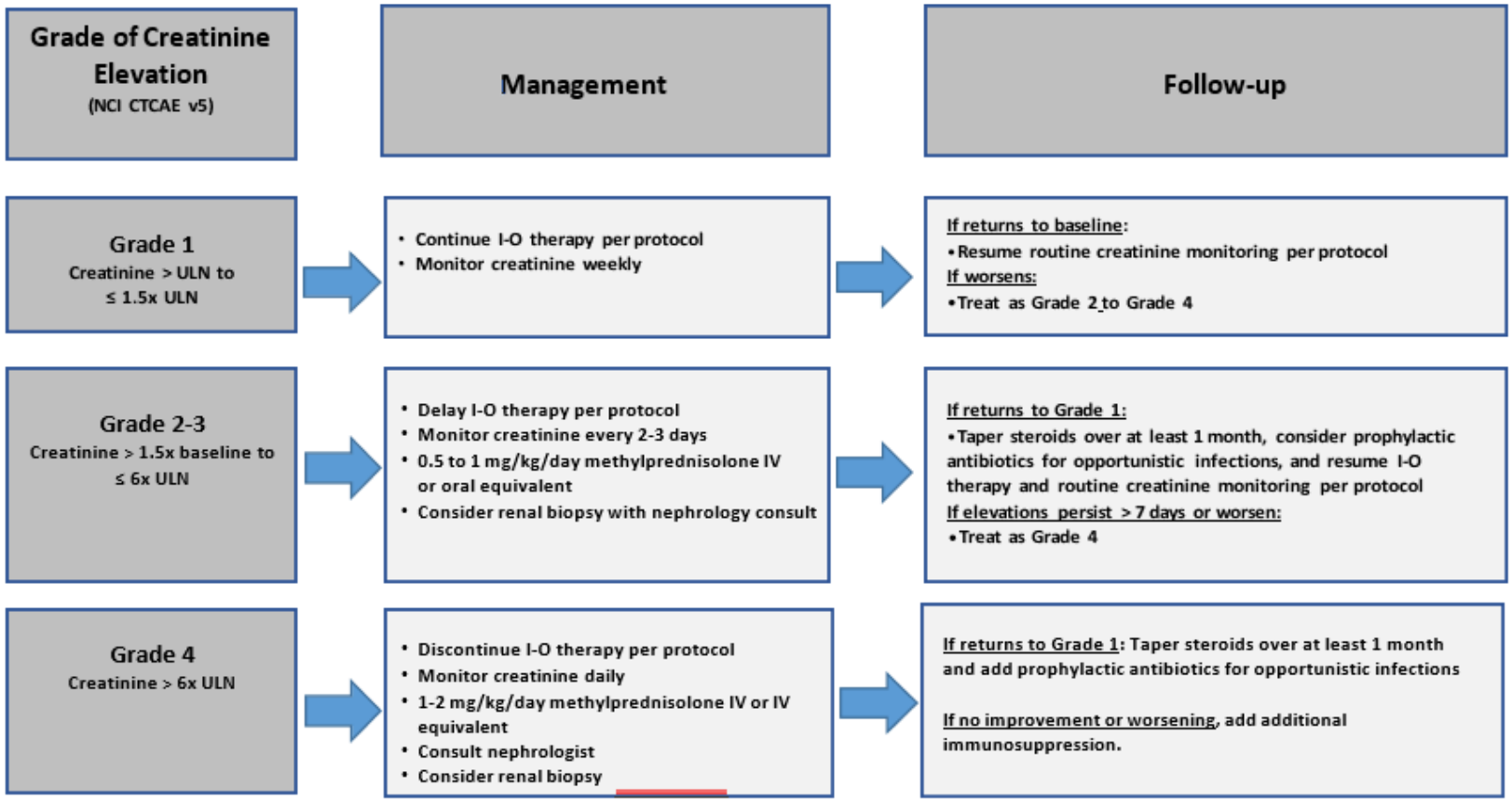
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after 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

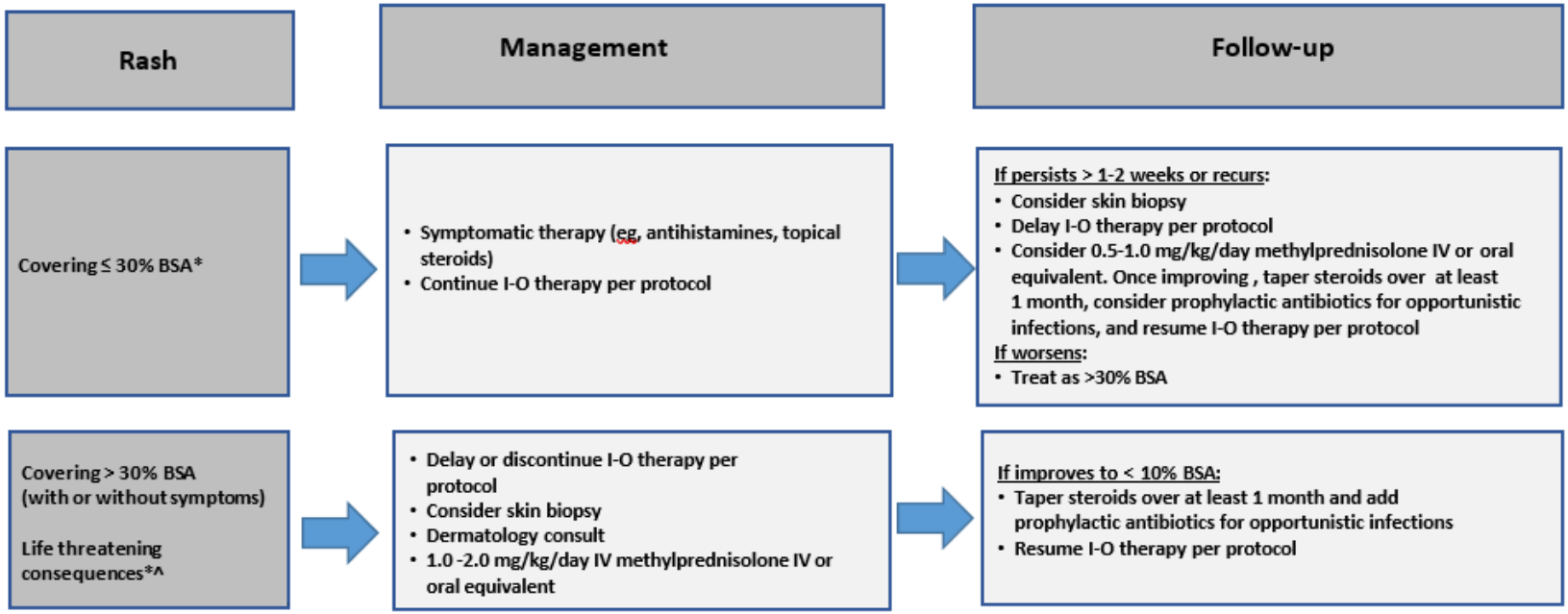
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Skin Adverse Event Management Algorithm

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



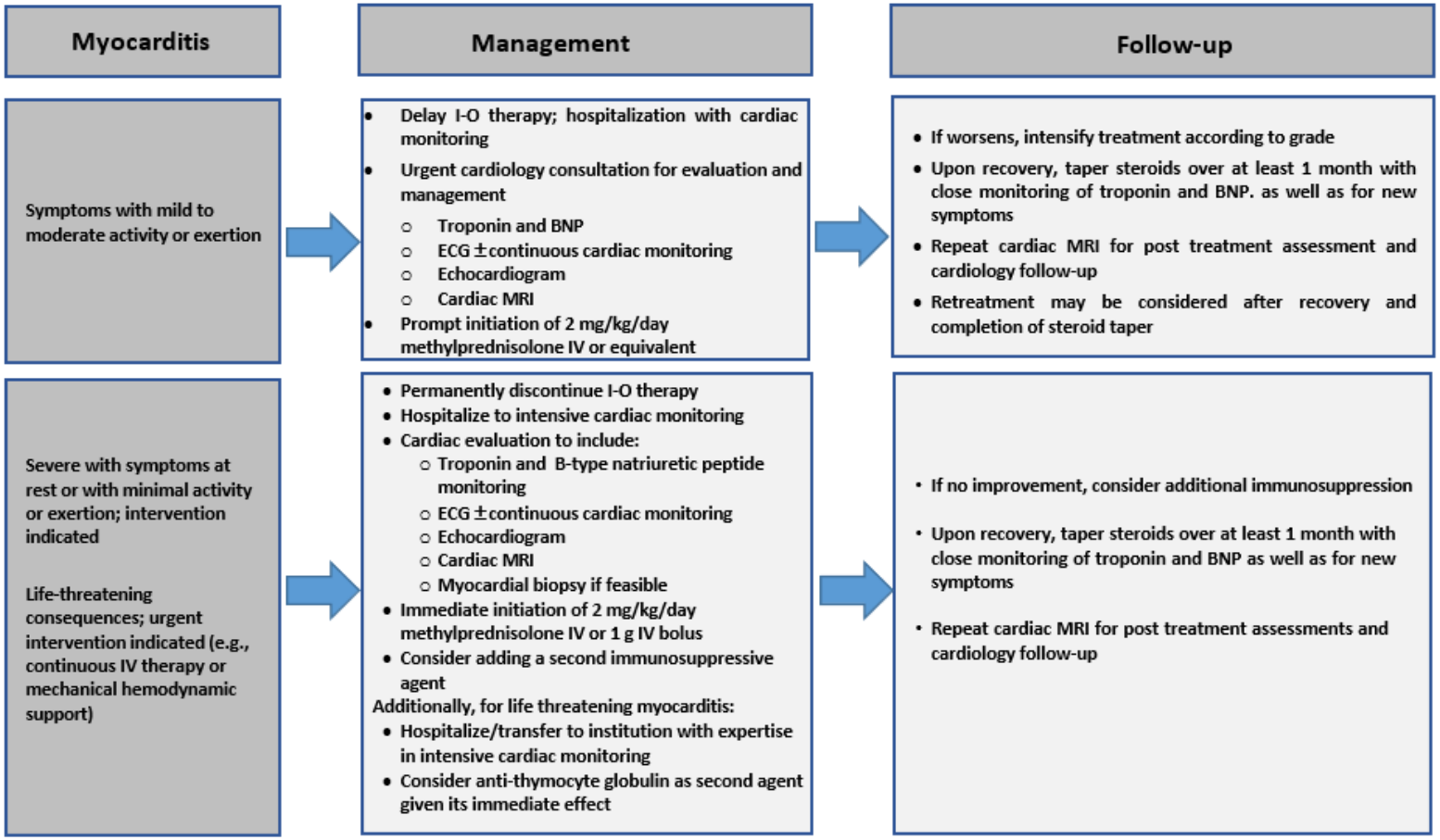
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Myocarditis 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 (eg, prednisone) at start of tapering or earlier, after 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.

APPENDIX III ePRO-CTCAE

1.0 Introduction

Electronic collection of patient-reported outcomes is preferred but not mandatory. Patients will need to use their own device (IOS or Android phone or tablet), **or** a device provided by their institution. Short term data will only appear on the patient's/site device until responses are completed. The patient data will import directly into the database once the patient clicks the submit button and will no longer be on the device.

Sites can use a site-specific tablet for different study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users.

Site staff access

Site users of ePRO and the Patient Cloud require the same access as those using Rave. Access to the trial in the Patient Cloud is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access the Patient Cloud via iMedidata, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in the Patient Cloud until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance).

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

2.0 Security

All data are encrypted on the device (128 bit on file +https transfer) and the app requires a user to have a username and password. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.
The data will only reside on the device for a short period of time. Once the user clicks "submit," the data is securely transferred over https between the device and internal relay. No identifying information is stored in iMedidata (only email address is stored).
The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and sponsors in the Patient Cloud Relay.

The ePRO application is Part 11 compliant and acts as a gateway between device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

3.0 CRP Training for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud for CRAs.

4.0 Checklist for activities prior to consenting a patient

- Site staff must have already completed required eLearning for the Patient Cloud application. See last bullet with hyperlink to training video library. See Section 1.0 of this Appendix for instructions on site staff access.
- Accept study invitation at iMedidata.com

Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

- Verify the IOS or Android operating system is using the most current version
- Verify Patient Cloud app is using the most current version
- Refer to https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html to review Quick reference guides

5.0 Instructions for ePRO patient registration

Please visit the Medidata Learning Tool for additional screen shots and video tutorials on how to register participants to the study.

i. The patient registration process starts in iMedidata. Begin by clicking on the Patient Cloud Registration link for this study.
ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now the first patient can be registered. (Please note that the patient must have already been registered in OPEN to generate a patient ID). Select subject ID (patient ID) and select a Country / Language from the drop down, (these are the only required data fields). The patient initials are optional, but may help in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The patient added will appear at the top of the table and will include the date the patient was added, the subject ID, initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which determines if the patient has registered. When the patient has registered the status will change from invited to registered.

6.0 Patient Users

To use the Patient Cloud app, patients will need to use their own device (IOS, Android phone or tablet) (for those who choose to use their own device). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Patient compliance: The patient data imports directly from her/his device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

Patient Instructions for Accessing the Patient Cloud App using their personal device

Downloading the Patient Cloud App:

Please ensure that the patient downloads the following app from the app store, and not Patient cloud ePRO (which is the legacy app).

If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. **If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section**.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e- mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:
1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the App Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:
1. A Google account is required for downloading the Patient Cloud app.
2. Tap the Play Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Registering on the App:
You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud app.

Note: You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.
1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.

5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App after registration:

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap Forgot Password, and follow the instructions provided.

Setting a PIN Code:

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap Forgot PIN and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password:

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms:

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

APPENDIX IV A091902 CABOZANTINIB MEDICATION DIARY

Cycle #_____

Patient Name _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each Cycle.
2. Your dose is _____ mg.
3. You will take ___ cabozantinib pills once each day on an empty stomach (do not eat **2 hours** before and **1 hour** after taking cabozantinib). Do not crush or chew.
4. Record the date, the number of pills you took, and what time you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. **Please bring your pill bottles and this form to your physician when you go for your next appointment.**
7. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled. Record missed dose(s) in the diary.
8. You should avoid grapefruit, grapefruit juice and Seville oranges while taking cabozantinib.
9. If vomiting occurs after taking cabozantinib, only take a replacement dose if vomiting occurs within 30 minutes of taking the capsule. If you have consistent vomiting please notify your study doctors. Record missed dose(s) in the diary.
10. Cabozantinib tablets should be stored at controlled room temperature.

Date	Day	# pills taken	Time taken	# pills missed	Comments
	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
	13				
	14				
	15				
	16				
	17				
	18				
	19				
	20				

	21				
	22				
	23				
	24				
	25				
	26				
	27				
	28				

Patient's Signature: _____ Date: _____

Staff Signature: _____ Date: _____

(To be completed by Staff)

Number of Pills Given:_____

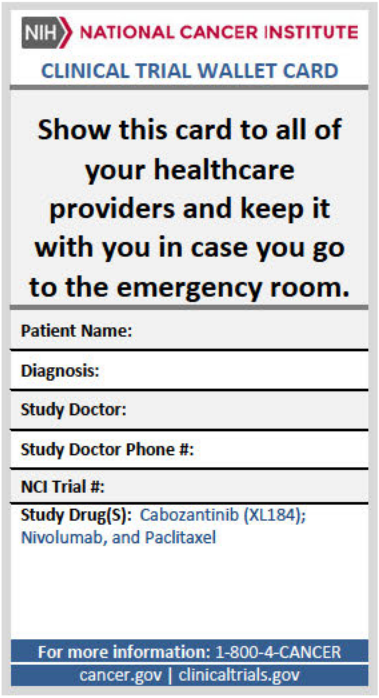
Total Daily Dose:_____

Pill Bottle(s) returned: Circle Yes or No

Number of Pills returned:_____

APPENDIX V: PATIENT CLINICAL TRIAL WALLET CARD

Note: The wallet card has fillable field that needs to be completed by the sites before providing the card to study patients at the enrollment.


NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S): Cabozantinib (XL184); Nivolumab, and Paclitaxel

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX VI ALLIANCE PATIENT THANK YOU EXAMPLE AND GUIDANCE

Guidance for Disseminating
Thank You Letters to Trial Participants

Trial Participant Thank You Letter

We ask that the physician use the template to prepare a letter thanking the participant for enrolling in this Alliance trial. The template is intended as a guide and can be downloaded from the study page on the Alliance website at www.AllianceNCTN.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by Alliance and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through.

We appreciate your help in this effort.

Sample Template

[PARTICIPANT NAME] [DATE] [PARTICIPANT ADDRESS]

Dear [PARTICIPANT SALUTATION],

Thank you for agreeing to take part in this important research study. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

There are many reasons why individuals choose to participate in a clinical trial. Sometimes it is because they want access to a specific medication or because they want to do whatever they can to help someone else with cancer. Whatever your reason for participating, you are making a contribution towards finding better treatments and ultimately eliminating this disease for future patients.

You will receive high quality care while participating in this clinical trial. My research staff and I will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other participants.

On behalf of [INSTITUTION] and the Alliance for Clinical Trials in Oncology, we thank you again for your participation in this clinical trial and look forward to partnering with you.

Sincerely, [PHYSICIAN NAME]

APPENDIX VII A091902 CORRELATIVE SCIENCE

A. Background

Angiosarcomas (AS) are classified according to the primary site of the tumor into cutaneous (scalp/face) versus visceral, and primary versus secondary (i.e. radiation induced) angiosarcoma. While a subset of predominantly cutaneous face/scalp angiosarcomas are characterized by high mutational burden and UV signature mutations, most other subtypes have low mutational burden [Painter]. Radiation associated angiosarcomas of the breast can occur following treatment for breast cancer, and may behave biologically more akin to cutaneous/UV signature associated angiosarcomas; in contrast primary breast angiosarcomas may be more akin to visceral angiosarcomas.

Immunotherapy, especially immune checkpoint inhibition (ICI) strategies, have emerged as promising lines of treatment for angiosarcoma. Combinations of chemotherapy with ICI, and combination of nivolumab (a PD-1 inhibitor) with paclitaxel, in particular, have previously been evaluated in clinical trials with encouraging results. In addition, studies evaluating other ICI in combination with standard chemotherapy have also demonstrated positive results in solid tumors. Hamacher R, et al. tested tumor tissue of 130 angiosarcoma cases and observed several cases of cutaneous angiosarcoma that showed a significant expression of PD-L1 between 10-20% on tumor cells, and infiltration of immune cells with the presence of CD8+ T cells. Several case reports of patients with cutaneous angiosarcoma treated by PD-1/PD-L1 therapy showed sustainable response. One of three angiosarcoma patients enrolled in the combination arm of the A091401 study of nivolumab with or without ipilimumab in patients with metastatic sarcoma not amenable to surgery (NCT02500797), sustained a confirmed response. A phase II study to assess the efficacy of a combination immunotherapy is currently enrolling patients with advanced sarcoma in the United States (NCT02815995). Florou et al. performed a retrospective analysis of seven angiosarcoma patients, mostly cutaneous angiosarcoma, treated with immune checkpoint inhibitors: four patients received pembrolizumab monotherapy, two received CTLA-4 inhibitor (AGEN1884) monotherapy and one patient received a combination of pembrolizumab and axitinib. Twelve weeks post-initiation of treatment, 5/7 patients (71%) had a PR of their lesions, 2 patients (29%) had progressive disease. At the time of the publication, 6/7 patients including all cutaneous angiosarcomas were still alive and only 3/7 patients (43%) had progressed (median 3.4 months). Importantly, none of the patients experienced any ≥ grade 2 toxicities. The one subject who received AGEN1884 additionally had mononuclear cells isolated from the peripheral blood on the first day of the first 4 cycles and had correlative analysis performed. Peripheral B cells and CD8+ T cells increased from 35.8 to 47.5% and 37.8 to 43.8%, respectively, above baseline with treatment whereas, CD4+ T cells and natural killer (NK) cells decreased.

Given these promising but still somewhat mixed results of immunotherapy, we propose here a comprehensive immunological characterization of A091902 patients, in the context of subtypes (cutaneous/visceral and primary/radiation-induced) as well as outcomes. The tumor-based assay (mIHC) will allow an analysis of tumor-infiltrating immune cells and mutational burden (including UV signature), respectively. The blood-based assays (CyTOF, TCRseq, ctDNA, and Olink) will characterize the peripheral immune system at the level of immune cells and their activation profile (CyTOF), T cell receptor usage (TCRseq), ctDNA profiles, and cytokines (Olink). ctDNA sequencing will definitively distinguish somatic from germline multations. Selected primary readouts of these assays are in the biomarker list below; but additional readouts will be tested on an exploratory basis. Together, these assays will provide data to test the hypotheses listed below.

B. Hypothesis and Objectives:

Primary Hypotheses:

1. UV signature in blood and CD8 T-cell density in tissue will be higher on average at baseline in taxane pre-treated patients (Arm 3) than taxane-naïve patients (Arm 1+2). (UV signature is defined by Chan et al. (2020)).
2. UV signature in blood and CD8 T-cell density in tissue will be higher on average at baseline in responders than non-responders, regardless of treatment arm.
3. Baseline levels of UV signature in blood and CD8 T-cell density in tissue interact with treatment arm in the prediction of responder/non-responder status.

These hypotheses will help distinguish the role of taxane pre-treatment as well as determining biomarkers of response globally or in response to nivolumab or cabozantinib specifically. We will exclude rapid off-study patients due to toxicity, but include rapid progressors.
cfDNA assay(s) will be used to evaluate UV signature. mIHC will be used to evaluate CD8 T-cell density.

Secondary Hypotheses (exploratory):

1. The biomarkers listed below will be higher on average at baseline in cutaneous than visceral patients, regardless of treatment arm.
2. Baseline levels of the biomarkers listed below interact with treatment arm in the prediction of cutaneous/visceral status.
3. The biomarkers listed below will be similar on average at baseline (+/-20%) in radiation associated breast angiosarcoma as in cutaneous angiosarcoma patients (pooling all data) based on (Thibodeau et al. 2018; Hadj-Hamou et al. 2012).
4. The biomarkers listed below will be similar on average at baseline (+/-20%) in primary breast angiosarcoma as in other non-cutaneous, non radiation associated breast angiosarcoma.

Biomarkers:

a) UV signature as defined by Chan et al. (2020), MSI status, and TMB (Assay: ctDNA)
b) CD8 T cell density, TLS, PD-L1, and other immune cells (Assay: mIHC)
c) Blood inflammatory signature (Assays: Olink)
d) Activated T cell and other immune cell subsets (Assay: CyTOF)

These hypotheses will allow exploration of patient subtypes (cutaneous/visceral and primary/radiation-induced) as determinants of biomarker profiles, but are considered exploratory due to the relatively small number of patients per subtype.

Additional exploratory analyses (subject to sample availability)

Our primary hypotheses focus on the discovery of prognostic biomarkers. Samples permitting, we will make the following exploratory comparisons, following the same template of the primary and secondary hypotheses, for individual arms:

1. Arm 3: Primary Hypothesis 2 will be analyzed in S1609 cohort 51 (visceral and cutaneous angiosarcoma) to look for concordance (i.e., to see if the same or similar biomarkers are significantly different in responders vs. non-responders). This analysis will help to further

validate our findings regarding biomarkers in angiosarcoma treated by treatment combination including nivolumab.

2. Arm 2 (Paclitaxel only arm): Primary Hypotheses 2 will be explored for responders vs. non-responders to look for potential biomarkers predictive of response to paclitaxel chemotherapy.
3. Arms 1 and 3: Primary Hypotheses 1 and 3 will be explored comparing the subset of Arm 1 (paclitaxel/nivo) [visceral non-scalp/face + primary but not radiation-associated breast angiosarcoma] vs. same population on Arm 3 (cabo/nivo) to explore potential biomarkers suggestive of response specific to cabo/nivo (or at least cabo) in responders.
4. Arm 1, 2, 3: All other biomarkers from the CIMAC assays will be tested according to Primary Hypotheses 1 and 2, on an exploratory basis. These analyses will be relevant in regard to the cross-trial analyses we perform on all CIMAC trials dataset.

C. Biomarkers table

Priority	**Biomarker Name**	**Assay**	**Use in the Trial** (Integral, Integrated, or Exploratory) **AND Purpose**	**Specimens Tested**	**Collection Time Points**	**Assay Lab**
Tissue-based Biomarkers						
1	In situ Immuno-profiling	**mIHC**	• Exploratory • To determine and to integrate tumor microarchitecture and spatial immune changes in TME	5x 4-6 µm unstained tissue slides	• Baseline	CIMAC
Blood-based Biomarkers						
1	Peripheral blood Immunophenotyping	**CyTOF**	• Exploratory • To identify biomarkers of response and immune network	PBMCs from ACD tubes	• Baseline • Cycle 4 Day 1 • Progression	CIMAC
2	TCR clonality	**TCRseq**	• Exploratory • To identify tumor-specific T cell alteration	PBMCs from ACD tubes	• Baseline • Cycle 4 Day 1 • Progression	Adaptive through CIMAC
3	Soluble Biomarker Analysis	**Olink**	• Exploratory • To evaluate if plasma proteins can be biomarkers for AS	Plasma from EDTA tubes	• Baseline • Cycle 4 Day 1 • Progression	CIMAC
4	Germline Genome Comparison	**WES germline for cfDNA sequencing**	• Exploratory • To compare to ctDNA sequencing	Buffy coat from Streck tube	• Baseline	The Broad Institute through CIMAC

Priority	Biomarker Name	Assay	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Assay Lab
5	Cell free circulating tumor DNA	**cfDNA**	• Exploratory • To determine tumor mutation profile and correlate baseline ctDNA mutations with treatment response; • To correlate changes in ctDNA variant allele frequencies with responses. • To compare to response as assessed by CT scans	Plasma from Streck tubes	• Baseline • Cycle 4 Day 1 • Progression	The Broad Institute through CIMAC

D. Materials and Methods

Exploratory CIMAC biomarker: UV signature and Tumor Mutational Burden (TMB)

Rationale for use in trial: This assay will allow to correlate baseline ctDNA mutations with treatment response, and correlate changes in ctDNA variant allele frequencies with responses. To monitor changes in tumor burden and compare against response and tumor size as assessed by serial CT scans, revealing new insights into tumor growth dynamics. The Broad Institute has a PanCan targeted seq panel that accepts cfDNA libraries as input. This may be able to provide UV and TMB signatures depending on the tumor fraction, sensitivity and duplex depth achieved by the sample. Another process for assessing mutation signatures from cfDNA that may be an option is their new CODEC product. https://www.nature.com/articles/s41588-023-01376-0 Ultra-low-pass whole genome sequencing (ULP WGS) and whole-exome sequencing (cfDNA WES) will also be considered as cfDNA assays.

Assay: cfDNA (Streck tubes)

Exploratory CIMAC biomarker(s): CD8 T cell density, Densities of other immune cells, Tertiary Lymphoid Structure (TLS) presence, and PD-L1 expression by mIHC.

Rationale for use in trial: Multiplexed ImmunoHistoChemistry (mIHC) will be used to identify biomarkers of response within the tumor microenvironment (TME) in baseline unstained tissue slides. Our primary aim is to profile tumor-infiltrating immune cells, including the CD8 T cells. We predict that infiltrating CD8 T cells will be associated with response, and may be higher in cutaneous and radiation-induced subtypes of angiosarcoma. This assay will also assess the presence of TLS and level of expression of PD-L1. Both biomarkers are expected to be correlated with the clinical response.

Assay: mIHC

Exploratory CIMAC biomarker(s): Immune activation by CyTOF

Rationale for use in trial: Mass cytometry, or CyTOF, enables a high-parameter single-cell phenotyping of blood immune cells. Systemic immune cell activation or phenotypic changes may be predictive markers of immunotherapy response, either at baseline or early on therapy. These cellular phenotypes may also be altered between subtypes of angiosarcoma.

Assay: CyTOF

Exploratory CIMAC biomarker(s): TCR clonality in PBMC

Rationale for use in trial: T-cell receptor (TCR) clonality, diversity, and density will be evaluated in blood using ImmunoSEQ (Adaptive Biotechnologies). Peripheral TCR clonality, especially changes in clonality early on therapy, may be a predictor of immunotherapy response. We expect to see early changes in clonality in responders to immunotherapy. There may also be differences, either at baseline or in response to therapy, between subtypes of angiosarcoma.

Assay: TCRseq

Exploratory CIMAC biomarker(s): Cytokine profiling by Olink

Rationale for use in trial: Circulating cytokine changes, e.g., release of soluble PD-1 and increases in chemokines like CCL9, have been associated with immunotherapy and/or immunotherapy response. Olink will measure 92 inflammation-associated cytokines, providing additional information to CyTOF on the systemic inflammatory state at baseline and on therapy. We expect to see differences based on angiosarcoma subtypes as well as responder status.

Assay: Olink

Exploratory CIMAC biomarker: Germline comparison

Rationale for use in trial: Germline DNA WES will provide the potential to identify natural genetic variants as opposed to somatic mutations in the tumor obtained by ctDNA assay. This will ensure that calculation of a UV signature, for example, is based on true somatic mutations in the tumor.

Assay: WES germline (control for cfDNA WES)

E. Statistical Considerations

All biomarkers will be summarized overall and by treatment arm as sample sizes, means with 95% confidence intervals, medians, and interquartile ranges for continuously-scaled biomarkers and as sample sizes and proportions with 95% confidence intervals for binary biomarkers.

Primary Hypotheses 1 and 2 will be tested using baseline values of biomarkers, with a one-sided two-sample t-test for unequal variances for continuously-scaled biomarkers and a one-sided risk difference Wald test for binary biomarkers.

Primary Hypothesis 3 will be tested using logistic regression where the outcome will be responder/non-responder status and the candidate predictors will be 1) baseline levels of the biomarker (dichotomized at the median), 2) treatment arm (all three arms), and 3) their interaction.

Primary Hypotheses:

1. UV signature as defined by Chan et al. (2020) and CD8 T-cell density will be higher on average at baseline in taxane pre-treated patients (Arm 3) than taxane-naïve patients (Arm 1+2).
2. UV signature and CD8 T-cell density will be higher on average at baseline in responders than non-responders, regardless of treatment arm.
3. Baseline levels of UV signature and CD8 T-cell density interact with treatment arm in the prediction of responder/non-responder status.

Sample size / Power calculation for key biomarkers:

Power calculations were performed assuming a Type I error rate of 2.5% because there are two co-primary outcomes.

- **For Primary Hypothesis 1 for CD8 T-cell density, sample sizes are:**
    - Arm 1: 23 patients
    - Arm 2: 23 patients
    - Arm 3: 18 patients

Preliminary estimates for neither the mean difference nor the within-group standard deviation are available; however, we can make a statement about statistical power given the relative sizes of these two parameters expressed as their ratio: effect size = difference in means / within-group standard deviation (Cohen 1988). For reference, Cohen's "large" effect size is ±0.8 (e.g., a mean difference of 16 cells/mm^2 with a within-group standard deviation of 20 cells/mm^2).. Approximately 80% statistical power obtains at an effect size of -0.81.

- **For Primary Hypothesis 1 for UV signature, sample sizes are:**
    - Arm 1: 22 patients
    - Arm 2: 21 patients
    - Arm 3: 18 patients

  Assuming that the proportion with UV signature will be approximately 0.2 in the taxane pretreated arm (Arm 3), statistical power will be approximately 72% for a difference in proportions of -0.19 between groups.

- **For Primary Hypothesis 2 for CD8 T-cell density, sample sizes are:**
    - Responders: 29 patients
    - Non-responders: 35 patients

  Approximately 80% statistical power obtains for an effect size of -0.72.

- **For Primary Hypothesis 2 for UV signature, sample sizes:**
    - Responders: 26 patients
    - Non-responders: 35 patients

  Assuming that the proportion of responders with UV signature is 0.4, statistical power is approximately 82% for a difference in UV-signature proportions between responders and non-responders of -0.31.

- **For the logistic regression analysis of Primary Hypothesis 3, we conservatively used a sample size per arm (for Streck tubes) as follows:**
    - Arm 1: 22 patients
    - Arm 2: 21 patients
    - Arm 3: 18 patients

Assuming odds ratios of 2, 1.08, and 2.19, for the main effects of the baseline biomarker, Arm 2, and Arm 3, respectively, and assuming a multiple correlation of 0.75 between main effects and interaction

term, statistical power will be approximately 80% for an interaction odds ratio of 2 for Arm 2 and approximately 80% for an interaction odds ratio of 2.2 for Arm 3. All power analyses were conducted using the power procedure in SAS® (SAS Institute, Cary, NC, USA).

Brief description of how the data will be analyzed for the exploratory biomarkers:

Secondary hypotheses:

1. The biomarkers listed below will be higher on average at baseline in cutaneous than visceral patients, regardless of treatment arm.
2. Baseline levels of the biomarkers listed below interact with treatment arm in the prediction of cutaneous/visceral status.
3. The biomarkers listed below will be similar on average at baseline (+/-20%) in radiation associated breast angiosarcoma as in cutaneous angiosarcoma patients (pooling all data) based on (Thibodeau et al. 2018; Hadj-Hamou et al. 2012).
4. The biomarkers listed below will be similar on average at baseline (+/-20%) in primary breast angiosarcoma as in other non-cutaneous, non radiation associated breast angiosarcoma.

- For Secondary Hypothesis 1, baseline levels of biomarkers will be employed, with one-sided two-sample t-tests for unequal variances used for continuously-scaled biomarkers and one-sided risk difference Wald tests used for binary biomarkers.
- For Secondary Hypothesis 2, logistic regression will be employed with cutaneous vs. visceral status as the outcome and 1) baseline levels of the biomarker (dichotomized at the median), 2) treatment (all three arms), and 3) their interaction as candidate predictors.
- The third and fourth Secondary Hypotheses will be limited to continuously-scaled baseline biomarkers. For these two hypotheses, equivalence testing will be performed (TOST), where equivalence will be defined as a mean ratio between 0.8 and 1.2.
- Specific Analyses per arm 1 through 4 will employ t-tests, risk difference Wald tests, and logistic regression as per the Primary Hypotheses as appropriate. For the Olink assay, we will employ quantile regression, as a distribution-free method. For Specific Analysis 4, across all exploratory biomarkers within an assay type (e.g., CyTOF), p-values will be adjusted (Benjamini et al. 2006, Kim and van de Wiel 2008) to control the false discovery rate at 5%.

Throughout all analyses (primary, secondary (exploratory), additional), $p < 0.05$ (adjusted, for Specifics Analysis 4) will be declared to be statistically significant.

Integrative analyses will be performed using cooperative learning (Ding et al. 2022).

F. References

1. Painter CA, Jain E, Tomson BN, et al. The angiosarcoma project: Enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. Nat Med. 2020;26(2):181. doi: 10.1038/s41591-019-0749-z.
2. Hamacher R, Kampfe D, Reuter-Jessen K, et al. Dramatic response of a PD-L1-positive advanced angiosarcoma of the scalp to pembrolizumab. JCO Precis Oncol. 2018;2:1–7. doi: 10.1200/PO.17.00107.

3. Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: A case series of seven patients from a single institution. j immunotherapy cancer. 2019;7(1). doi: 10.1186/s40425-019-0689-7.
4. Chan JY, Lim JQ, Yeong J, et al. Multiomic analysis and immunoprofiling reveal distinct subtypes of human angiosarcoma. J Clin Invest. 2020;130(11):5833–5846. doi: 10.1172/JCI139080.
5. Thibodeau BJ, Lavergne V, Dekhne N, et al. Mutational landscape of radiation-associated angiosarcoma of the breast. Oncotarget. 2018;9(11):10042–10053. doi: 10.18632/oncotarget.24273.
6. Hadj-Hamou N, Lae M, Almeida A, et al. A transcriptome signature of endothelial lymphatic cells coexists with the chronic oxidative stress signature in radiation-induced post-radiotherapy breast angiosarcomas. Carcinogenesis. 2012;33(7):1399–1405. doi: 10.1093/carcin/bgs155.
7. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, N.J.: L. Erlbaum Associates; 1988:567. http://www.loc.gov/catdir/enhancements/fy0731/88012110-d.html.
8. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. Biometrika. 2006;93(3):491–507. http://www.jstor.org/stable/20441303.
9. Kim KI, van de Wiel MA. Effects of dependence in high-dimensional multiple testing problems. BMC Bioinformatics. 2008;9:114–114. doi: 10.1186/1471-2105-9-114.
10. Ding DY, Li S, Narasimhan B, Tibshirani R. Cooperative learning for multiview analysis. Proc Natl Acad Sci U S A. 2022;119(38):e2202113119. doi: 10.1073/pnas.2202113119.