April 4, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #4 to EA5152, *A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC.*

This addendum is in response to Dr. John Wright's March 29, 2019 Request for Rapid Amendment for cabozantinib.

Please replace your current copy of the protocol and Informed Consent document (if ICD changed) with this (these) updated version(s). We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

An expedited review by the IRB can be considered for this amendment. However, please consult your local IRB's standard operating procedures, since their requirements may differ and require a full board review. It is the decision of the local IRB whether or not subjects are to be re-consented.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

The following are ECOG-ACRIN's responses to CTEP review comments from the "Review of Amendment #03 of Protocol # EA5152", dated August 30, 2018. Please note that the Principal Investigator's comments appear in bold below.

I. Recommendations:

#	Section	Comments
1.	Protocol: 8.1.5	Information about the permitted temperature excursion is valuable to the sites. Strongly recommend to updating it in your next amendment request. **"Storage:** Store intact bottles at controlled room temperature 20^0 C to 25^0C (68^0 F to 77^0 F); temperature excursions are permitted between 15^0 C and 30^0 C (59^0 F to 86^0 F) [see USP Controlled Room Temperature].

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#	Section	Comments
		If a storage temperature excursion is identified, promptly return XL184 (Cabozantinib) to 20^0 to 25^0C (68^0 to 77^0 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." **PI Response: This change has been made.**
2.	Protocol: 8.2.6	Replace current section with the following: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP so as not to exceed a total infusion volume of ~~120~~ **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. **PI Response: This change has been made.**
3.	Protocol: 8	In the first paragraph, change the following sentence as indicated: The responsible investigator 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**, ~~Curriculum Vitae, Supplemental Investigator Data Form (IDF),~~ and Financial Disclosure Form (FDF). **PI Response: This change has been made.**
4.	Protocol: 8	Change the third paragraph as indicated: ~~Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can s~~Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (~~https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx~~). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management. **PI Response: This change has been made.**

The following are ECOG-ACRIN's responses to CTEP review comments from the "Review of Amendment #02 of Protocol # EA5152", dated July 13, 2018. Please note that the Principal Investigator's comments appear in bold below.

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
5.	General	No further details of the analysis nor statistical plan are provided. No early stopping point is noted. These must all be provided prior to possible approval. These will also require statistical assessment. Therefore these changes cannot be approved currently. **PI Response: Thank you for the suggestion. Since the study is suspended and is likely to be terminated soon, due to slow accrual, further design changes are no longer being implemented.**

#	Section	Comments
6.	General	Please provide the specific reasons for doing the comparative imaging at the indicated timepoints per the published literature. **PI Response: Thank you for the suggestion. Since the study is suspended and is likely to be terminated soon, due to slow accrual, further design changes are no longer being implemented.**
7.	Protocol: 9.2	Discusses study endpoints but not in detail. Statistical considerations in section 9 will have to be assessed by others. In particular anything that would relate to the exploratory imaging study. **PI Response: Thank you for the suggestion. Since the study is suspended and is likely to be terminated soon, due to slow accrual, further design changes are no longer being implemented.**

II. Comments Requiring a Response – Administrative & Editorial Issues:

#	Section	Comments
8.	Protocol: 8.1.5	The drug storage has been updated to include permitted temperature excursion. Please update in your next amendment request. **"Storage:** Store intact bottles at controlled room temperature 20^0 C to 25^0C (68^0 F to 77^0 F); temperature excursions are permitted between 15^0 C and 30^0 C (59^0 F to 86^0 F) [see USP Controlled Room Temperature]. If a storage temperature excursion is identified, promptly return XL184 (Cabozantinib) to 20^0 to 25^0C (68^0 to 77^0 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." **PI Response: This change has been made.**
9.	Protocol: 8	Replace "Useful Links and Contacts" with the following: • CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/ • NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov • PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm • PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP • 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) **PI Response: This change has been made.**

#	Section	Comments
10.	ICF: "What possible risks can I expect from taking part in this study?"	What are the risks? Add Group C to the possible side effects of cabozantinib table, or remove all references to study groups. **PI Response: This change has been made.**

The following revisions to EA5152 protocol have been made in this addendum:

	Section	Change
1.	Global	Various minor administrative edits made throughout.
2.	Cover Page	Updated version date.
3.	3.1.1	Revised language for eligibility criteria clarification.
4.	5.2	Revised language for clarification of adverse event reporting.
5.	5.2.2	Added section for clarification of adverse event reporting.
6.	5.2.3	Added section for clarification of adverse event reporting.
7.	5.3.1	Updated CAEPR to version 2.4, December 17, 2018.
8.	5.4.14	Removed grade 4 fatigue as it does not exist in CTCAE.
9.	6.1.4.4	Updated remark in table to be consistent with section 6.1.4.1.
10.	7.1	Added language to footnote 4 for screening TSH and reflex free T4.
11.	8	Revised language per CTEP recommendations. Updated useful links and contacts information.
12.	8.1.5	Updated storage information for cabozantinib.
13.	8.2.4	Added description section for nivolumab.
14.	8.2.5	Updated storage information for nivolumab.
15.	8.2.7	Updated preparation information for nivolumab.
16.	8.2.8	Updated route of administration information for nivolumab.
17.	8.2.10	Updated availability information for nivolumab.
18.	8.3.4	Added description section for ipilimumab.
19.	8.3.7	Updated preparation information for ipilimumab.
20.	8.3.8	Updated route and method of administration information for ipilimumab.
21.	8.3.9	Added availability information for ipilimumuab.
22.	8.3.11	Updated nursing/patient implications information for ipilimumab.
23.	Appendix VI	Updated language of pregnancy reporting to be more consistent with current version of template.
24.	Appendix VIII	Removed CTCAE incorrect version number.

The following revisions to EA5152 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated version date.
2.	"What possible risks can I expect from taking part in this study?"	Added group C to heading for tables describing "possible side effects of cabozantinib." Updated cabozantinib risk profile per CAEPR version 2.4, December 17, 2018.

If you have any questions regarding this addendum, please contact Elanna Radomyshelsky at eradomyshelsky@ecog-acrin.org or 617-632-3610.

We request review and approval of this addendum to EA5152 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

CC: Joel Neal, MD, PhD
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ECOG-ACRIN
cancer research group
Reshaping the future of patient care

EA5152

A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC

STUDY CHAIR: Joel Neal, M.D., Ph.D.
STUDY CO-CHAIR: Heather Wakelee, M.D.
STUDY STATISTICIAN: Suzanne Dahlberg, Ph.D.
IMAGING STATISTICAN Zheng Zhang, Ph.D.
THORACIC COMMITTEE CHAIR: Suresh Ramalingam, M.D.
PATHOLOGY CO-CHAIR: Seena Aisner, M.D.
IMAGING CO-CHAIR Sharyn Katz, M.D
BIOLOGY CO-CHAIR: Christine M. Lovly, MD, Ph.D.

Version Date: April 4, 2019

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

US Sites Only

ACTIVATION DATE

March 1, 2018

Addendum #1
Addendum #2
Addendum #3
Addendum #4

NCTN GROUP STUDY CHAMPIONS

ALLIANCE: Muhammad Furqan, MD

Agents	IND#	NSC#	Supply
XL184 (Cabozantinib)		761968	DCTD
BMS-936558 (Nivolumab, MDX-1106)		748726	DCTD
Ipilimumab (MDX-010)		732442	DCTD

Table of Contents

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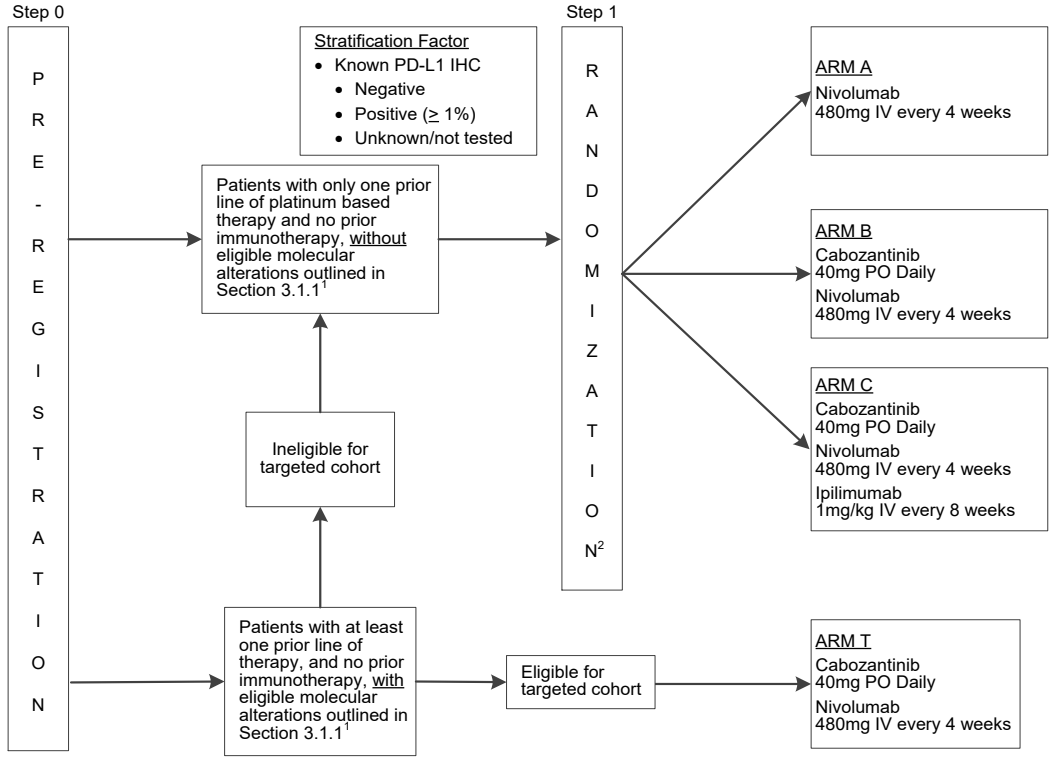
Rev. Add2

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**	**For image submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.	All CT and FDG-PET/CT imaging data obtained for patients participating in this clinical trial at baseline and through the first 3 follow-up imaging time points will be de-identified and uploaded from the study site to the ACR Imaging Core Laboratory within 48 hrs. of completion using TRIAD software. See the section “Image Submission for Central Review” in this protocol for further information. For questions regarding TRIAD installation, please contact the TRIAD helpdesk at TRIAD-Support@acr.org or https://triadhelp.acr.org/clinicaltrials
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members’ website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.			
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.			
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.			
The CTSU Web site is located at https://www.ctsu.org			

Rev. Add1

Schema



N = 169
Cycle = 4 weeks

1. Tumors must be known to be negative for EGFR or ALK mutations for patients with or without eligible molecular alterations. Patients with eligible molecular alterations (MET mutation, MET amplification, ROS1 rearrangement, RET rearrangement) must submit testing results per Section 4.2.4.
2. 1:1:1 Randomization across Arms A-C.

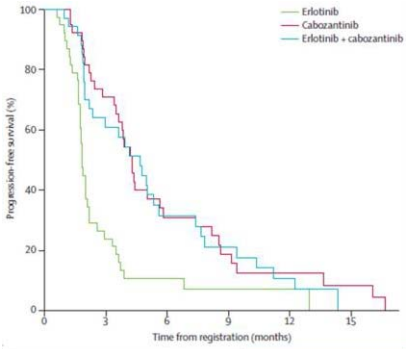
1. Introduction

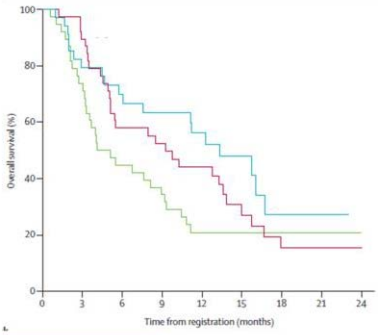
1.1 Background and antitumor effects of cabozantinib, nivolumab, and ipilimumab in NSCLC

Lung cancer remains the leading cause of cancer-related deaths in the United States, estimated to be responsible for over 160,000 deaths, and worldwide killing more than 1.3 million people annually.[1, 2] Non-small cell lung cancer (NSCLC) comprises 87% of all lung cancers. Despite many available treatment options, metastatic non-small cell lung cancer remains an incurable disease. First-line chemotherapy with a platinum-based doublet for advanced NSCLC has a response rate of only approximately 20% and a median overall survival of 8-10 months.[3] Second-line chemotherapeutic agents such as docetaxel and pemetrexed confer response rates of approximately 10% and progression-free survival times of approximately 3 months.[4] The majority of patients with NSCLC receive multiple lines of therapy, including cytotoxic chemotherapy, targeted small molecule tyrosine kinase in selected patients, and increasingly immunotherapy with anti-PD-1 drugs.

Activity of Cabozantinib in NSCLC

Cabozantinib has demonstrated activity in patients with previously treated NSCLC. Recently, the ECOG-ACRIN group studied the use of cabozantinib, an oral small molecule inhibitor of MET, RET and VEGFR2, in previously treated patients with EGFR wild type NSCLC. Compared with the erlotinib control group, treatment with cabozantinib led to clinically relevant improvements in progression-free and overall survival.[6] In this study, 125 patients were randomized between erlotinib (E), cabozantinib (C), and the combination (EC). The study met its primary endpoints, demonstrating an improvement in progression-free survival for both of the cabozantinib-containing arms versus erlotinib, and also showed an improvement in overall survival (Figure, below).





	Erlotinib (n=38)	Cabozantinib (n=38)	Erlotinib plus Cabozantinib (n=35)
Progression-free survival			
Deaths or disease progression	36 (95%)	34 (89%)	30 (86%)
Progression-free survival (months)	1·8 (1·7–2·2)	4·3 (3·6–7·4)	4·7 (2·4–7·4)
Overall survival			
Deaths	30 (79%)	29 (76%)	19 (54%)
Overall survival (months)	5·1 (3·3–9·3)	9·2 (5·1–15·0)	13·3 (7·6–NR)

Based on these results, cabozantinib appears to be an active drug in the treatment of NSCLC. Furthermore, MET IHC testing was performed and does not appear to be correlated with PFS benefit. We do not believe that the additional contribution of erlotinib in the combination is a meaningful difference that should be pursued, particularly as the indication for erlotinib in EGFR wild-type NSCLC has recently been rescinded by the FDA.[7]

The current FDA approved dose of nivolumab is 240 mg IV every 2 weeks (recently changed from 3 mg/kg IV every 2 weeks). However, an alternative dosing strategy of 480 mg IV every 4 weeks is being pursued for approval as well. In anticipation of this, we will plan to administer nivolumab at the every 4 week schedule on this trial.

Activity of Nivolumab in NSCLC

Nivolumab, a monoclonal anti-PD-1 immunotherapeutic checkpoint inhibitor, is FDA approved for the treatment of squamous and non-squamous NSCLC. Of the second line treatment options currently available, immunotherapies more often result in prolonged benefit for a population of patients, with about 20% of patients having >12 month PFS. There is excitement about this new platform of therapy, but there is an unmet need to find drugs which synergize immunologically to allow a larger proportion of patients to benefit long term from therapy.

Nivolumab is also active in the second line treatment of non-squamous NSCLC, as demonstrated in the trial Phase III, Randomized Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC) ".[8] In this trial, nivolumab had an overall survival benefit compared with docetaxel.

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4
HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015		
mPFS, mo	2.3	4.2
HR = 0.92 (95% CI: 0.77, 1.11); P = 0.3932		

The question of whether positive PD-L1 testing is necessary to predict benefit is currently an area of active investigation. With FDA approval of nivolumab, an optional "complementary diagnostic" of PD-L1 testing was also released. This diagnostic may help predict the likelihood of response, but is not required for treatment.

Activity of Nivolumab and Ipilimumab in NSCLC

Nivolumab and ipilimumab is an FDA approved combination therapy in melanoma, and is being extensively tested in NSCLC. In the CheckMate-012 study published in Lancet Oncology, four dose regimens were tested of nivolumab and ipilimumab.[9] In the two arms potentially suitable for moving forward, the treatment responses were as follows:

	Nivolumab 3 mg/kg q2 weeks + Ipilimumab 1 mg/kg q 6 weeks (n = 38)	Nivolumab 3 mg/kg q2 weeks + Ipilimumab 1 mg/kg q 12 weeks (n = 39)
Response rate	38%	47%
Median progression free survival	3.9 months	8.1 months
1 year overall survival	69%	Not calculated

These numbers suggest that this combination could compete with first line platinum based therapy in the treatment of NSCLC. Grade 3 or higher adverse events occurred in 28% of patients (5% GI, 5% endocrine, 5% hepatic, 3% pulmonary, and others not reported), suggesting that this combination does have more toxicity than nivolumab alone.

There are two large ongoing trials using nivolumab and ipilimumab. The CheckMate-568 trial (NCT02659059) is a single arm phase 2 study treating 340 patients with advanced NSCLC using first line nivolumab and ipilimumab. This study will identify whether efficacy of the combination is numerically better than historical controls with chemotherapy. Separately, the CheckMate 227 study (NCT02477826) is being conducted in 1980 patients with NSCLC assigning previously untreated patients to nivolumab, nivolumab plus ipilimumab, nivolumab plus platinum-doublet chemotherapy, or platinum doublet chemotherapy as the comparator arm in patients with advanced NSCLC. Therefore, there is justification for using the combination of cabozantinib, nivolumab, and ipilimumab as one of the investigational arms of this randomized 3-arm trial.

1.2 Combination Data

Based on these data, using ipilimumab either every 6 weeks or every 12 weeks is reasonable, and the every 12 week dosing was numerically even a bit better. Therefore, we have chosen to dose every 8 weeks for this protocol to match with intended radiographic assessment frequency. Safety of the combination of cabozantinib, nivolumab, and ipilimumab

The combination of nivolumab and cabozantinib is currently being tested for safety of dose in a phase I study, "Cabozantinib Plus Nivolumab (CaboNivo) Alone or in Combination With Ipilimumab (CaboNivoIpi) in Patients With Advanced/Metastatic Urothelial Carcinoma and Other Genitourinary Tumors" (NCT02496208). Preliminary results were presented in 2017, with a 30% overall response rate and toxicity information presented below.[10] The recommended phase II doses described were cabozantinib 40 mg + nivolumab 3 mg/kg every 3 weeks, and cabozantinib 40 mg + nivolumab 3 mg/kg every 3 weeks + ipilimumab 1mg/kg every 3 weeks (for 4 doses total). We anticipate additional information regarding safety of this combination will continue to become available as this trial is conducted.

Adverse Event	CaboNivo N=30			CaboNivoIpi N=18		
	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Any Grade N (%)	Grade 3 N (%)	Grade 4 |N (%)
Alanine Aminotransferase Increased	20 (67)	0	0	8 (44)	1(6)	0
Fatigue	19 (63)	2 (7)	0	13 (72)	2 (13)	0
Diarrhea	18 (60)	2 (7)	0	11 (61)	0	0
Hypothyroidism	17 (57)	0	0	5 (28)	0	0
Aspartate Aminotransferase Increased	15 (50)	0	0	4 (22)	0	0
Anorexia	14 (47)	0	0	11 (61)	1 (6)	0
Hoarseness	12 (40)	0	0	4(22)	0	0
Mucositis	12 (40)	0	0	6 (33)	0	0
Hypocalcemia	12 (40)	0	0	4 (22)	0	0
Hyponatremia	11 (37)	1 (3)	0	5(28)	2 (13)	0
Hypophosphatemia	11 (37)	4 (13)	0	8(44)	3 (17)	0
Palmar Plantar Erythrodysesthesia	11 (37)	0	0	5 (28)	0	0
Thrombocytopenia	11 (37)	1 (3)	1 (3)	6 (33)	0	0
Dysgeusia	9 (30)	0	0	8 (44)	0	0
Hypoalbuminemia	9 (30)	0	0	3(17)	0	0
Myalgia	9 (30)	0	0	3(17)	0	0
Nausea	9 (30)	0	0	7(39)	2(13)	0
Rash€	8 (27)	0	0	6(33)	1 (6)	0
Neutropenia	8 (27)	5 (17)	0	4(22)	0	0
Dry mouth	7 (23)	0	0	6(33)	0	0

Adverse Event	CaboNivo N=30			CaboNivolpi N=18		
	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)	Any Grade N (%)	Grade 3 N (%)	Grade 4 |N (%)
Dry skin	7 (23)	0	0	4 (22)	0	0
Vomiting	7 (23)	1 (3)	0	4 (22)	0	0
Hypertension	7 (23)	3 (10)	0	3(17)	3 (17)	0
Hypomagnesemia	7 (23)	0	0	2(11)	0	0
Proteinuria	7 (23)	1 (3)	0	2 (11)	0	0
Headache	7 (23)	0	0	0	0	0
Anemia	6 (20)	1 (3)	0	4(22)	0	0
Weight loss	6 (20)	0	0	5 (28)	0	0
Abdominal Pain	5 (17)	0	0	3(17)	0	0
Hypokalemia	5 (17)	0	0	4(22)	0	0
Lipase increase	5 (17)	2 (7)	2 (7)	8 (44)	2 (13)	1 (6)
Cough	3 (10)	0	0	5 (28)	0	0
Dehydration	3 (10)	2 (7)	0	3 (17)	0	0
Hyperthyroidism	3 (10)	1 (3)	0	2 (11)	0	0
Amylase increase	4 (13)	1 (3)	0	1(6)	0	0
Thromboembolic Event	1 (3)	1 (3)	0	0	0	0
Colitis	0	0	0	1 (6)	1 (6)	0
Aseptic meningitis	1 (3)	1 (3)	0	0	0	0

1.3 Preclinical and clinical rationale for the combination of cabozantinib, nivolumab, and ipilimumab in NSCLC

There is emerging preclinical evidence that the combination of nivolumab and cabozantinib might offer synergistic activity. In a publication from Jim Hodges' lab at the NCI, it was observed that cabozantinib changes both the tumor and the immune system in a mouse model to be more permissive for immune-mediated tumor killing, both in cell culture and in murine cell line grafts.[11] Mice were implanted with the MC38-CEA murine colon carcinoma cell line, which expresses VEGFR2 and MET. When a poxviral-based colon cancer vaccine was administered, the observed T cell tumor infiltration was modest, but cabozantinib significantly boosted this effect for CD3, CD4, and CD8-positive T cells. Additionally, cytokine production was markedly higher with the combination. In another report, these authors observe regression of tumors in 5/10 mice treated with the combination of vaccine and cabozantinib, but 0/10 mice with vaccine or cabozantinib alone:[12] In another study, Patnaik et al used a murine mouse endogenous prostate cancer model to study the effects of cabozantinib on the immune system. [13] Cabozantinib induced tumor regression via an inflammatory, not apoptotic, mechanism. There was evidence of potent infiltration of polymorphonuclear leukocytes and release of a neutrophil chemoattractant, HMGB1. Tumor regression could be blocked by dexamethasone or an anti-Ly6G antibody which depleted neutrophils. This appeared to be a MET-inhibitor independent effect. Finally, early clinical support for the combination of cabozantinib and anti-PD-1 therapy comes from a phase II trial in which

treatment with cabozantinib has been shown to upregulate PD-L1 expression on regulatory T cells in patients with metastatic urothelial carcinoma, which may confer sensitivity to anti-PD-1 therapy.[14] Together, these studies suggest that cabozantinib has a pro-inflammatory mechanism of action and support the use of cabozantinib in combination with a checkpoint inhibitor. Based on these pre-clinical observations, and the clinical efficacy of these two agents independently in NSCLC, we propose to conduct a randomized phase 2 study in advanced NSCLC.

Clinically, based on the observed activity of cabozantinib and nivolumab independently in the second and third line treatment of NSCLC, and the potential immunostimulatory activity of cabozantinib observed in the preclinical setting, we propose that combining these drugs together may lead to superior outcome compared with nivolumab alone. Furthermore, given the efficacy data leading to the FDA approval in melanoma[15, 16] and the promising phase 2 evidence for the combination of nivolumab and ipilimumab in NSCLC,[9] we propose also testing the safety and efficacy of cabozantinib/nivolumab/ipilimumab as well

1.4 Evidence for using cabozantinib as a targeted therapy in NSCLC

In addition to the activity against VEGFR2, cabozantinib is active as a MET inhibitor, ROS1 inhibitor, and RET inhibitor. MET exon 14 splice mutations comprise up to 3% of NSCLC, and are highly sensitive to the MET inhibitor crizotinib.[17-19] Reported confirmed response rates have been as high as 43%.[20] Additionally, they have been reported to be sensitive to cabozantinib.[18] Because cabozantinib is a type II MET inhibitor, which is still active after acquired resistance solvent front mutations develop, it may even work after resistance to crizotinib has developed.[21] One patient with CNS progression after crizotinib with a response to cabozantinib has been described.[22]

MET amplification is likely found in less than 1% of NSCLC, but these tumors are also highly sensitive to MET inhibitors even independently of the presence of MET exon 14 splice alterations.[23] It is reported that the highest level of MET amplification, characterized by a fluorescence in situ hybridization MET/CEP7 ratio of 5 or higher defines the "MET-amplified" group.[23]

RET gene rearrangements occur in about 1% of NSCLC. Responses to the RET inhibitor cabozantinib have been reported by many groups, with a response rate of 28% or higher.[24] [25]

Finally, ROS1-rearranged NSCLC, which is highly sensitive to the FDA approved drug crizotinib, also develops acquired resistance that may respond to cabozantinib.[26, 27]

A single arm phase II study ongoing examining the effect of single agent cabozantinib in many of these targeted patient populations is currently ongoing (NCT01639508). However, the combination of cabozantinib and nivolumab in this targeted population is novel and may exceed the response expected from either cabozantinib or nivolumab alone. Therefore, we propose an exploratory targeted therapy to test the response to the combination of these agents.

1.5 Cabozantinib (XL184) - Further information

Cabozantinib (XL184) is an inhibitor of multiple receptor tyrosine kinases (RTKs). It is provided as both capsules and tablets, but the two formulations are not

interchangeable. Cometriq® (cabozantinib capsules, 140 mg) was approved by the United States Food and Drug Administration (FDA) on 29 November 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). On 21 March 2014, cabozantinib capsules were approved by the European Commission for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. Cabometyx™ (cabozantinib tablets, 60 mg) was approved by FDA on 25 April 2016 for patients with advanced renal cell carcinoma (RCC) who have received prior anti angiogenic therapy and by the European Commission on 09 September 2016 for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF) targeted therapy.

The targets of cabozantinib include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET (hepatocyte growth factor [HGF] receptor), vascular endothelial growth factor receptor 2 (VEGFR2, also known as KDR), AXL, and RET. Other recognized targets of cabozantinib include ROS1, TRKA, TRKB, TYRO3, MER, two additional members of the VEGFR family (VEGFR1, VEGFR3), and the closely related RTKs KIT and FLT-3. In vivo pharmacodynamic activity of cabozantinib against MET, VEGFR2, AXL, and RET has been demonstrated in preclinical studies and has been associated with tumor growth inhibition and tumor regression. In preclinical studies, cabozantinib treatment has also been shown to inhibit tumor angiogenesis and tumor invasiveness and metastasis.

In nonclinical toxicology studies of cabozantinib in rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, adrenal, and reproductive tract tissues, and secondary changes were observed in bone and pancreas. Cabozantinib tested negative in bacterial and mammalian cell genotoxicity assays in vitro. In reproductive toxicity studies, cabozantinib was embryotoxic in rats, produced fetal soft tissue changes in rabbits, produced fetal external malformations in rats, and decreased fertility in male and female rats. The metabolite present at highest concentrations in humans administered cabozantinib, EXEL-1644, was negative in an in vitro bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats. In a 2 year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes. No clinical cases of pheochromocytoma have occurred to date. No carcinogenic signal has was observed in a rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks.

Nonclinical Development of XL184

In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes *et al*., 2009). In RIP-Tag2 transgenic mice, tumors treated with XL184 were smaller (P <0.05) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive (P <0.05) and had no liver metastases (Sennino *et al*., 2009). All mice treated with XL184 (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8)

reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days (You *et al*., 2011). Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg (Yakes *et al*., 2011). XL184 increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, XL184 disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors (P <0.001) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses (P <0.01), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, XL184 inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of XL184 was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang *et al*., 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 or vehicle daily (qd) for 7 weeks of treatment (Investigator's brochure, 2017). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 treated animals appeared mostly normal. Thus, XL184 treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of XL184 and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2017). XL184 produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of XL184. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of XL184 resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2016). Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met (Yakes *et al*., 2011). This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Toxicology

In rodents and non-rodents, histopathological changes associated with XL184 administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues (Investigator's Brochure, 2017). Histopathological changes present in the bone and pancreas were considered secondary to XL184 administration. Adverse effects following oral exposure to XL184 were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, XL184 administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg XL184 capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study (Investigator's Brochure, 2017). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184-treated rats or on cardiovascular function in XL184-treated dogs.

Summary of Clinical Trials

This document summarizes 17 clinical studies of cabozantinib for oncology indications including four Phase 1 studies, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 studies (a placebo controlled study in subjects with MTC, two active-controlled studies in subjects with CRPC, one ongoing open-label, active-controlled study in subjects with RCC, and one ongoing and enrolling double-blinded placebo-controlled study in subjects with hepatocellular carcinoma [HCC]), one ongoing and enrolling Phase 4 study in MTC, one ongoing maintenance "roll over" study, and one expanded access study. In addition, there are eleven clinical pharmacology studies; nine were conducted in healthy subjects alone, one study was conducted that included healthy subjects and subjects with renal impairment, and one study was conducted that included healthy subjects and subjects with hepatic impairment. In addition to these company-sponsored clinical studies, twenty-nine externally-sponsored studies (ESSs; previously referred to as investigator-sponsored trials [ISTs]) and seventeen National Cancer Institute (NCI)-Cancer Therapy Evaluation Program (CTEP) trials have enrolled subjects in oncology indications.

A pooled analysis of safety data in 2467 subjects with cancer treated with cabozantinib in company-sponsored single-agent studies (XL184 001, XL184 008, XL184 201, XL184 203, XL184 205, XL184 301, XL184 306, XL184 307,

XL184 308, and XL184-401) has been performed. For ongoing studies, serious adverse event (SAE) data are presented through February 28, 2017.

Clinical study protocols have expressed cabozantinib dose as either the malate salt weight or the freebase equivalent (FBE) weight. In this Investigator's Brochure, dose strengths are expressed as the FBE weight. For the dosage form, formulation, and dosage strengths used in a particular study, please refer to the study protocol.

Cabozantinib is administered as either capsules or tablets. In a bioequivalence study comparing capsules with tablets in healthy adult subjects (Study XL184-010), the geometric mean ratios for both AUC parameters (AUC0-t and AUC0-inf) comparing 140 mg cabozantinib doses of the tablet formulation with the capsule formulation were 108% (90% confidence interval [CI]%: 101, 117). The ratio of geometric means for Cmax (119%; 90% CI%: 107, 132) had a 90% CI upper bound that slightly exceeds the standard accepted limit of 125%. Therefore, bioequivalence of the cabozantinib capsule and tablet formulations cannot be concluded, and the two formulations are not interchangeable.

The single agent maximum tolerated dose (MTD) of the capsule in a daily dosing schedule based on 28 days of dosing in Study XL184-001 was determined to be 140 mg. The 140 mg capsule dose level was evaluated in placebo-controlled Phase 3 Study XL184-301 in subjects with MTC. Dose modifications (reductions or interruptions) occurred frequently in the cabozantinib arm of this study. Lower doses of cabozantinib have been explored in other indications. A tablet dose of 60 mg once daily (qd) was evaluated in two Phase 3 studies in prostate cancer, and is being evaluated in two ongoing Phase 3 studies, one in RCC and one in HCC. Ongoing double-blind Study XL184-401 compares the efficacy and safety of cabozantinib 140 mg qd (capsule formulation) with cabozantinib 60 mg qd (tablet formulation) in subjects with MTC. Common to all studies is the titration of the dose to individual patient tolerability.

Clinical Experience

As of February 29, 2016, 3447 patients have been studied in 28 completed or ongoing Exelixis-sponsored clinical trials with XL184 treatment. There are 17 clinical studies of cabozantinib for oncology indications including four Phase 1 studies, one Phase 1b/2 study, four Phase 2 studies, five Phase 3 studies (a placebo-controlled study in subjects with MTC, two active-controlled studies in subjects with castration-resistant prostate cancer [CRPC], one ongoing open-label, active-controlled study in subjects with RCC, and one ongoing and enrolling double-blinded placebo-controlled study in subjects with hepatocellular carcinoma [HCC]), one ongoing and enrolling Phase 4 study in MTC, one ongoing maintenance "roll-over" study, and one expanded access study

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2016). Safety and efficacy information, from the 2016 Investigator's Brochure, is summarized below.

Adverse Events

As of February 28, 2017, AE data are available for 3002 subjects who have been dosed with XL184 (2410 in single-agent studies and 592 in combination studies of XL184 with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2017). Data from the 2410 subjects who received single-agent XL184 show that the most frequently (> 20%) observed AEs regardless of causality

were diarrhea, fatigue, decreased appetite, nausea, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination XL184 studies. The most commonly reported SAEs that were assessed as related to study treatment with XL184 (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

Thirty-three (34) subjects with Grade 5 AEs had events assessed as related to the study treatment. The only related Grade 5 AEs that occurred more than once were pulmonary embolism (n=4), death (unspecified; n=3), hemorrhage (n=2), respiratory failure (n=2), and sudden death (n=2). (Investigator's Brochure, 2017).

Pharmacokinetics

Following oral administration of cabozantinib capsules or tablets, median time to maximum plasma concentrations (Tmax) for cabozantinib ranged from 2 to 5 h post-dose. The terminal half life (for predicting drug washout) was approximately 120 h. Repeat daily dosing of cabozantinib capsules at 140 mg for 19 days resulted in 4- to 5-fold higher mean cabozantinib accumulation (based on area under the plasma concentration-vs-time curve [AUC]) compared with a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Two population pharmacokinetics (PopPK) analyses have been conducted using cabozantinib clinical data. The first included data from subjects with MTC, glioblastoma (GB), and other solid tumors who received repeated oral daily dosing of cabozantinib capsules at 140 mg. From this analysis, the predicted effective half-life was approximately 55 h, the oral apparent volume of distribution (V/F) was approximately 349 L, and the oral apparent clearance (CL/F) at steadystate was estimated to be 4.4 L/h. The analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11% [<4% were Asian]). Cabozantinib pharmacokinetics (PK) was not affected by age (20-86 years).

A second PopPK analysis was conducted in subjects with RCC who received repeated oral daily cabozantinib tablet dosing at 60 mg (with protocol-permitted dose reductions to 40 mg and 20 mg) combined with healthy subjects who received a single oral cabozantinib tablet dose of 20, 40, or 60 mg. This analysis indicated that for a White male subject the predicted terminal plasma half-life of cabozantinib was approximately 99 h; the terminal phase volume of distribution (Vz) was approximately 319 L; and the CL/F at steady-state was estimated to be approximately 2.2 L/h. Female gender and Asian race were significant covariates on CL/F, and while the attributes were statistically significant, they were not deemed clinically meaningful given the magnitude of the effects. Further evaluation of the differences in the two PopPK analyses revealed that compared with other cancer subject groups (ie, RCC, castrationresistant prostate cancer [CRPC], GB), MTC subjects cleared cabozantinib faster and thus had lower dose-normalized steady-state plasma exposures. Several possible factors may

underlie the higher cabozantinib clearance observed in MTC subjects in the first PopPK analysis; however, an exact cause has yet to be identified.

Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Results from a PK study of cabozantinib in subjects with renal impairment indicated that the ratios of geometric least squares (LS) mean for maximum plasma concentration (Cmax) and AUCs (AUC from 0 h to the last sampling time point [AUC0-t] and AUC from 0 h to infinity [AUC0-inf]) were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. For subjects with moderate renal impairment, both Cmax and AUCs appeared to be similar when compared with subjects with normal renal function (differences: < 3% and < 7%, respectively). Results from a PK evaluation of cabozantinib in subjects with hepatic impairment indicated that exposure (AUC0-inf) to cabozantinib was increased by about 81% and 63% in subjects with mild and moderate hepatic impairment, respectively. There are no PK data in subjects with severe renal or hepatic impairment.

A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively, relative to fasted conditions in healthy subjects administered a single 140-mg oral cabozantinib capsule dose.

Cabozantinib is a substrate of cytochrome P450 (CYP)3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the cabozantinib N-oxide metabolite by > 80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib N-oxide metabolite formation (ie, a < 20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib N-oxide metabolite formation. In healthy subjects, cabozantinib plasma AUC0-inf was increased 38% with coadministration of the strong CYP3A4 inhibitor ketoconazole and decreased 77% with coadministration of the strong CYP3A4 inducer rifampin (rifampicin).

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsome (HLM) preparations. Concentration associated with 50% inhibition (IC50) values > 20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems. Cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily dosing for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (Cmax and AUC) in subjects with solid tumors.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (ie, 75-100% of CYP1A1 positive control β-naphthoflavone induction) but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Concomitant administration of proton pump inhibitor (PPI) esomeprazole resulted in no clinically relevant effect on cabozantinib plasma PK in healthy subjects.

Cabozantinib is an inhibitor (IC50 = 7.0 μM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. In addition, cabozantinib was shown to be a substrate of

drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay.

1.6 Nivolumab and ipilimumab – further information

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, 2016). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok et al., 2013).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2016). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2

results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphastase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment (Woo et al., 2012). Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube et al., 2012), renal (Thompson et al., 2004; Thompson et al., 2005; Thompson et al., 2006), esophageal (Ohigashi, et al. 2005), gastric (Wu et al., 2006), ovarian (Dong et al., 2003), pancreatic (Nomi, et al., 2007), lung (Zitvogel, et al., 2006), and other cancers (Investigator Brochure, 2016).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2016). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a Kd = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 2016). In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2016). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses (Sznol et al., 2013). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively (Brahmer et al., 2013). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year (Drake et al., 2013).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok et al., 2013). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi et al., 2013). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined (Topalian et al., 2012). Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group (Wolchok et al., 2013), grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these events.

Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count (Wolchok et al., 2013). With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon-γ (IFN- γ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4, YervoyTM) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells (Ipilimumab Investigator Brochure, 2017). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and inhibits its interaction with ligands on antigen-presenting cells (APCs). The proposed mechanism of action for ipilimumab's effects in subjects with melanoma is indirect, possibly through T-cell potentiation and mediation of antitumor immune responses.

Ipilimumab has been approved for the treatment of unresectable metastatic melanoma in over 40 countries including the United States (US, March 2011), the European Union (July 2011), and Australia (July 2011).

BMS and Medarex (acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing > 13,800 subjects in several cancer types in completed and ongoing studies, including a compassionate use program (Ipilimumab Investigator Brochure, 2017). The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

CTEP's clinical development of ipilimumab focuses on cervical, gastrointestinal, ovarian, prostate cancer, chronic lymphocytic leukemia, head and neck squamous cell carcinoma, solid tumors, Hodgkin and non-Hodgkin lymphomas, melanoma, and myelodysplastic syndrome.

While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for each of the single agents.

Preclinical data support the combinations of nivolumab and ipilimumab (Curran et al., 2010).

The combination of ipilimumab with nivolumab has been reported to result in improved responses in advanced melanoma marked by time to response, number of responses, depth and duration of responses, PFS, and OS compared to single agent ipilimumab (Wolchok et al., 2013).

For RCC results have been reported (Hammers et al., 2014).

The combination is being evaluated in other disease settings typically with 3mg/kg nivolumab and 1mg/kg ipilimumab q 3 weeks x 4 induction doses.

The rationale for the doses selected in this trial is outline in Section 1.2, above.

1.7 Imaging of therapy response to immune checkpoint inhibition

Therapy with immune checkpoint inhibitors can lead to unconventional tumor responses resulting from immune activation [90,91,92]. Radiologic pseudoprogression describes an unconventional imaging pattern of tumor response where tumors initially exhibit features of progression, including tumor enlargement and/or development of new lesions, with subsequent radiologic tumor response evident on serial imaging with sustained therapy [90]. Several new imaging response criteria have been proposed for measurement of tumor response in solid tumors undergoing immune checkpoint inhibitor therapy including the immune related response criteria (irRC) [90], an adaption of the irRC termed the uni-dimensional iRRC [93] and, most recently, the iRECIST criteria [94]. These immune criteria have been put forth with the goal of more accurately classifying unconventional tumor responses as non-progression. However, it is yet unclear if any of these new criteria present a benefit over the conventional Response Evaluation in Solid Tumor (RECIST) 1.1 [95] for use as an imaging endpoint in clinical trials of immune checkpoint inhibition in solid tumors. Here we propose an explorative correlative imaging aim to define tumor response assessed by RECIST1.1, unidimensional irRC and iRECIST, assessed by central review. The hypothesis for this imaging aim will be that significant differences exist in the calculation of best overall response and progression-free survival amount the examined tumor response criteria. Interpretation of the response data will be performed noting the bias in the availability patient imaging for analysis with immune criteria since only patients maintained on therapy beyond imaging evidence of progression (ie. clinically suspected of radiologic pseudoprogression) will have the required imaging data (subsequent re-imaging to confirm suspected progression). While this is a limitation to the interpretation to the immune criteria imaging response data, the data obtained is felt to be valuable in better understanding the application of these imaging criteria to clinical trials of immunotherapeutics.

Finally, this clinical trial utilizes a study site calculation of RECIST1.1 response for patients enrolled in this study. Typically these measurements are calculated by study personnel that are trained in RECIST1.1 measurement but are not radiologists. This strategy is employed in many clinical trials that do not include a central reading of imaging response. Here we will compare the RECIST1.1 calculations determined at the study sites to those generated by central review to determine if there are significant differences in the measurements obtained between these two imaging assessment approaches. The hypothesis will be that no significant difference exists between measurements of RECIST1.1 between study imaging site and central review.

1.8 Rationale for Tobacco Use Assessment

NOTE: Please refer to Appendix VIII for EAQ16T references.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis, [1-5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors [6,-11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist, [12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited.

Tobacco use following a cancer diagnosis compromises treatment outcomes but is not well understood. About 10% to 30% of cancer patients are smoking at the time of diagnosis, [1-4, 14, 1 5] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis [3, 16]. Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors, [9,11,17-21] and improve chances of survival [1,22-24]. Conversely, continuing to smoke may result in diminished QOL [1, 25, 26], treatment delays and increased treatment complications [2, 6–8, 22, 27–34].

Tobacco use following a cancer diagnosis may compromise patient reported outcomes. It is hypothesized that smoking may be used as a means of reducing symptom burden among cancer patients, which may be a barrier to smoking cessation. Relatedly, research has shown that cancer patients who are smoking experience more difficulty with physical and psychological symptom control, compared to nonsmokers [35–38]. Research is needed to examine how symptom levels differ, by tobacco use and exposure and how tobacco use changes may affect reported symptom burden.

National initiatives emphasize the importance of identifying tobacco use in cancer care settings. Smoking status was designated as a core objective in the 2010 federal government “Meaningful Use” electronic health record documentation [39, 40]. In 2013, the American Association for Cancer Research (AACR) released guidelines emphasizing the provision of tobacco cessation services to cancer patients [41]. The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers by their second oncology visit as a core quality indicator [42]. The National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives [43].

Integrated, evidence-based services are needed during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment be delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care [44]. This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued abstinence [1,45-48] effective interventions exist, [1,45-48] and many cancer patients who smoke want to quit smoking[45,46,49,50]. Little work has been done to explore the delivery and effectiveness of tobacco treatment among

racial/ethnic minority cancer patients who are at elevated risk of continued smoking [51-53].

Tobacco use is often not being assessed or intervened upon during cancer care. Recent surveys of oncologists and of clinical practices at comprehensive cancer centers and community oncology settings demonstrate that assessment of tobacco dependence is lacking [54-57]. During treatment, most cancer patients do not get assistance with smoking cessation support.58–60 Tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials [61]. No one has assessed cancer patients' reports of their oncology providers' assistance behaviors.

The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force developed the Cancer Patient Tobacco Use [1-4,13,14]. Questionnaire (C-TUQ). We propose that administering selected C-TUQ items to participants enrolling in 8 Phase II and Phase III ECOG ACRIN (EA) therapeutic trials will add value to parent trial research questions by advancing the field. Specifically, among patients with varied cancers (tobacco-related and non tobacco-related) and cancer treatments, we will administer C-TUQ questions at EA trial enrollment and 3 and 6 month follow-up.

We have the following aims:

1. Treatment toxicity: To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).
2. Symptom burden: To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.
3. Cessation patterns and treatment: To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.
4. Trial outcomes: To explore the effect of tobacco use and exposure on treatment duration and relative dose intensity, and on therapeutic benefit, of 8 selected EA trials.

The findings will advance the nascent field of tobacco use in the context of cancer care by: 1) longitudinal assessment of cigarette smoking, other forms of tobacco use and secondhand smoke exposure at trial enrollment and at 3 and 6 month follow-up; 2) increase knowledge about the effects of tobacco use and exposure on treatment toxicity, physical and psychological symptoms and 3) oncology provider delivery, and 4) patient's perceptions of stigma and utilization of behavioral and pharmacological treatment of tobacco dependence. Finally, the use of this assessment would provide a unique additional value to the hypothesis of this trial, by allowing investigation of previously unanswered questions about the effects of tobacco use and exposure on trial adherence and outcomes among patients with smoking-related and non-smoking related cancers.

2. Objectives

2.1 Primary Endpoint

2.1.1 The primary objective of this trial is to demonstrate whether combination therapy of nivolumab and cabozantinib, or of nivolumab and cabozantinib, and ipilimumab as compared to nivolumab alone, extends progression-free survival (PFS) for this patient population with non-squamous NSCLC.

2.2 Secondary Endpoints

2.2.1 To estimate the overall survival for each arm of the trial

2.2.2 To estimate the best overall response rate for each arm of the trial

2.2.3 To estimate the progression free survival of the targeted therapy arm of the trial

2.2.4 To describe the toxicity profile of monotherapy with nivolumab, and the combination of nivolumab and cabozantinib, and the combination of nivolumab and cabozantinib and ipilimumab, in this patient population with non-squamous NSCLC.

2.3 Correlative Endpoints

2.3.1 To adjust progression free survival for each arm based on PD-L1 tumor status

Rev. Add2

2.4 Imaging Endpoints

2.4.1 To describe time point tumor response assessment, overall best response and progression-free survival using the conventional RECIST1.1 criteria and the exploratory uni-dimensional immune response criteria (iRRC) and the iRECIST criteria with all measurements performed by the central review.

2.4.2 To compare RECIST1.1 imaging response assessment measurements (time point response assessment and overall best response) assess by site study personnel to those performed by central review.

2.5 Exploratory Tobacco Use Objectives

2.5.1 To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

2.5.2 To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

2.5.3 To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

2.5.4 To explore the effect of tobacco use and exposure on treatment duration, relative dose intensity, and therapeutic benefit.

NOTE: Tobacco Use objectives described above are ancillary for the Tobacco Use Assessment project approved by NCI. A combined analysis of the data from the selected ECOG-ACRIN trials is planned. Data collected from the tobacco use assessment in each parent study will not be analyzed and reported in the clinical study report.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria for Step 0

Rev. Add4

_____ 3.1.1 Patients with tumors with the following molecular alterations must submit testing results via Medidata Rave to determine eligibility to Arm T. The Study Chair, Co-Chair, Biology Co-Chair, or a delegate must review the molecular testing and agree that the testing meets one of the molecular eligibility criteria outlined below (please see Section 4.2.4 for instructions):

- ROS1 gene rearrangement by FISH or DNA analysis (may have progressed on prior crizotinib therapy)
- MET exon 14 splice mutations on DNA analysis (may have progressed on prior crizotinib therapy)
- MET high amplification by FISH or DNA analysis or other MET mutations predicted to be sensitive to MET inhibitor (no prior targeted therapy allowed)
- RET gene rearrangement by FISH or DNA analysis (no prior targeted therapy allowed)

Institutions will be notified of the patient's eligibility status for Arm T within two (2) business days of submission of the molecular testing reports.

If patients do not have tumors with the above molecular alterations noted proceed directly to Step 1.

3.2 Eligibility Criteria for Step 1

_____ 3.2.1 For patients with known molecular alterations, institution has been notified that patient is deemed eligible for Arm T per review of molecular testing reports

_____ 3.2.2 Pathologically confirmed non-squamous non-small cell lung carcinoma (NSCLC)

_____ 3.2.3 Stage IV disease (includes M1a, M1b, or recurrent disease), according to the 7th edition of the lung cancer TNM classification system.

_____ 3.2.4 Predominant non-squamous histology (patients with NSCLC NOS are eligible). Mixed tumors will be categorized by the predominant cell type. If small cell elements are present the patient is ineligible.

_____ 3.2.5 Tumors must be tested and known negative for EGFR TKI sensitizing mutations (EGFR Exon 19 deletions, L858R, L861Q, G719X) and ALK gene rearrangements by routine CLIA-certified clinical testing methods. Negative circulating tumor DNA results alone are not acceptable. Prior testing for tumor PD-L1 status is not required.

_____ 3.2.6 Patients must have progressed radiographically following first line platinum-based chemotherapy, No additional lines of therapy are permitted.

NOTE: Prior adjuvant chemotherapy for early stage disease does not count as one line of therapy if 12 months or greater elapsed between completion of adjuvant therapy and initiation of first-line systemic therapy. If less than 12 months elapsed, adjuvant chemotherapy counts as one line of therapy.

Exception for targeted therapy sub-study (Arm T): At least one line of prior chemotherapy or targeted therapy is required, but there is no limit on number of prior treatments.

_____ 3.2.7 Patients must have measurable disease as defined by RECIST v1.1 criteria in Section 6. Baseline measurements and evaluation of ALL sites of disease must be obtained within 4 weeks prior to registration

_____ 3.2.8 No prior anti-MET therapy such as crizotinib or cabozantinib, or PD-1/PD-L1 immune checkpoint inhibitor therapy (such as nivolumab, pembrolizumab, atezolizumab) or CTLA4 inhibitor therapy (such as ipilimumab). No prior allergic reaction to small molecule tyrosine kinase inhibitors or monoclonal antibodies.

Exception for targeted therapy sub-study (Arm T): Prior crizotinib may be allowed depending on the gene alteration (see Section 3.1.1)

Rev. Add1 _____ 3.2.9 Any prior chemotherapy (based on administration schedule) must have been completed in greater than or equal to the following times prior to registration:

Chemotherapy/ targeted oral therapy administered in a daily or weekly schedule must be completed ≥ 1 week prior to registration;

Any chemotherapy administered in an every 2 week or greater schedule must be completed ≥ 2 weeks prior to registration.

Rev. Add3

Additionally, patients should be recovered to equal to or less than grade 1 toxicities related to any prior treatment, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

_____ 3.2.10 No prior radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks prior to registration.

_____ 3.2.11 Patients with no known brain metastasis must have baseline brain imaging within 12 weeks prior to study registration not demonstrating brain metastases.

OR

Patients with known brain metastases must have baseline brain imaging within 4 weeks prior to study registration and meet all of the following criteria:

3.2.11.1 Have completed treatment to all symptomatic brain metastases (with whole brain radiation or radiosurgery) ≥ 4 weeks prior to registration, or have undergone complete neurosurgical resection ≥ 3 months prior to registration.

3.2.11.2 Be clinically stable from brain metastases at time of screening, if no treatment was administered.

3.2.11.3 Known leptomeningeal disease is not allowed.

_____ 3.2.12 Patients must have ECOG performance status 0-1

NOTE: Participants with impaired decision-making capacity (IDMC) should not be allowed to participate in this study due to its complexity.

_____ 3.2.13 Patients must have anticipated life expectancy greater than 3 months.

_____ 3.2.14 Patients must have acceptable bone marrow, renal hepatic, and coagulation function within 2 weeks prior to registration as defined below:

ULN = institutional upper limit of normal LLN=institutional lower limit of normal

- Absolute neutrophil count ≥ 1,500/ mm^3

  Absolute neutrophil count ≥ 1,500/ mm^3? (Yes/No)_____
  Date of Test_____
- Platelets ≥ 100,000/mm^3

  Platelets ≥ 100,000/mm^3? (Yes/No)_____ Date of Test_____
- Hemoglobin ≥ 9 g/dL

  Hemoglobin ≥ 9 g/dL? (Yes/No)_____ Date of test_____
- Subject has prothrombin time (PT)/INR and partial thromboplastin time (PTT) test ≤ 1.3 x the laboratory ULN

- PT/INR ≤ 1.3 x ULN? (Yes/No)_____ Date of test_____

  PTT ≤ 1.3 x ULN? (Yes/No)____Date of test_____
- Total bilirubin ≤ 1.5 × ULN

  Total bilirubin ≤ 1.5 × ULN? (Yes/No)____ Date of Test_____
- AST (SGOT) and ALT(SGPT) ≤ 3 X ULN

  AST (SGOT) ≤ 3 X ULN? (Yes/No)_____ Date of Test_____

  ALT (SGPT) ≤ 3 X ULN? (Yes/No)_____ Date of Test_____
- Serum albumin ≥ 2.8g/dL

  Serum albumin ≥ 2.8g/dL? (Yes/No)_____ Date of test_____
- Serum calcium (absolute or albumin corrected), magnesium and potassium ≥ LLN

  Ca (absolute or albumin corrected), Mg, K ≥ LLN?

  (Yes/No)_____ Date of test_____

  NOTE: Serum calcium, magnesium and potassium can be replaced if values are below LLN.
- Creatinine ≤1.5 X ULN

  (or)

  Calculated (Crockoft-Gault formula) or measured creatinine clearance ≥ 50 mL/min/1.73m^2 (normalized to BSA) for patients with creatinine levels greater than 1.5 times the institutional normal Creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 50ml/min/1.73m^2?

  (Yes/No)_____ Date of test_____
- Screening urine dipstick must equal 0 or "trace." If urine dipstick results are ≥ 1+, or if dipstick was not performed, calculation of Urine Protein Creatinine (UPC) is required and patients must have a UPC ratio ≤ 1 to participate in the study.

  Urine dipstick = 0 or "trace?" (Yes/No)_____ Date of test_____

  If no, UPC ratio ≤ 1? (Yes/No)_____ Date of test_____

_____ 3.2.15 No history of the following:

- Clinically-significant gastrointestinal bleeding within 6 months prior to registration.
- Hemoptysis of ≥ 0.5 teaspoon (2.5 mL) of red blood within 3 months prior to registration.
- Drug induced pneumonitis within 3 months prior to registration
- Signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment
- Radiographic evidence of cavitating pulmonary lesion(s)
- Tumor invading any major blood vessels
- Evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of

endotracheal or mainstem endobronchial tumor within 28 days before the first dose of cabozantinib

——— 3.2.16 No concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel). Allowed anticoagulants are the following:

- Low-dose aspirin for cardioprotection (per local applicable guidelines) is permitted.
- Low molecular weight heparins (LMWH) or unfractionated heparin is permitted.
- Anticoagulation with therapeutic doses of LMWH is allowed in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

_____ 3.2.17 No concomitant treatment of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort).

_____ 3.2.18 No cardiovascular disorders including:

a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
b) Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days prior to registration
c) Any of the following within 6 months prior to registration:
    - unstable angina pectoris
    - clinically-significant cardiac arrhythmias
    - stroke (including TIA, or other ischemic event)
    - myocardial infarction

_____ 3.2.19 No gastrointestinal disorders associated with a high risk of perforation or fistula formation within 3 months prior to registration:

- active peptic ulcer disease,
- inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
- known malabsorption syndrome
- bowel obstruction or gastric outlet obstruction
- PEG tube placement

_____ 3.2.20 No gastrointestinal disorders associated with a high risk of perforation or fistula formation within 6 months prior to registration:

- abdominal fistula
- gastrointestinal perforation
- intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment

with cabozantinib even if the abscess occurred more than 6 months prior to registration.

_____ 3.2.21 None of the following conditions:

a) Grade 3 or greater infection, or infection requiring intravenous systemic treatment within 28 days prior to registration. Patients should be off antibiotics at the time of registration.

b) serious non-healing wound/ulcer/bone fracture within 28 days prior to registration

c) history of organ transplant

d) concurrent symptomatic untreated hypothyroidism within 7 days prior to registration

e) history of surgery as follows:

- Major surgery (as an example, surgery requiring anesthesia and a > 24 hour hospital stay) within 3 months prior to registration , with wound healing at least 28 days prior to registration.
- Minor surgery within 28 days prior to registration with complete wound healing at least 10 days prior to registration.
- Minor procedures within 7 days prior to registration such as thoracentesis, paracentesis, or 18g or smaller needle biopsy of tumor
- Patients with clinically relevant ongoing complications from prior surgery are not eligible.

_____ 3.2.22 Patients must have corrected QT interval calculated by the Fridericia formula (QTcF) ≤ 500 ms within 28 days before registration.

QTcF = QT divided by cube root of the RR interval ($QT/RR^{0.333}$)

_____ 3.2.23 Patients must be able to swallow tablets.

_____ 3.2.24 No currently active other malignancies which require systemic treatment

_____ 3.2.25 No patients that 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). Physiologic replacement doses of systemic corticosteroids are permitted, even if < 10 mg/day prednisone equivalents. 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.

_____ 3.2.26 No patients with known active autoimmune disease or known history of autoimmune disease for which recurrence may affect vital organ function or require immune suppressive treatment including systemic

corticosteroids. 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, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, autoimmune hepatitis. 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. Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus or thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

_____ 3.2.27 Age ≥ 18 years on day of consent. Because no dosing or adverse event data are currently available on the use of cabozantinib, nivolumab, or ipilimumab in patients < 18 years of age, children are excluded from this study.

_____ 3.2.28 No ongoing major illness or psychosocial issues that would limit compliance with the protocol.

_____ 3.2.29 Women must not be pregnant or breast-feeding due to contraindications with the study agents.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Women of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.2.30 Women of childbearing potential (WOCBP) and males who are sexually active with WOCBP must use an accepted and effective method of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment for women of childbearing potential and 7 months after the last dose of protocol treatment for males who are sexually active with WOCBP.

_____ 3.2.31 Patients with known HIV disease taking antiretroviral therapy are excluded, because there are no safety data with the combination of

antiretroviral therapy and cabozantinib or ipilimumab or nivolumab with ipilimumab.

Patients with known chronic active hepatitis B (defined as a positive hepatitis B surface antigen and/or hepatitis B viral load in the last 12 months) are excluded, regardless of antiviral treatment.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add1

4. Registration and Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <TBD>. For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval

- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EA5152 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA5152
- Click LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For *EA5152* Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation and IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Declaration of Exception Form, or combination is accepted)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

Rev. Add1

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the

patient in the Rave Database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes, including verifying availability of tumor tissue as per eligibility criteria.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Preregistration (Step 0)

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.4 Additional Requirements

4.1.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.1.4.2 Patients with tumors with known molecular alternations being considered for Arm T must have molecular testing results reviewed by the Study Chair or delegate. Please

send de-identified molecular testing information via Medidata Rave.

Institutions will be notified of the patient's eligibility status for Arm T within two (2) business days of submission of the molecular testing report.

4.2 Randomization/Registration (Step 1)

4.2.1 Protocol Number

4.2.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

Targeted Therapy (Arm T) Registration: Patients considered for Arm T must have molecular testing results reviewed by the Study Chair or delegate. Please submit de-identified molecular testing information via Medidata Rave. Institutions will be notified of the patient's eligibility status for Arm T within two (2) business days of submission of the molecular testing reports.

4.2.5 Stratification Factors

Known PD-L1 status (negative vs. positive (≥1%) vs. unknown by IHC/not tested). Any clinically validated testing platform is allowed, for example platforms using but not restricted to the antibodies 28-8, 22C3, SP142, SP263.

4.2.6 Additional Requirements

4.2.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.6.2 Pathology materials must be submitted for defined laboratory research studies as indicated in Section 10.

Rev. Add1

4.2.6.3 Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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 (https://login.imedidata.com/selectlogin) 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 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 link in the upper right pane of the iMedidata screen.

Users that 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.

Rev. Add2

4.2.7 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically

registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

4.3 Submission of Images for Central Review

Each participating site is required to submit all acquired diagnostic and follow-up images of study participants to the ACR Imaging Core Laboratory. Imaging should be submitted to the ACR Imaging Core Lab via TRIAD 4 and any associated data forms should be completed within 48 hours of acquisition. Prompt submission of all image data is essential to ensure adequate image quality assessment.

TRIAD® is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory.

4.3.1 TRIAD Access Requirements:

Staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to the beginning of Section 4 for instructions on how to request a CTEP-IAM account.

To submit images, the user must be assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. ECOG-ACRIN users should contact your site Lead RA to be added to your site roster.

4.3.2 TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. Support and information on installation of TRIAD can be found at https://triadhelp.acr.org/clinicaltrials. The TRIAD helpdesk can be reached at TRIAD-Support@acr.org. This process can be done in parallel to obtaining your CTEP-IAM account username and password.

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave and EASEE-PRO according to the schedule in the ***EA5152*** Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

Treatment should start within seven working days after registration.

Cycle = 4 weeks (28 days)

Cabozantinib will be dispensed every cycle.

Rev. Add1

NOTE: Cabozantinib should be taken on an empty stomach (i.e. do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew. No not take missed dose within 12 hours of the next dose. Please refer to Appendix VII for more information.

Patients will continue receiving treatment until disease progression is observed or an adverse event requiring discontinuation occurs.

All therapy should start on the same day, but cabozantinib may start the morning following infusional therapy if morning dosing is desired.

5.1.1 ARM A

Nivolumab 480 mg IV over 60 minutes every 4 weeks, ongoing

5.1.2 ARM B

Nivolumab 480 mg IV over 60 minutes every 4 weeks, ongoing

Cabozantinib 40 mg PO daily, ongoing

5.1.3 ARM C

Nivolumab 480 mg IV over 60 minutes every 4 weeks, ongoing

Cabozantinib 40 mg PO daily, ongoing

Ipilimumab 1 mg/kg over 90 minutes every 8 weeks, ongoing

NOTE: On days when both nivolumab and ipilimumab are administered, nivolumab is administered prior to ipilimumab.

5.1.4 Targeted therapy arm (ARM T)

Nivolumab 480 mg IV over 60 minutes every 4 weeks, ongoing

Cabozantinib 40 mg PO daily, ongoing

Rev. Add3

5.2 Adverse Event Reporting Requirements

Rev. Add4

All toxicity grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Rev. Add3

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and

regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents

5.2.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA5152 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.2.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.2.4 Terminology

Rev. Add3

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.

Rev. Add1

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Rev. Add3

5.2.5 Mechanisms for Adverse Event Reporting

Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA5152 forms packet for instructions on where and when adverse events are to be reported routinely.

Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provide information and instructions regarding expedited adverse event reporting

Rev. Add1
Rev. Add3

5.2.6 Expedited Adverse Event Reporting Procedure

Adverse Events requiring expediting reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS

report via the CTEP-AERS website. Once the event is reported in CTEP-AERS, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the NCI (301-897-7497)

An electronic CTEP-AERS report MUST be initiated via Medidata Rave immediately upon re-establishment of internet connection

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.7 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol EA5152 and outline the specific expedited adverse event reporting requirements for study EA5152.

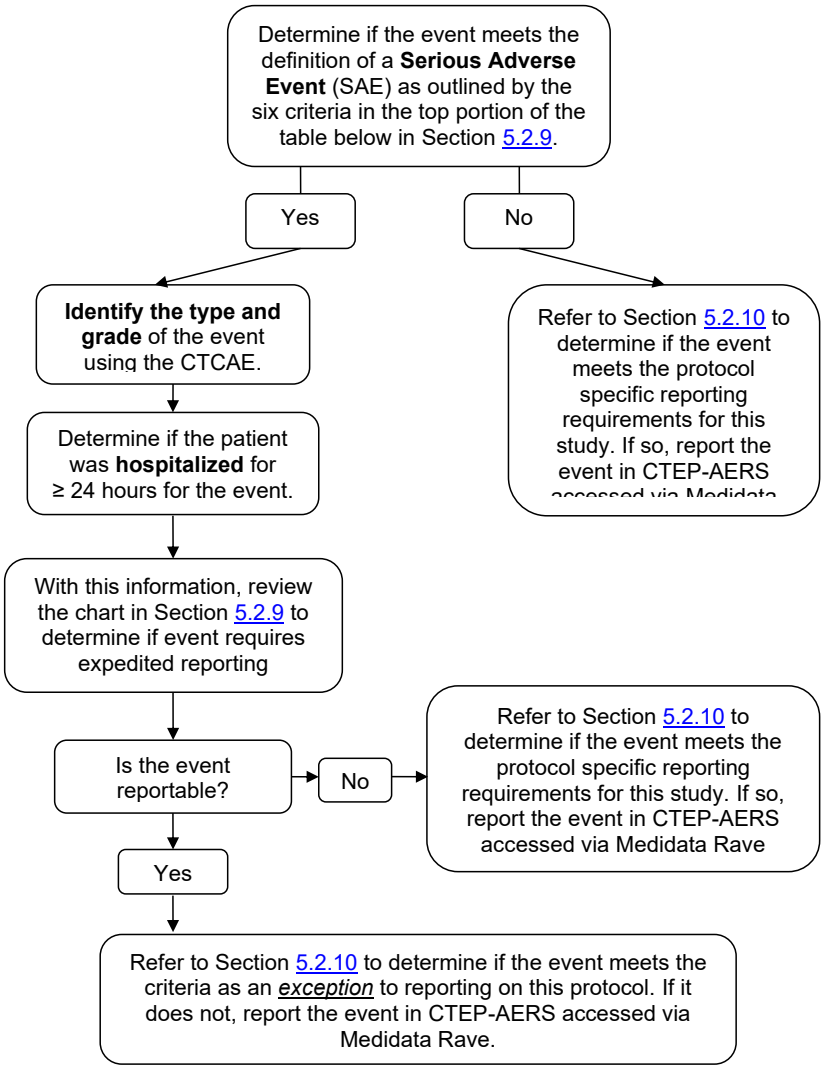
Rev. Add3

5.2.8 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A, B, C, T

Rev. Add1

5.2.8.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

NOTE: **For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave.** Once the adverse event is entered into Rave, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. We encourage all sites to confirm the Rules Engine assessment with the charts below.


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.9.
Yes
No
Identify the type and grade of the event using the CTCAE.
Refer to Section 5.2.10 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in CTEP-AERS
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
With this information, review the chart in Section 5.2.9 to determine if event requires expedited reporting
Is the event reportable?
No
Refer to Section 5.2.10 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in CTEP-AERS accessed via Medidata Rave
Yes
Refer to Section 5.2.10 to determine if the event meets the criteria as an *exception* to reporting on this protocol. If it does not, report the event in CTEP-AERS accessed via Medidata Rave.

Rev. Add1
Rev. Add3

5.2.8.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

NOTE: **For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave.** Once the adverse event is entered into Rave, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event/Late Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. We encourage all sites to confirm the Rules Engine assessment with the requirements outlined below.

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.9, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported expeditiously even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Rev. Add3

5.2.9 Expedited Reporting Requirements for Arm A, B, C, and T on protocol EA5152

Investigational Agents: Nivolumab, Cabozantinib, Ipilimumab

Commercial Agents: None

Phase 1 and Early Phase 2 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

Rev. Add1

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

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

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

1. Death
2. A life-threatening adverse event
3. An adverse event 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 SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events 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 notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Rev. Add1
Rev. Add3

5.2.10 Additional instructions, requirements and exceptions for protocol EA5152

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Reporting a death on study: A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder 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.

EA5152 specific expedited reporting requirements:

- **Colitis:** Any grade 3-5 colitis that is considered treatment related must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **Pneumonitis:** Any grade 3-5 pneumonitis that is considered treatment related must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **Infusion Reactions:** Any grade 3-5 infusion reaction must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **Pregnancies:** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on Cabozantinib, Nivolumab or Ipilimumab, or within 28 days of the subject's last dose of Cabozantinib, Nivolumab or Ipilimumab, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of the Investigator's knowledge. Please refer to Appendix VI for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA5152 specific expedited reporting exceptions:

For study arms A, B, C, T, the adverse events listed below **do not** require expedited reporting

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

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5.2.11 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.12 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.

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  2. Report the diagnosis expeditiously by initially reporting it on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. The CTEP-AERS report must then be initiated

directly from the Adverse Event/Late Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR)

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib s-malate, 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 3219patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

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NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 17, 2018[1]

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		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Diarrhea	Constipation		***Constipation (Gr 2)*** ***Diarrhea (Gr 3)***
	Dry mouth Dyspepsia	Gastrointestinal fistula[2]	***Dry mouth (Gr 2)*** ***Dyspepsia (Gr 2)***
		Gastrointestinal hemorrhage[3] Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***

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%)**	
Nausea			***Nausea (Gr 3)***
Vomiting	Oral pain		***Oral pain (Gr 2)*** ***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	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
Weight loss	Platelet count decreased		***Platelet count decreased (Gr 3)*** ***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia	Dehydration		***Anorexia (Gr 3)***
	Hypocalcemia		
	Hypokalemia Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	

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%)**	
		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)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
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; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); 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); Wound dehiscence; 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; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; 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; Nail changes; 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.

Rev. Add3

5.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, 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 BMS-936558 (Nivolumab, MDX-1106).

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NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, June 18, 2018[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (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 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hypophysitis[3]		
	Hyperthyroidism[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[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)***
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma)[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)***

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
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)	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[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 disorders -Other (bullous pemphigoid)	
	Skin and subcutaneous 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]BMS-936558 (Nivolumab, MDX-1106) 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 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 BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) 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 BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) 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); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

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; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

NOTE: BMS-936558 (Nivolumab, MDX-1106) 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.

Rev. Add3

5.3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

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 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

Rev. Add1

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

NOTE: For Arm C, although colitis appears in the SPEER list below as an exception to expedited reporting, **all grades 3-5 colitis that are considered treatment related must be reported in CTEP-AERS accessed via Medidata Rave** because it is a protocol specific requirement, as outlined in Section 5.2.10.

Version 2.9, December 20, 2017[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2] Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2] Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain Colitis[2]	 Colonic perforation[3]	***Colitis (Gr 3)***
	Constipation		
Diarrhea	 Enterocolitis		***Diarrhea (Gr 3)***
	Esophagitis		
 Nausea		Ileus	 ***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever	 General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS]) Multi-organ failure	***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]	 Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia Dehydration Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder		
	Guillain-Barre syndrome[2]		
	Headache Myasthenia gravis[2]		
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis	Respiratory failure Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia) Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's syndrome)		
		Stevens-Johnson syndrome Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[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]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]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.

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

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia

CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy

EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)

GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure[2]

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infection[7]

INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation

VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

NOTE: Ipilimumab (MDX-010) 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.

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5.4 Dose Modifications

5.4.1 Cabozantinib Dose Levels

Dose Level	Cabozantinib Dosage
0	40 mg daily
-1	20 mg daily

Missed or vomited doses of cabozantinib should be considered missed and not made up.

5.4.2 Nivolumab and Ipilimumab Dose Levels

Missed doses of nivolumab and ipilimumab drugs should not be made up if not administered within the window specified by the protocol. Administration of nivolumab and ipilimumab should remain synchronized for patients on both drugs. No dose levels or schedule changes exist for nivolumab and ipilimumab – the drugs are either administered (together for the combination arm) or held at each given time. If held they may be given at the next specified interval in the protocol.

If all treatment is held for more than 56 days (8 weeks), the patient must be permanently discontinued from study therapy unless study chair approval is obtained for unusual circumstances.

5.4.3 General principles for management of toxicity with combination therapy

The combinations of cabozantinib and immunotherapy are still investigational, and unanticipated or synergistic side effects may be observed. Toxicity from combination therapy may be difficult to attribute to cabozantinib versus nivolumab (with or without ipilimumab). Guidance is provided below in defining attribution by holding cabozantinib, or by empirically starting corticosteroids.

As a general approach, it is suggested that AEs be treated with supportive care when possible at the earliest signs of toxicity. The below management guidelines are provided based on what is known individually about cabozantinib and nivolumab/ipilimumab, with additional guidance in the areas of overlap. They are not mandatory and investigator discretion may be used

There are many circumstances in which the instructions below dictate permanent discontinuation of therapy. If an investigator feels that it is in the patient's best interest to continue on study therapy, study chair approval may be obtained prior to restarting drug.

Table of relative likelihood of cabozantinib-related and immune-related toxicities.

++ More common

+ Less common

- Infrequent

Toxicity	Cabozantinib-related	Immune-related	Protocol management section
Diarrhea	++	++	5.4.6
Nausea and Vomiting	++	+	5.4.7
Oral mucositis	++	-	5.4.8
Hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome)	++	-	5.4.8
Skin Rash	+	+	5.4.8
Transaminitis (AST/ALT increased)	+	++	5.4.9
Hyperbilirubinemia (bililrubin increased)	-	+	5.4.9
Amylase/lipase increased; pancreatitis	+	-	5.4.9
Pneumonitis	+	++	5.4.10
Hypothyroidism	++	++	5.4.11
Adrenal insufficiency	-	+	5.4.11
Neurologic events	-	+	5.4.12
Renal dysfunction	-	-	5.4.13
Proteinuria	+	-	5.4.13
Fatigue	++	++	5.4.14
Fever	-	-	5.4.15
Infusion reaction	N/A	-	5.4.16
Thrombosis/embolism	+	-	5.4.17
Hypertension	++	-	5.4.18
Cardiomyopathy/myocarditis	-	+	5.4.19
Hemorrhagic events	+	-	5.4.20
Fistula formation/perforation	+	-	5.4.21
Wound healing problems	+	-	5.4.22
Osteonecrosis of the jaw	+	-	5.4.23
Cardiac QTc prolongation	+	-	5.4.24

5.4.4 Cabozantinib-associated adverse events

Most adverse events related to cabozantinib should start to improve within 1-2 weeks of drug hold with supportive management. For patients with possible cabozantinib toxicity of any grade, the investigator has the option to hold cabozantinib to determine whether the toxicity resolves (therefore it is more likely from cabozantinib) or the toxicity persists (therefore it is more likely from immunotherapy). If the toxicity is more likely from cabozantinib, the investigator has the option to continue cabozantinib, or dose reduce one level. If cabozantinib has already been dose reduced and toxicity recurs, it

may be permanently discontinued while the other study drug(s) are continued, if appropriate.

5.4.5 Immune-related adverse events

Immune-related adverse events can happen with any onset in relationship to immune therapy administration, even months after discontinuation of therapy. Corticosteroids are the mainstay of therapy for immune-related adverse events. Most should improve or resolve with an adequate dose of steroids. Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and reflex T4 to document baseline is strongly recommended.

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. Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after an observation period without further symptoms at the discretion of the investigator. Any patients who require additional immune suppressive treatment beyond steroids should go off immune therapy study treatment (but may continue cabozantinib as appropriate).

If AE's are felt to be immune related and drugs are held, nivolumab and ipilimumab should either be given together or both held. Cabozantinib may be either continued, or held, as felt appropriate by the investigator depending on the particular toxicity. The study chair may be contacted for individual circumstances to provide additional guidance.

5.4.6 Diarrhea

Overall management of diarrhea:

Management of diarrhea may be challenging for patients on combination therapy on this protocol, because cabozantinib and immune-related diarrhea have different etiologies and management.

In general, cabozantinib-associated diarrhea tends to be more crampy (not painful) and generally mild in nature. If there is bloody colitis, or abdominal pain, also consider the likelihood of immune-related colitis.

For patients on cabozantinib containing arms, it is suggested they hold for grade 2 and higher diarrhea to monitor for clinical improvement. Antidiarrheals may be used. If the diarrhea is refractory to 1 week or more of drug hold, a trial of steroid therapy may be indicated according to the immune-mediated management algorithm below. Rechallenge may be considered for grade 3 and below diarrhea after resolution to grade 1, but for grade 4 diarrhea study chair approval is required after resolution before rechallenge.

Management of cabozantinib-associated diarrhea:

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased

frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown in the table below. Administration of antidiarrheal/antimotility agents can be considered for diarrhea as initial management, but are not generally recommended for immune related colitis. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

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

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.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

5.4.7 Nausea and Vomiting

Management of cabozantinib-associated nausea and vomiting:

Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. The dose modification guidance should be followed for non-hematologic events (Section 5.4.25).

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.)

Immune-related nausea and vomiting

Other GI N-V	Management/Next Dose for Nivolumab+/-Ipilimumab
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

5.4.8 Stomatitis, Mucositis, and Skin Rash

Management of cabozantinib-associated stomatitis/mucositis:

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

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

Management of cabozantinib-associated skin conditions:

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be

advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

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

Treatment guidelines for stomatitis and other general skin reactions should be followed as in Section 5.4.25

Treatment guidelines for hand-foot reactions related to study treatment are presented in the table below.

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Cabozantinib associated Hand-Foot Reactions

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

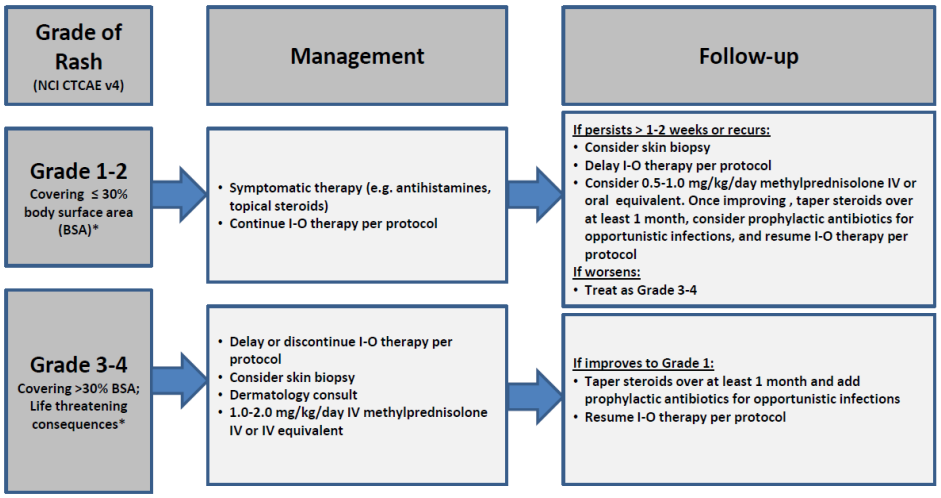
GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

Immune-related skin rash and oral lesions

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab+/-Ipilimumab
≤ Grade 1	No change in dose *
Grade 2	Hold* until 1≤ Grade resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off 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: See Skin AE management Algorithm	

Skin Adverse Event Management Algorithm

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



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

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5.4.9 Hepatobiliary Disorders

Management of cabozantinib-associated hepatobiliary disorders: The following tables should be used for dose modifications for AST/ALT elevations and/or bilirubin elevations:

Cabozantinib associated Transaminase and/or Bilirubin Elevations

Notes	In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters, i.e. 2 or more times per week. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases.
Transaminase elevation Grade	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib and consider weekly monitoring of liver function tests (LFTs) until stable. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with weekly monitoring of LFTs for 6 weeks. If LFTs continue to rise within Grade 2, hold cabozantinib treatment. Then continue with weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Hold cabozantinib treatment and monitor with twice weekly LFTs until Grade ≤ 2. Then continue with weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue all study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and Study Chair but only with Study Chair approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 50% increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with weekly monitoring of LFTs for 8 weeks. If LFTs continue to rise, hold all study treatment. Then continue with weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
≥ 50% increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Hold all study treatment and monitor with twice weekly LFTs until Grade ≤ 2.Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.

Grade 4	Discontinue all study treatment permanently. LFTs should be monitored as clinically indicated, i.e. 2 times per week or more, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment with cabozantinib at a lower dose as determined by the investigator and Study Chair but only with Study Chair approval.
Bilirubin elevation Grade	**Intervention**
Grade 2 Bilirubin	Continue study treatment. Consider more frequent monitoring of bilirubin, i.e weekly or more
Grade 2 or greater Bilirubin (and > 2.0 ULN), with Grade 3 or greater transaminase elevation, without evidence of biliary obstruction (i.e. elevation of alkaline phosphatase) or alternative explanation	Permanently discontinue all study treatment due to likely signal of severe liver injury
Grade 3 Bilirubin (> 3.0 ULN), isolated	Hold all study treatment until recovered to Grade ≤ 1 or baseline, INR < 1.5 ULN or baseline, and aminotransferases Grade ≤ 1 or baseline. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4 Bilirubin (> 10.0 ULN)	Permanently discontinue cabozantinib

Cabozantinib associated asymptomatic Lipase or Amylase Elevations

NOTES: Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.	
Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	Hold all study treatment Monitor lipase and amylase twice weekly Upon resolution to Grade ≤ 1 or baseline, study treatment may be restarted at the same dose or at a reduced dose provided that this occurs within 4 weeks. If retreatment following Grade 3 lipase or amylase elevation is at the same cabozantinib dose and Grade 3 or Grade 4 elevations recur, then all study treatment must be held again until lipase and amylase levels have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 4	Hold all study treatment Monitor lipase and amylase twice weekly Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 4 weeks. If retreatment following Grade 4 lipase or amylase elevation is at the same cabozantinib dose and Grade 3 or 4 elevations recur, then all study treatment must be held again until lipase and amylase have resolved to Grade ≤ 1 or

	baseline and retreatment must be at a reduced dose.

Cabozantinib-associated Pancreatitis

Pancreatitis	
Grade 3	Hold cabozantinib treatment. Radiographic evaluation is recommended. Monitor lipase and amylase weekly. Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at a reduced dose.
Grade 4	Permanently discontinue all study treatment. However, if the subject was unequivocally deriving benefit from therapy, cabozantinib treatment may resume at a reduced at a reduced dose agreed to by the investigator and Study Chair but only with Study Chair approval.

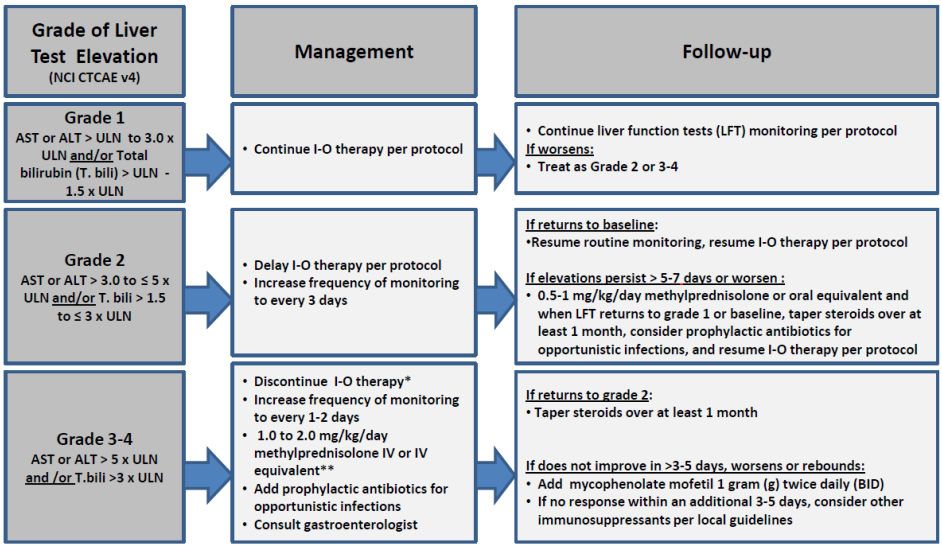
Immune-related hepatobiliary disorders

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab+/-Ipilimumab**
≤ Grade 1	Hold until UNL or baseline. Resume at same dose level.
Grade 2	Hold until UNL or baseline. Resume at same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
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.	
Recommended management: see Hepatic AE management algorithm	

Pancreatitis Amylapse/Lipase	**Management/Next Dose for Nivolumab+/-Ipilimumab**
≤ Grade 1	May continue at same dose level if asymptomatic; consider liver ultrasound and/or abdominal CT scan if no resolution.
Grade 2	May continue at same dose level if asymptomatic; consider liver ultrasound and/or abdominal CT scan if no resolution.
Grade 3	May continue at same dose level if asymptomatic; consider liver ultrasound and/or abdominal CT scan if no resolution.
Grade 4	Hold drug. Perform liver ultrasound and/or abdominal CT scan to rule out radiographic pancreatitis. Resume at same dose level if asymptomatic and no radiographic clinical concerns. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
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	

Hepatic Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**
****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

5.4.10 Pneumonitis

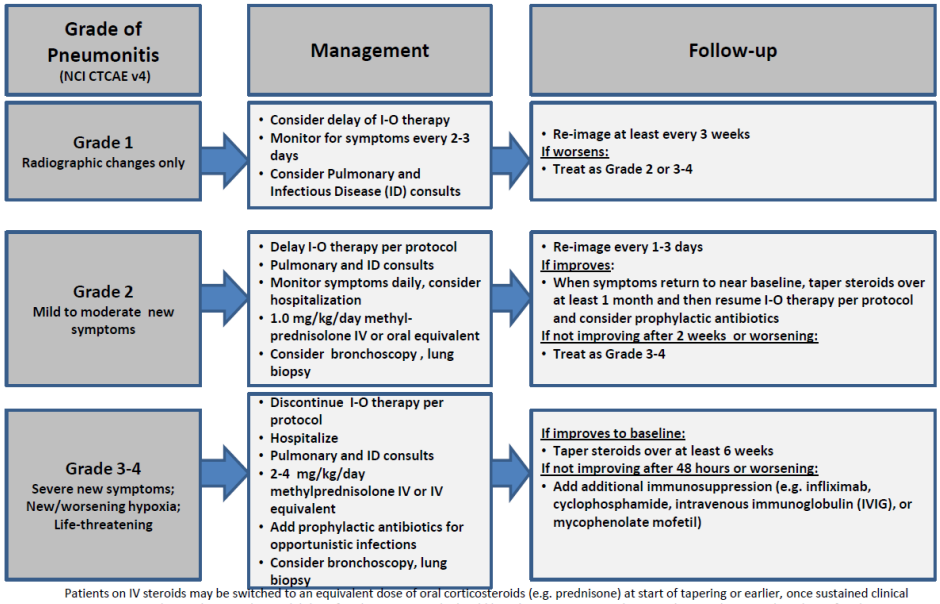
Management of cabozantinib associated pneumonitis

Pneumonitis has been associated with cabozantinib, nivolumab, and ipilimumab therapies individually. In general it is difficult to definitively diagnose and can be life threatening. Patients with proven symptomatic clinically proven pneumonitis refractory to management guidelines for nivolumab +/- ipilimumab (below) should have cabozantinib permanently discontinued, if they were on cabozantinib therapy.

Pneumonitis	Management/Next Dose for Nivolumab+/-Ipilimumab
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required. ^
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required
Grade 4	Off 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	

Pulmonary Adverse Event Management Algorithm

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



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

5.4.11 Endocrine Disorders

Management of cabozantinib associated endocrine disorders: Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects (see Cabozantinib Investigator's Brochure). Routine 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 and clinical examination prior to initiation and during treatment with cabozantinib is required.

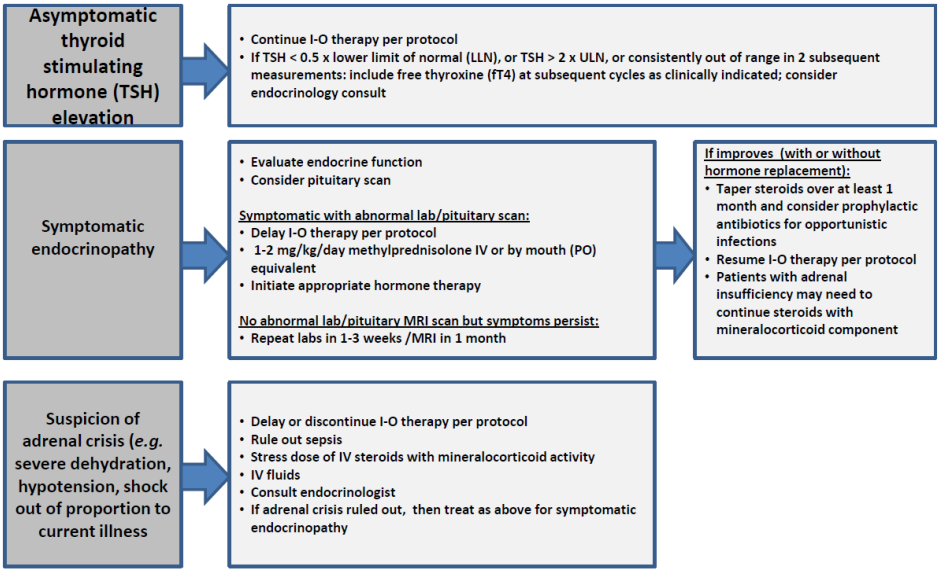
Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

Immune-related endocrine disorders

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab+/-Ipilimumab**
≤ Grade 1	Asymptomatic TSH elevation * Consider thyroid replacement therapy and endocrine consult
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Off study treatment.
Grade 4	Off 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. 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. * Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. - 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.	
Recommended management: See Endocrine Management Algorithm	

Endocrinopathy Management Algorithm

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



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

5.4.12 Neurologic Events

Management of cabozantinib associated neurologic events:

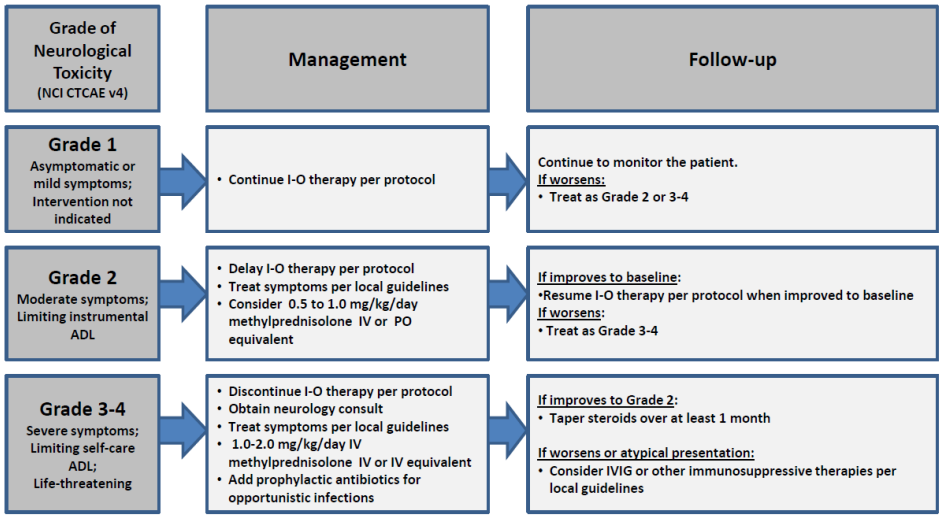
Neurologic events are unusual with cabozantinib. Reversible leukoencephalopathy syndrome (RPLS) can be considered, but generally immune related events should be excluded as well. If a diagnosis of RPLS is confirmed, cabozantinib should be permanently discontinued.

Immune-related neurologic events

Neurologic events	Management/Next Dose for Nivolumab
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
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 n. VII (Bell's palsy)^
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
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	

Neurological Adverse Event Management Algorithm

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



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

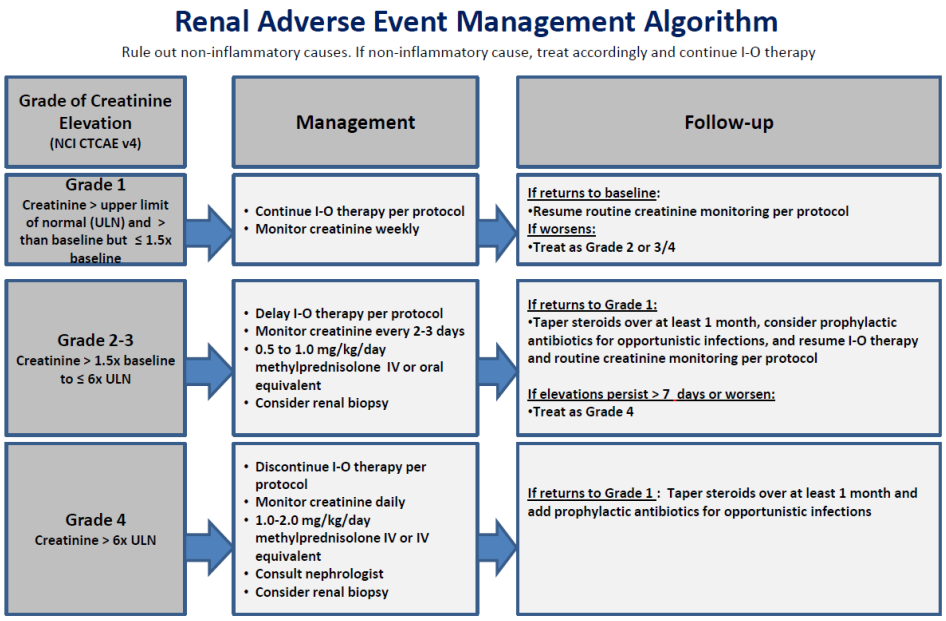
5.4.13 Renal dysfunction and proteinuria

Management of cabozantinib related proteinuria: Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR(mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in the next Table below

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

Immune-related renal dysfunction

Renal	Management/Next Dose for Nivolumab and Nivo/Ipi combination
≤ Grade 1	Continue study therapy
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off 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	



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

Rev. Add4

5.4.14 Fatigue

Management of cabozantinib associated fatigue: Fatigue is common with cabozantinib treatment and generally should resolve within 2 weeks of discontinuing therapy. Dose reduction can be considered.

Immune-related fatigue

Fatigue	Management/Next Dose for Nivolumab+/-Ipilimumab
≤ Grade 1	No change in dose.
Grade 2	No change in dose

Fatigue	Management/Next Dose for Nivolumab+/-Ipilimumab
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
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.	

5.4.15 Fever

Management of cabozantinib associated fever. Fever is unusual with cabozantinib treatment. Infection and immune related etiologies should be considered.

Immune related fever

Fever	Management/Next Dose for Nivolumab and Nivo/Ipi combination
≤ Grade 1	Evaluate and continue at same dose level
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off 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	

Rev. Add1
Rev. Add3

5.4.16 Infusion reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE according to Section 5.2.9 if reporting criteria are met. Infusion reactions should be graded according to NCI CTCAE guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms

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

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes

before additional nivolumab administrations, slowing infusion rate as above.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours), and no further nivolumab will be administered at that visit.

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction),

Grade 3 symptoms: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated)

Nivolumab will be permanently discontinued

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

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

5.4.17 Embolism and Thrombosis

Management of cabozantinib associated embolism and thrombosis: Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator Brochure). Subjects who develop a PE or DVT should have all study treatment held until therapeutic anticoagulation is initiated.

Anticoagulation with warfarin is not allowed due to drug interactions with both cabozantinib; therefore ONLY heparins or low molecular weight heparin is allowed. Patients with brain metastases should be treated with caution and the investigator should consider the potential benefit to outweigh the risks.

Grade 2-3 DVT or PE: All study treatment may be resumed without a dose-level reduction in subjects who have uncomplicated PE or DCT. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding.

Grade 4 DVT or PE: Subjects with life-threatening PE or DVT should have cabozantinib discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Study Chair. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, cabozantinib can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue cabozantinib after a second thrombotic event. 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.

5.4.18 Hypertension

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

Guidelines for management are presented in the table below.

Table: Management of Hypertension Related to Cabozantinib

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

BP, blood pressure.

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

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

5.4.19 Myocarditis

Management of cabozantinib related cardiomyopathy/myocarditis: Cardiomyopathy has been reported with VEGF-pathway inhibitors, but myocarditis is very infrequent at most. Therefore, immune related causes should be primarily suspected but cabozantinib should also be held while workup is ongoing.

Management of immune related cardiomyopathy/myocarditis: Myocarditis, that may result in cardiomyopathy, has been increasingly reported as a complication of immunotherapy.

Guidelines for management are presented in the table below.

- Drug will be held for grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

Cardiac*	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab 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, Troponin I. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
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. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. 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 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.	

5.4.20 Prevention and Treatment of Hemorrhagic Events

Management of cabozantinib associated hemorrhagic events: 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 with cavitations or tumor lesions which invade, encase, or abut major blood vessels.
- 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.

Management: Cabozantinib should be discontinued in subjects with serious (Grade 3) and life-threatening (Grade 4) bleeding events or recent hemoptysis (≥ 0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be held if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the Study Chair and the investigator. Therapy

of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment should be considered for discontinuation of cabozantinib treatment.

5.4.21 Rectal and Perirectal Abscess and GI and non-GI Perforation/Fistula Formation/

Management of cabozantinib-associated rectal and perirectal abscess: Rectal and perirectal abscesses have been reported, often 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.

Management of cabozantinib associated GI Perforation/Fistula:

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.

Risk factors include 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.
- Radiation to the GI tract

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.

Management of cabozantinib associated 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. Patients with tumor invading the respiratory tract are also considered a risk for non-GI fistula formation.

Management: Cabozantinib should be discontinued in subjects who have been diagnosed with GI or non GI perforation/fistula that is related to treatment.

5.4.22 Wound Healing and Surgery

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

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

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. When possible, cabozantinib should be stopped at least 28 days prior to elective surgery.

5.4.23 Osteonecrosis of the Jaw

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

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

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

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

5.4.24 QT (QTcF) Prolongation

Management of cabozantinib-associated QT 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 http://www.qtdrugs.org).
- Treatment with CyP 3A4 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.

Treatment with drugs that cause QTc prolongation as well as CyP 3A4 inhibitors is discouraged on this study, but not prohibited. Subjects having any of these additional risk factors while on cabozantinib should have ECGs performed approximately one week after the onset of these factors.

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.

The Sponsor should be notified immediately of any QTc prolongation event.

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 cabozantinib 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 Study Chair.

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 and the Study Chair.

5.4.25 Guidelines for General Toxicities Commonly Associated with Cabozantinib

As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. Additional information can be found in the Cabozantinib Investigator's Brochure.

Once reduced, the dose of cabozantinib should not be re-escalated.

Rev. Add3

General Approach to the Management of Other Cabozantinib-Related Non-Hematologic Adverse Events

Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	Continue cabozantinib treatment at the current dose level with supportive care. At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care
NOTE: A table referencing dose delay and modification criteria for specific medical conditions is provided in Section 5.4.3. Study treatment dose adjustment is only needed if the toxicity was deemed possibly, probably, or definitely related to cabozantinib treatment.	

5.4.26 Management of other Immune related events

ALL OTHER EVENTS	Management/Next Dose for Nivolumab and combination Nivolumab/Ipilimumab
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline(exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
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 does not require discontinuation.

5.5 Supportive Care and Concomitant Treatments

All supportive measures consistent with optimal patient care will be given throughout the study. There is no mandatory supportive care recommended for study therapy, but general guidelines and doses for specific symptoms are outlined above in the dose modification section.

5.5.1 Concomitant Systemic Treatments

Chemotherapy: Participants are not allowed to receive other anticancer treatment such as chemotherapy while on this trial.

Other Medications: See Appendix VII for a list of prohibited medications and medications which are permissible but should be used with caution with cabozantinib.

5.5.1.1 Cytochrome P450 substrates

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007) http://medicine.iupui.edu/clinpharm/ddis/

The FDA drug interaction tables are another source of lists of inducers and inhibitors. “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers”

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Potent CYP3A4 inducers (see Appendix VII) are not allowed due to interaction with the metabolism of cabozantinib. Dexamethasone can be used with caution but alternate medications should be considered.

Potent CYP3A4 inhibitors should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended. Consider dose reduction of cabozantinib in the event of drug interaction.

NOTE: Grapefruit / grapefruit juice and Seville oranges are also strong CYP3A4 inhibitors and consumption should be avoided.

Drugs Associated with QTcF Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTcF interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTcF prolongation. Additional QTcF monitoring is suggested for subjects who are treated concomitantly with QTcF prolonging drugs.

5.5.1.2 Other Drugs

Concomitant medications that are highly protein bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein.

Cabozantinib was also shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

5.5.1.3 Bone Resorption Inhibitors

Bisphosphonates or denosumab should not be added while on study. Patients on these agents prior to

registration are allowed to continue but caution is advised due to increased risk of osteonecrosis of the jaw.

5.5.1.4 Gastric Acid Inhibitors

Administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers (Study XL184-018). Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. Cimetidine should be avoided due to potential CYP interactions.

5.5.1.5 Anticoagulants

Anticoagulation with LMWH and unfractionated heparin is permitted. Low-dose aspirin use is permitted (100mg daily or lower)

No anticoagulation with warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, fodaparinux, antiplatelet agents such as clopidogrel, or aspirin above low dose levels.

5.5.2 Radiation Therapy

Radiotherapy for symptomatic management of non-target areas is allowed for up to 10 total fractions of treatment while on trial. Cabozantinib should be held for at least 7 days prior to radiation starting, preferably up to 28 days if feasible. Cabozantinib should continue to be held on days of radiotherapy and for 14 days (2 weeks) after if the radiation is to bone, and for 28 days (4 weeks) for other sites of radiation. Immunotherapy may be continued except on days of radiation.

5.5.3 Invasive Procedures

Minor procedures (not involving general anesthesia) are allowed on the study but are discouraged. These include chest tube placement and invasive dental procedures. For patients receiving cabozantinib, it is recommended that patients discontinue treatment 28 days prior and resume treatment after complete wound healing has occurred.

Patients undergoing major surgical procedures may only resume treatment with the approval of the Study Chair.

5.6 Patient Reported Outcome Measures: Tobacco Use Assessment

Assessments will be captured directly from the participants using the EASEE-PRO portal. When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is

activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

The Core and Extension C-TUQ items will be assessed, together with patient-reported physical and psychological symptoms (See Table 2). Specifically, these items will be administered using the EASEE-PRO system described in the companion EA NCORP application. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, sleep difficulties, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU). Detailed information on various measures is outlined in Appendix VI.

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1 – Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4 – Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15 – Q16	Q11 – Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17 – Q18	Q13 – Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20 – 21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

Rev. Add2

i. Assessment Schedule

Survey of Tobacco Use will be administered at the following time points:

1. at baseline (trial enrollment)
2. at 3 month follow-up from study registration
3. at 6 month follow-up from study registration

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Patient declines further treatment to withdrawal of consent (Note that patients may decline further treatment without withdrawing consent for follow-up. The different levels of consent withdrawal should be documented in iMedidata/Rave
- Disease progression by RECIST 1.1 criteria or clinically determined progression.

  NOTE: Patients with disease progression by RECIST 1.1 may be continued on treatment as long as they are believed to still have potential clinical benefit from the study therapy and are otherwise medically stable. Generally this is most appropriate for patients with mild asymptomatic radiographic progression.
- Non-protocol anticancer therapies are administered (as outlined in Section 5.5, above)
- All study drugs have been held for more than 56 days, unless study chair approves resuming therapy after this point.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA5152 Forms Packet.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for radiographic response until progression, even if non-protocol therapy is initiated, and for survival for 5 years following treatment discontinuation. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response approximately every 8 weeks.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions. It is sometimes permissible to not re-image all non-target lesions at every timepoint, for example, if there are non-clinically significant bone lesions outside of the normal restaging area included in a CT of the chest, abdomen, and pelvis.

6.1.2 Disease Parameters

Measurable Disease

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

NOTE: Tumor lesions that are situated in a previously irradiated area may be considered measurable if they have grown subsequent to previous radiation.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be

≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

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

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the 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 or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

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

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

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences

used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

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

Ultrasound

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. For Arm T patients, to be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met. Arm A, B, and C patients do not require confirmation scans for CR.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. For Arm T patients, to be assigned a status of partial response, changes in tumor measurements must be

confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met. Arm A, B, and C patients do not require confirmation scans for CR.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.2.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 7 weeks (as scans are ideally performed every 8 weeks).

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesion(s.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the

basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or
b) it increases in size and there is new pathological confirmation that it is disease (regardless of size).

A new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

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

For Arm T patients, to be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met. Arm A, B, and C patients do not require confirmation scans for complete or partial response.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 7 weeks.

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For Arm A, B, C Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 7 wks. from study entry
PD	Any	Yes or No	PD	
Any	PD**	Yes or No	PD***	No prior SD, PR or CR***
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

For Arm T Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	Confirmation needed: ≥ 4 weeks confirmation****
CR	Non-CR/Non-PD***	No	PR	Confirmation needed: ≥ 4 weeks confirmation****
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 7 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR***
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

**** It is recommended that the confirmation be obtained at the next scheduled evaluation

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

6.1.4.5 First Documentation of Response (for Arm T patients only)

The time between initiation of therapy and first documentation of PR or CR.

6.1.4.6 Confirmation of Response (for Arm T patients only)

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

6.1.4.7 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after entry to that step at a minimum interval 7 weeks.

6.2 Exploratory imaging correlatives:

Imaging correlatives performed for this study will be performed using the baseline study and 1st 3 follow-up time points, when available. All CT and FDG-PET/CT imaging data obtained for patients participating in this clinical trial at baseline and through the first 3 follow-up imaging time points will be de-identified and uploaded from the study site into Transmission of Imaging and Data (TRIAD®) database and delivered to the ACR Imaging Core Laboratory within 48 hrs. of completion. Using this submitted imaging data, the following measurements will be performed.

6.2.1 RECIST1.1 (central review)

Measurements of RECIST1.1 response will be performed as described in Section 6.1 with time point and overall best response assessments categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). These measurements will be performed by the central review and will only be used for analyses for the exploratory imaging correlatives.

6.2.2 Uni-dimensional immune related criteria (iRRC): (**central review**)

Measurements of iRRC response will be performed as described by Nishino et al (Nishino ref) with time point and over all response assessments categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD).

As per the iRRC, assessments of PD will be deferred to the following reimaging time point (performed at least 4 weeks later). Therefore, in patients with progressive disease, this criteria can only be performed on the patients that are maintained on therapy following evidence of progression on imaging with subsequent re-imaging acquired during the imaging window specified by the criteria. As such, this criteria will only be calculated on study patients with the available imaging.

6.2.2.1 Definitions

Evaluable disease

As detailed for RECIST1.1 in Section 6.1.1

Measureable disease

As detailed for RECIST1.1 in Section 6.1.2 with the following differences. Since iRRC is a metric of tumor burden, disease measured at each imaging time point includes up to 5 target lesions/organ (10 maximum visceral target lesions) and up to 5 new target lesions/organ

(maximum 10 new visceral lesions) to be included in the sum of disease measurement at each time point.

Tumor Burden = $Sum_{Index\ lesions}$ + $Sum_{new\ lesions}$

6.2.2.2 Target lesion assessment by Unidimensional Immune related Response Criteria (irRC)

Immune response Complete Response (irCR), partial response (irPR) and stable disease (irSD)

As per RECIST1.1 (Section 6.1.4.1) noting that target lesion sums calculated at each imaging time point include baseline target and new target lesions.

Progressive disease (irPD)

At least a 20% increase in the sum of the diameters of the sums of target lesions and new lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan

is required. Since imaging is being acquired for SOC, this will also be possible for patients that have the available imaging and are maintained on therapy beyond evidence of progression on imaging.

NOTE: The appearance of one or more new lesions is NOT automatically considered progression with the uni-dimensional irRC.

6.2.2.3 Non Non-measureable disease assessment by uni-dimensional irRC.

Immune related Complete Response (irCR): Disappearance of all non-measurable lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Immune related Non-CR/Non-PD: Persistence of one or more non-measureable lesion(s.

Immune related Progressive Disease (irPD): Non-measurable disease does not contribute to PD.

6.2.2.4 Best overall response by iRRC

For iRRC the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation.

6.2.3 Immune Response Evaluation Criteria in Solid Tumors (iRECIST: central review only

Measurements of iRECIST response will be performed as described by Seymour et al (Seymour ref) with time point and over all response assessments categorized as immune complete response (iCR), immune partial response (iPR), immune stable disease (iSD), immune unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD).

As per the iRECIST, all assessments of iUPD will be confirmed at subsequent reimaging (4-8 weeks later). Therefore, in patients with progressive disease, this criteria can only be performed on the patients that are maintained on therapy following evidence of progression on imaging with subsequent re-imaging acquired during the imaging window specified by the criteria. As such, this criteria will only be calculated on study patients with the available imaging.

6.2.3.1 Definitions

Evaluable disease

As detailed for RECIST1.1 in Section 6.1.1

Measureable disease

As detailed for RECIST1.1 in Section 6.1.2 with the following differences. New target lesions are tabulated separately, measured with unidimensional measurements and summed separately. New lesions should be considered measureable or non-measureable by RECIST1.1 criteria principles (see Section 6.1.2). Up to 2 new target lesions/organ (maximum 5 new visceral lesions) to be included in the sum of new lesions which are tabulated and summed separately at each time point

6.2.3.2 Assessment of target lesions by Immune Response Evaluation Criteria in Solid Tumor Criteria (iRECIST)

Immune Complete Response (iCR), partial response (iPR) and stable disease (iSD)

iCR, iPR and iSD are calculated in a manner identical to RECIST1.1

Unconfirmed Progressive Disease (iUPD)

iRECIST defines iUPD using RECIST1.1 principles for progression namely a requirement for at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered to meet the criteria for iUPD, Measurements for new lesions are tabulated separately (not included in the sum of baseline

target lesions) and considered separately at subsequent re-imaging (4-8 weeks later).

Confirmation of PD at subsequent re-imaging is necessary for iUPD to become iCPD.

Confirmed Progressive Disease (iCPD)

Assessment for possible iCPD occurs at re-imaging 4-8 weeks following an assessment of iUPD which is done on the basis of observing either a further increase in size in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. For the new lesion category, iUPD is considered confirmed if the sum of the new lesions increases by greater than 5 mm or new lesions appear.

NOTE: If iUPD is not confirmed by further progression of the tumor (see iCPD), however tumor shrinkage occurs and meets the criteria for iCR, iPR, iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned.

If no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD

6.2.3.3 Assessment of non-target lesions by iRECIST

The iRECIST assessment of non-target lesions at each timepoint follows similar principles to evaluation of the iRECIST target lesions. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST 1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST 1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.)

6.2.3.4 Assessment of Best overall Response by iRECIST

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study

treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR, meaning that iPR or iSD can be assigned (timepoint response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met.

6.2.4 Image Acquisition

6.2.4.1 CT Exam Acquisition

Recognizing that this protocol is collecting standard of care (SOC) imaging, the following imaging parameters have been chosen as a guide to accommodate a variety of Multi-Detector CT Scanners. It is recommended that the imaging studies be acquired in full inspiration.

Series	Guideline
Scout/Topogram	• 100 kv • 10-40 mA • Aquire on inspiration
Axial	• Slice Thickness/Spacing: Standard of Care • mA: As Low As Reasonably Attainable • Dose Modulation: On – if available • Aquire on Inspiration

Post Processing Reconstructions from Raw Data	• Axial Plane (Optional)
	  • Slice Thickness: 1mm
	  • Slice Spacing: 1mm
	  • Soft Tissue Algorithm (Kernel)
	  • Bone/Lung Algorithm (Kernel)

	• Sagittal Plane (optional)
	  • Slice Thickness: 1mm
	  • Slice Spacing: 1mm
	  • Soft Tissue Algorithm (Kernel)
	  • Bone/Lung Algorithm (Kernel)

	• Coronal Plane (optional)
	  • Slice Thickness: 1mm
	  • Slice Spacing: 1mm
	  • Soft Tissue Algorithm (Kernel)
	  • Bone/Lung Algorithm (Kernel)

6.3 Submission of Images for Central Review

6.3.1 Each participating site is required to submit all acquired diagnostic and follow-up images of study participants to the ACR Imaging Core Laboratory. Imaging should be submitted to the ACR Imaging Core Lab via TRIAD 4 and any associated data forms should be completed within 48 hours of acquisition. Prompt submission of all image data is essential to ensure adequate image quality assessment.

6.3.2 TRIAD® is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory.

TRIAD Access Requirements:

- Staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to the beginning of Section 4 for instructions on how to request a CTEP-IAM account.
- To submit images, the user must be assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. ECOG-ACRIN users should contact your site Lead RA to be added to your site roster.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. Support and information on installation of TRIAD can be found at https://triadhelp.acr.org/clinicaltrials. The TRIAD helpdesk can be reached at TRIAD-Support@acr.org. This process can be done in parallel to obtaining your CTEP-IAM account username and password.

7. Therapeutic Parameters

7.1 Step 1: Therapeutic Parameters

Treatment should start within seven working days after registration (see Section 5)

	Screening[1]	Cycle 1[1,2] (day 1)	Cycle 1 mid[2] (day 15)	Cycle 2[2] (day 29)	Cycle 2 mid[2] (day 43)	Cycle 3+[2] (day 57)	Post Treatment Follow Up[3]
History and physical exam[5]	X	X	X	X	X	X	X
Performance status, vital signs[5]	X	X	X	X	X	X	
Complete blood count with differential[6]	X		X	X	X	X	
Blood chemistry tests[7]	X		X	X	X	X	
PT/INR and PTT	X						
Thyroid tests (TSH and reflex free T4)[4]	X			X		X	
Electrocardiogram (ECG)[4]	X			X		X	
Echocardiogram/MUGA[8]	X						
Urine protein assessment[9]	X			X		X	
Serum or Urine Pregnancy Test[10]	X						
Toxicity Assessment		X	X	X	X	X	X
Tumor assessment imaging[11,16]	X					X[11]	X[3]
Brain Imaging[12]	X[12]					X[12]	
Nivolumab (Arms A, B, C, T)		X		X		X	
Cabozantinib (Arms B, C, T)[18]		X	X	X	X	X	
Ipilimumab (Arm C)		X				X[15]	
MANDATORY: Tumor Tissue[14]	X						
Tobacco Use Assessment PROs[17]	See Section 5.6						

Cycle Length = 28 days

1. All baseline assessments must be done ≤ 2 weeks before registration with the exception of imaging studies that must be done ≤ 4 weeks before registration and brain imaging studies that must be done ≤ 12 weeks before registration in patients without known brain metastases. Patients

with known brain metastases at baseline must have a brain MRI or head CT with contrast ≤ 4 weeks prior to registration. All baseline laboratory tests can be used for Cycle 1 Day 1 treatment purposes.

2. Window for study visits and drug administration is ± 3 days. Mid-cycle 1 and 2 visits are required for all arms. Starting with cycle 3, in-person visit by investigator is only required once per cycle.

   NOTE: All hematology and chemistry assessments must be done ≤ 72 hours prior to day 1 of the treatment cycle except for Cycle 1 Day 1 (see footnote 1).

3. Every 3 months until patient is 5 years from registration. Physical exam not required. If in person visit is not possible, patient should be contacted for follow up of vital status and assessment of any study-related toxicities until resolution. For patients that discontinued study therapy prior to radiographic progressive disease, tumor assessments should be performed at least every 3 months during long term follow up until progressive disease is documented.

Rev. Add4 4. Screening TSH and reflex free T4 to be done only if clinically indicated. Every cycle (4 weeks) for these tests. ECG, TSH and reflex free T4 for all arms. ECG required to monitor patients on cabozantinib containing arms for QTcF ≤ 500 msec, and monitor for evidence of myocarditis on all arms.

5. Smoking status and height are to be collected once prior to treatment. ECOG performance status. Vital signs include heart rate, blood pressure, O2 saturation, respiratory rate, and weight.

6. CBCs (with differential and platelet count) includes WBC, ANC, Platelets, Hgb, and Hct and must be done ≤ 72hours prior to day 1 of the treatment cycle, except for Cycle 1 Day 1 they may be performed within 2 weeks of registration.

7. Blood chemistry tests include measurement of magnesium and phosphorus plus comprehensive metabolic panel (ALT, AST, alkaline phosphatase, bilirubin, creatinine, blood urea nitrogen, calcium, sodium, potassium, albumin, chloride, and bicarbonate (or CO_2). All blood chemistries must be done ≤ 72 hours prior to day 1 of the treatment cycle, except for Cycle 1 Day 1 they may be performed within 2 weeks of registration.

8. Baseline Echocardiogram OR MUGA to evaluate ejection fraction to be performed during screening ONLY as clinically indicated - in patients with a history of CHF or at risk because of underlying cardiovascular disease or prior exposure to cardiotoxic drugs.

9. Urine protein analysis required at screening, then only for patients receiving cabozantinib (Arms B, C, T). Urine dipstick at baseline must be < 1 + (0 or “trace”) or Urine Protein Creatinine (UPC) must have been performed If urine dipstick results are ≥ 1+, UPC ratio is clinically indicated and Section 5 should be referred to for management.

10. Women of childbearing potential only. All women of childbearing potential must have a negative pregnancy test ≤ 2 weeks before registration.

11. All efforts must be made to assess tumor from the same type of scan that was performed at baseline. A CT scan with contrast involving known systemic areas of disease is recommended. Imagine studies should be done within **4 weeks** prior to registration and every 8 weeks (based on Cycle 1 Day 1) during treatment until PD. The imaging should be done within 7 days prior to cycle 3, 5, 7, 9 etc. but may be performed after the treatment for unusual circumstances such as holidays. If drugs are held, the imaging should still be performed every 8 weeks counting from Cycle 1 Day 1.

12. Patients must have a brain MRI or head CT with contrast at baseline within 12 weeks prior to registration. Patients with known brain metastases at baseline must have a brain MRI or head CT within 4 weeks prior to registration. Patients with known brain metastases should have repeat imaging at least every 16 weeks (4 cycles). Repeat brain imaging is not required for patients without known brain metastases at baseline.

13. Tumor tissue specimens are required to be submitted for defined laboratory research studies as outlined in Section 10.

14. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

15. Ipilimumab administration every 8 weeks (cycle 1, 3, 5, 7, etc.)
16. For Arm T patients, to be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met. Arm A, B, and C patients do not require confirmation scans for complete or partial response.
17. Tobacco use assessment PROs will be collected using EASEE-PRO.
18. Oral daily dosing

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8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

Drug Ordering: Bristol-Myers Squibb and Exelixis are supplying Nivolumab, Ipilimumab, and Cabozantinib, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Drugs may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator 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 investigator at that institution.

No starter supplies will be provided. Study agents must be ordered after the patient is enrolled on the assigned treatment arm. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record 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.

Investigator Brochure Availability: The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.1 Cabozantinib (NSC 761968

8.1.1 Other Names

XL-184, Cabozantinib s-malate, EXEL-7184, EXEL-02977184, Cabometyx®

8.1.2 Classification

Receptor Tyrosine Kinases Inhibitor (RTK)

8.1.3 Mode of Action

XL184 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.

8.1.4 How Supplied

XL184 is supplied by Exelixis and distributed by the DCTD. XL184 will be provided in 20 mg tablets. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and they are packaged as 30 tablets per bottle.

XL184 should be dispensed in its original container; however, XL184 tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours. It can also be repackaged in a pharmacy dispensing bottle with expiration date not to exceed 7 days.

XL184 Tablet Components and Composition

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

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8.1.5 Storage and Stability

Store intact bottles at controlled room temperature, 20° 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 is identified, promptly return XL 184 (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.

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Stability testing of the intact bottles is on-going. XL184 is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

8.1.6 Dose Specifics

See Section 5 for dosing guidelines.

8.1.7 Route of Administration

Oral

8.1.8 Method of Administration

Take XL184 on an empty stomach; i.e., do not eat 2 hours before or 1 hour after each dose of XL184. Do not crush or chew. Do not take missed dose within 12 hours of the next dose.

8.1.9 Incompatibilities

CYP450 isozymes:

In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. In healthy volunteers, XL184 AUC increased 38% with co-administration of ketoconazole, a strong inhibitor of CYP3A4, and decreased by 77% with a strong CYP3A4 inducer rifampin.

Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications.

NOTE: Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.

XL184 is a noncompetitive inhibitor of CYP2C8 (Kiapp = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Kiapp = 10.4 μM) and CYP2C19 (Kiapp = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Kiapp = 282 μM) in human liver microsomal (HLM). IC50 values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2:

In vitro data indicate that XL184 is an inhibitor of P-glycoprotein transport activity (IC50 = 7.0 μM). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.).

XL184 is also a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, emtricitabine.

Protein bound:

XL184 is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Antacids, H2-blockers, PPIs:

Co-administration of gastric pH modifying drugs such as PPI, H2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is allowed.

QTc prolongation:

Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are

receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

Potential Food Effect

A high fat meal increased both XL184 Cmax and AUC values by 41% and 57%, respectively relative to fasted conditions; therefore, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each XL184 dose).

8.1.10 Side Effects

See Section 5.3 for side effects.

8.1.11 Nursing/Patient Implications

Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Refer to the protocol for management of adverse events.

8.2 Nivolumab (NSC 748726)

8.2.1 Other Names

BMS-936558, MDX1106

8.2.2 Classification

Anti-PD-1MAb

8.2.3 Mode of Action

Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Rev. Add4 8.2.4 Description

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

Rev. Add4 8.2.5 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 (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

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

8.2.6 Dose Specifics

See Section 5 for dosing guidelines.

Rev. Add4 8.2.7 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 (eg, 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.

Rev. Add4 8.2.8 Route of 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.

8.2.9 Incompatibilities

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.

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8.2.10 Availability

Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

8.2.11 Side Effects

See Section 5.3 for side effects

8.2.12 Nursing/Patient Implications

Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

8.3 Ipilimumab (NSC 732442)

8.3.1 Other Names

Anti-CTLA-4 monoclonal antibody, MDX-010, Yervoy™

8.3.2 Classification

Human monoclonal antibody

8.3.3 Mode of Action

Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

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8.3.4 Description

Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) with two manufacturing processes – ongoing trials have been using substances manufactured using Process B. New clinical trials will be using ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

8.3.5 Storage and Stability

Store intact vials refrigerated at (2° to 8° C), protected from light. Do not freeze.

Shelf-life surveillance of the intact vials is ongoing.

Solution as described above is stable up to 24 hours refrigerated at (2° to 8° C) or at room temperature/ room light.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Use prepared IV solution immediately. Discard partially used vials.

8.3.6 Dose Specifics

Dose adjustments do not need to be made every cycle for weight changes < 10% (but may if that is usual local practice). Dose must be adjusted if weight changes by 10% or more from the dosing weight. See Section 5.1.

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8.3.7 Preparation

Do not shake. Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2° to 8° C) or at room temperature/ room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Rev. Add4

8.3.8 Route and Method of Administration

Intravenous infusion over 90 minutes. Do not administer ipilimumab as an IV push or bolus injection.

Can use a volumetric pump to infuse ipilimumab at the protocol-specific dose(s) and rate(s) via a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron).

Rev. Add4

8.3.9 Availability

Bristol-Myers-Squibb (BMS) supplies ipilimumab to the DCTD/NCI. Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

8.3.10 Side Effects

See Section 5.3 for details.

8.3.11 Nursing/Patient Implications

Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes.

Rev. Add4

Women of childbearing potential should be advised to continue contraception for 3 months following the last dose of ipilimumab

Post-marketing surveillance identified a fatal toxic epidermal necrolysis (TEN) event in a patient who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy. Caution should be used

when considering the use of ipilimumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy.

9. Statistical Considerations

9.1 Study Design and Objectives

Main study: This is a randomized phase II study comparing nivolumab (N) to the combination of nivolumab with cabozantinib (NC) and to the combination of nivolumab with cabozantinib and ipilimumab (NCI) in patients with 2nd line metastatic non-squamous non-small cell lung cancer. Prior therapy must have included one line of platinum-based chemotherapy, and must not have included any prior MET/PD-L1/PD-1 inhibitors. Patients must also not have any known activating mutations in EGFR, ALK, ROS1, RET or MET amplification/MET mutations, except for the targeted sub-arm below.

The primary objective of the trial is to determine whether combination therapy including nivolumab and cabozantinib or nivolumab and cabozantinib and ipilimumab extends progression-free survival (PFS) for this patient population as compared to nivolumab alone. Secondary objectives include estimation of overall survival, best objective response, and toxicity.

Targeted cohort sub-study: A separate arm (Arm T) will evaluate the efficacy of the combination of nivolumab and cabozantinib in patients with NSCLC tumor subtypes predicted to be sensitive to targeted agent cabozantinib (MET exon 14 mutations, MET amplification/other mutations, ROS1 rearrangement, RET rearrangement).

Rev. Add1
Rev. Add3

9.2 Study Endpoints

Main study: Progression-free survival (PFS) is defined as the time from randomization to documented disease progression (site review of imaging) or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. Overall survival is defined as the time from randomization to death from any cause, and patients who are thought to be alive at the time of final analysis will be censored at the last date of contact. Best objective response will be evaluated via RECIST1.1 criteria, as described in Section 6 of this protocol document. Toxicity will be determined using the CTCAE criteria.

Targeted therapy sub-study: This group will be evaluated by PFS, overall survival, best objective response rate, and toxicity as above.

Exploratory Imaging Correlative Study: For RECIST1.1 (central review) and irRC PFS is defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. For iRECIST, PFS is defined as the date of the time from randomization to documented disease progression (date of the documented iUPD that is followed by subsequent iCPD) or death from any cause, whichever occurs first.

For the imaging correlatives, overall survival is defined as the time from randomization to death from any cause, and patients who are thought to be alive at the time of final analysis will be censored at the last date of contact. Best objective response will be evaluated for all three criteria performed by central review as defined in Section 6 of this protocol document.

9.3 Statistical Analysis Plan

The primary and some secondary analyses will include all eligible and treated patients. Exceptions to this include: analysis of toxicity data, which will include all patients who received study drug regardless of eligibility, and analyses of response, which will include eligible and treated patients with measurable and evaluable disease.

Time-to-event data, such as PFS and OS, will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate the treatment hazard ratios. The primary comparison of PFS will use a logrank test stratified on the randomization stratification factors with a one-sided type I error rate of 10%. Other comparisons of groups will be made using the logrank test and Cox modeling.

Categorical data, such as response rates (CR+PR) and toxicity, will be compared using Fisher's exact tests with a one-sided type I error rate of 10%; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes. Though none are currently planned, any continuous outcomes will be analyzed using Wilcoxon rank sum test, and multivariable linear regression models may be used to adjust for multiple associations with outcome.

Modeling procedures will implement backward selection; variables significant at the 0.10 level in the univariate setting will be chosen for inclusion in an initial full model, and at each step the least significant variable will be removed from the model. Only those covariates with $p<0.05$ will remain in any final models, unless there are factors identified by the study team as crucial to model interpretation.

Point estimates of all endpoints will be accompanied by the corresponding two-sided 80% confidence intervals.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses are planned for all stratification factors and all known prognostic factors, such as performance status, age, sites of metastases, gender, etc. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

9.4 Sample Size Considerations

The overall sample size for the trial is 169 patients.

Main study: The primary comparison will include all eligible and treated patients, of whom 129 will be accrued and randomized equally, for a total accrual of 43 patients per arm. After adjusting for an ineligibility rate of 10%, the total required sample size for randomization is 144 patients. Using an overall one-sided 0.10 level log rank test for each comparison, this study will have 89% power to detect a 44% reduction in the PFS hazard rate of 0.173 to 0.096 based on the estimated accrual and follow-up period. Assuming exponential survival, this corresponds to an 80% improvement in the median PFS of 4 months on nivolumab alone to 7.2 months on nivolumab plus cabozantinib or on nivolumab plus cabozantinib and

ipilimumab. The number of PFS events needed to achieve this power is 74 events under the alternative hypothesis for each of the two primary comparisons.

Targeted therapy sub-study: Up to 25 additional patients may be enrolled in Arm T. The best objective response rate and PFS will be described for this group of patients. Accrual to the study will stop when the total accrual goal for the randomized study is reached, even if 25 patients have not been enrolled to Arm T. If 25 patients enroll to Arm T before accrual to the randomized part of the study is reached, then Arm T only will be closed. With 25 patients enrolled, the maximum width of the 2-sided 90% exact binomial confidence interval for the best objective response rate will be 35%; with as few as 10 patients enrolled, it will be 56%.

9.5 Projected Accrual

As reflected by our prior E1512 study, it is estimated that patient accrual will be approximately 10 patients per month. It is estimated that the accrual goal will be reached within approximately 15 months with a follow up period of approximately 9-10 months, for a total study duration of 25 months.

9.6 Gender and Ethnicity

Based on previous data from E1512 the anticipated accrual in subgroups defined by gender and race is:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	4	1	0	0	5
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	6	7	0	0	13
White	78	65	1	1	145
More Than One Race	1	1	0	0	2
Total	91	76	1	1	169

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.7 Randomization Scheme

Main study: Randomization to treatment will be determined using permuted blocks within strata with dynamic balancing on main ECOG-ACRIN institutions plus affiliates. The randomization will be stratified by known PD-L1 status (negative vs. positive (≥ 1%) vs. unknown/not tested). It will be a 1:1:1 between arms A, B, and C.

9.8 Monitoring Plan

9.8.1 Interim Analysis: Efficacy

Main study: This study will also be monitored for futility and one interim analysis at roughly 50% information is planned for each comparison. At that time, if the point estimate of the PFS hazard ratio is consistent with detriment (HR > 1.0) on either of the two combination arms, then the data monitoring committee may consider terminating an arm early for overall lack of treatment difference.

9.8.2 Interim Analysis: Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

Because this is the first time that ipilimumab is being combined with nivolumab and cabozantinib in this population, close monitoring of toxicity is an important endpoint of the trial. We will collect data and conduct an interim safety analysis among the first 15 patients who have completed the first two cycles of treatment on each arm. This will be done without a planned suspension to accrual. The safety analysis will be done based on the case report form database and the CTEP-AERS database, although the focus will largely be placed on the CTEP-AERS data. The safety data will be reviewed with the sponsor (CTEP) to rule out the incidence of excessive toxicities. This preliminary toxicity analysis will occur in addition to the twice yearly monitoring for toxicity for the purposes of interim reporting.

In particular, there is concern for excessive rates of pneumonitis or colitis on the 3-drug regimen. With respect to colitis, prior studies have demonstrated that grade 3-5 colitis occurs in approximately 11% of patients with nivolumab and ipilimumab therapy. As such, if we observe 5 or more patients with grade 3-5 treatment-related colitis among 15 patients analyzed per arm, the lower bound of the two-sided 90% exact binomial confidence interval will have exceeded 11% and consideration may be given to terminating the arm associated with the higher rate of colitis.

With respect to pneumonitis, a similar approach will be used. Prior studies have demonstrated that grade 3-5 pneumonitis occurs in approximately 3% of patients treated with nivolumab and ipilimumab. Therefore, if we observe 3 or more grade 3-5 incidents of treatment-related pneumonitis in a cohort of 15 patients, then the lower bound of the two-sided 90% exact binomial confidence interval will have exceeded 3% and consideration may be given to terminating the arm associated with the higher rate of pneumonitis.

Rev. Add2

9.9 Tobacco Use Assessment

Detailed statistical considerations are outlined in Appendix VIII

10. Specimen Submissions

Tumor tissue specimens must be submitted for defined laboratory research studies described in Section 11.

It is required that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 10.2). An STS shipping manifest form is to be included with every submission.

All specimens must be labeled clearly with the ECOG-ACRIN protocol number (EA5152), ECOG-ACRIN patient sequence number, patient's initials, collection date, and specimen type.

10.1 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

If you have any questions concerning tumor tissue submission please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org

10.1.1 Pathological Material Submission

Representative tumor tissue specimens are to be submitted for defined laboratory research studies within one month of randomization.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID# as well as the information above.

10.1.1.1 Required Materials

Forms: Must be submitted with all pathology submissions.

- STS generated shipping manifest form
- Copy of the institutional pathology report
- Immunological study reports, if available

Tumor Tissue Submission:

- Formalin-fixed paraffin-embedded (FFPE) tumor tissue block

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide
- Twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420.

Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.1.2 Shipping Procedures

Pathology materials are to be shipped at ambient temperature within one month following randomization.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

10.2 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.3 Use of Specimens in Research

Digitally scanned H&E slides will be distributed to NeoGenomics Laboratories for PD-L1 Immunohistochemistry. See Section 11 for the description of the laboratory research studies to be performed.

Specimens from patients who consented to allow their specimens to be used for future undefined research studies will be retained in an ECOG-ACRIN designated central repository.

NOTE: Specimens will not be used for future research studies that are not defined in this protocol until an amendment to this treatment protocol or a separate correlative science protocol is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs).

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the institution. All other specimens will be destroyed per guidelines of the respective repository.

10.4 Sample Inventory Submission Guidelines

Inventories of all specimens submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Laboratory Research Studies

11.1 Reference PD-L1 Testing and Correlation with Outcome.

Reason for study: We propose to do PD-L1 testing on tumor tissue obtained for this study. In the CheckMate 057 nivolumab trial, improvements in overall survival and progression-free survival were predicted by PD-L1 expression on tumors. [8] However, some patients that responded did not have tumor PD-L1 expression. This biomarker was approved as a complementary diagnostic test to help predict the probability of response in patients who receive this therapy. It may not be done routinely under standard of care on patients enrolled in this study.

Since patients on both arms will be receiving nivolumab, we are integrating this test primarily to identify potential imbalances with regard to PD-L1 status. We are not proposing real-time testing because this would likely result in delays of treatment. Thus, we will batch test retrospectively and use this test to adjust the outcome results for the impact of PD-L1 expression status in multivariable models. We expect PD-L1 positive patients to have a PFS approximately double that of PD-L1 negative patients (PFS HR = 0.5) and will use this to adjust our outcome models.

Test details:

Test: PD-L1 IHC 28-8 pharmDx test

Formalin-fixed paraffin embedded tumor tissue (blocks or slides) will be collected at baseline. Archival specimens from prior biopsies are allowed. Cytologic specimens are allowed as long as they contain sufficient material for routine immunohistochemical testing.

This study is FDA approved and used for clinical care. Results from this testing will be used to retrospectively determine PD-L1 positivity in tumor specimens from this trial to evaluate its association with progression-free and overall survival, as well as RECIST response.

Specimens will be batched and analyzed at one central laboratory. This will be performed by the CLIA certified laboratory, NeoGenomics. This test will be performed by standard immunohistochemical methods as per the FDA approved criteria. More information is available here:

http://www.neogenomics.com/t_test/pd-l1/

Results will be reported as a percentage of tumor positivity ranging from 0-100%. Categories will be determined at the time of analysis, which may include any of the following or other cutpoints not listed below:

< 1% (zero) expression

≥ 1% expression

≥ 5% expression

≥ 10% expression

11.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

12. Electronic Data Capture

Please refer to the ***EA5152*** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and EASEE-PRO (for tobacco use assessment).

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP bust of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following pathology materials are to be submitted within one (1) month of randomization:

1. Pathology Submissions:
   - Formalin-fixed paraffin-embedded (FFPE) tumor tissue block

   NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:
   - One (1) H&E slide
   - Twenty (20) 5 µm unstained, uncharged air-dried plus slides from the thickest part of the tumor
   - One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420

   If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.
2. Forms and Reports:

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including pathologists).

   The following items are to be included with the pathology materials:
   - Institutional Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981) [if STS is unavailable]
   - Sample Tracking System (STS) Shipping Manifest Form
   - Immunological study reports, if available
3. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Boulevard
   Houston, TX 77030
   Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
   Fax: (713) 563-6506
   Email: eacbpf@mdanderson.org

   If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA5152: A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for defined laboratory research studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future research studies per patient consent. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory research studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.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 ECOG-ACRIN 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.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff 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 patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Pill Calendar

Cabozantinib Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. Do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew pills.
3. If you forget, the missed pills will not be taken later.
4. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

DAY	Date Month Day Year	Time pills taken (AM or PM)	Number of pills taken (AM or PM)	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
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Appendix IV

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively 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:

   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.

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Appendix V

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Rev. Add1
Rev. Add3
Rev. Add4

Appendix VI

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Nivolumab, Cabozantinib, or Ipilimumab, or within 28 days of the female patient's last dose of Nivolumab, Cabozantinib, or Ipilimumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the pregnancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report, accessed via Medidata Rave report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERs accessed via Medidata Rave.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN

Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* and separate CTEP-AERs report should be initiated (via Medidata Rave) reporting the outcome of the pregnancy. To do this, report the pregnancy on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle/Post Registration folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event/Late Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

For this study, it must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A newborn death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to Nivolumab, Cabozantinib, or Ipilimumab, must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm whether or not the event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC

Appendix VII

Prohibited Medications and Medications to Use with Caution

NOTE: This is not an exhaustive list. More information and references may be found in the protocol, Section 5.5.1.

Prohibited Medications

Strong CYP3A4 inducers

Carbamazepine
Modafinil
Phenobarbital
Phenytoin
Rifampin, rifabutin, rifapentin
St. John's Wort

CYP3A4 inhibitors

Cimetidine
Grapefruit / grapefruit juice and Seville oranges
Warfarin (May result in increased INR)

Medications to use with caution

Warfarin

Strong CYP3A4 inducers:

Dexamethasone

Strong CYP3A4 inhibitors:

Clarithromycin, ketoconazole, itraconazole, indinavir, nefazodone, nelfinavir, and ritonavir

Protein bound drugs

Diazepam, furosemide, dicloxacillin, and propranolol

Bone resorption inhibitors:

Bisphosphonates, denosumab

Gastric Acid Inhibitors

Proton pump inhibitors - omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole

H2 blockers (cimetidine which is prohibited) - ranitidine, famotidine, and nizatidine

Drugs associated with QTcF prolongation including the following (for full list see http://www.qtdrugs.org/)

High Risk of Torsades:

Amiodarone, Azithromycin, Bepridil, Chloroquine, Chlorpromazine, Cisapride, Citalopram, Clarithromycin, Dofetilide, Erythromycin, Flecainide, Haloperidol, Ibutilide, Methadone, Moxifloxacin, Pentamidine, Procainamide, Quinidine, Sotalol, Terfenadine, Thioridazine

Possible Risk of Torsades:

Amantadine, Atazanavir, Clozapine, Dolasetron, Escitalopram, Famotidine, Felbamate, Foscarnet, Fosphenytoin, Gatifloxacin, Granisetron, Levofloxacin, Lithium, Moexipril, Nicardipine, Octreotide, Ofloxacin, Ondansetron, Paliperidone, Quetiapine, Risperidone, Tacrolimus, Tamoxifen, Telithromycin, Tizanidine, Vardenafil, Venlafaxine, Voriconazole, Ziprasidone

Conditional Risk of Torsades:

Amitriptyline, Ciprofloxacin, Clomipramine, Desipramine, Diphenhydramine, Doxepin, Fluconazole, Fluoxetine, Imipramine, Itraconazole, Ketoconazole, Nortriptyline, Paroxetine, Protriptyline, Ritonavir, Sertraline, Trazodone, Trimethoprim-Sulfa, Trimipramine

A Randomized Phase II Trial of Nivolumab, Cabozantinib Plus Nivolumab, and Cabozantinib Plus Nivolumab Plus Ipilimumab in Patients with Previously Treated Non-Squamous NSCLC

Appendix VIII

Ancillary for Tobacco Use Assessment: EAQ16T

Study Co-Chairs: Elyse Park, Ilana Gareen, Lynne Wagner, Jamie Ostroff, Ben Herman

Patients registered to selected ECOG-ACRIN trials are eligible to participate in this ancillary study, once the appropriate amendment incorporating the study is activated.

The Ancillary for Tobacco Use Assessment is a project that seeks to address questions about patient-reported tobacco use and smoking behaviors that may span several studies and/or diseases. The tobacco use ancillary is embedded into parent protocols, with participation in the ancillary informed in the parent consent form and participation determined via providing email address to the sites. The general objectives of the tobacco use ancillary are not specific to any single parent protocol; however, specific objectives may be included in the parent or related parent protocols.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited. As a critical step in closing this knowledge gap, the NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). Through this ancillary, the modified C-TUQ measures will be administered to participants enrolling in selected Phase II and Phase III ECOG ACRIN (EA) therapeutic trials.

The major questions may be summarized:

1. What is the smoking status of cancer patients enrolled on EA clinical trials?
2. Do patients quit smoking or try to quit smoking after receiving a cancer diagnosis?
3. What forms of tobacco use do patients engage in?
4. What assistance do patients use or receive to try to quit?
5. How does tobacco use, other forms of tobacco use, and/or environmental tobacco exposure affect patient's treatment toxicity, patient-reported physical and psychological symptoms, trial adherence, and therapeutic outcomes?

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO), and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will

be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Measures

The selected Core and Extension C-TUQ items will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, insomnia, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy)) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU) (baseline and follow-up).

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1 – Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4 – Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15 – Q16	Q11 – Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17 – Q18	Q13 – Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20 – 21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

Tobacco Use. The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed in the baseline and follow-up Survey of Tobacco Use.

Oncology Provider Assistance. C-TUQ Question 13 assesses "cancer doctors" Advise. We will add 4 As to assess participants' reported 5As (Ask (Q12a), Advise (Q12b), Assess (Q12c), Assist (Q12d-Q12f), and Arrange follow-up (Q12g), as in Baseline STU).[80]

Psychological Symptom Assessment. Anxiety & Depression: *(The Patient Reported Outcomes Measurement Information System (PROMIS®)).* We will administer the 4-item Short Form PROMIS® for anxiety and depression (Q17 in Baseline STU). Stigma: The Lung Cancer Stigma scale measures the extent to which shame is internalized (Q18 in Baseline STU).[81]

Physical Symptom Assessment *Physical Symptom Assessment (Functional Assessment of Chronic Illness Therapy (FACIT)). FACIT, a measurement system with a collection of quality-of-life questionnaires, expands the more familiar FACT (Functional Assessment of Cancer Therapy) questionnaires into other chronic illness and conditions. FACIT consists of many*

individual questions to assess various symptoms from the patient perspective. We will use 6 FACIT items, selected based on the therapeutic regimens, expected toxicity, and malignancy type of the parent trials. In addition, we have created modifications of these same six questions to address the degree of bother associated with each symptom" The symptoms of general pain, fatigue, nausea, cough, sleep difficulty, and shortness of breath will be assessed, first using the standard and validated FACT item, and then asking the degree of "bother" imposed by each symptom, on the same 5-point scale. These clusters of symptoms were specifically chosen based on potential interactions between tobacco use and longitudinal symptoms.

Sociodemographic Variables. Sociodemographic variables, including age, sex, zip code, and race/ethnicity are collected for all NCTN trial participants at registration. At baseline, participants will provide information on marital status (Q20 in Baseline STU) and education level (Q21 in Baseline STU) as part of the tobacco supplemental assessment.

Cancer Treatment Variables. Clinical variables including date of diagnosis, malignancy type (smoking related vs. non-smoking related, cancer stage), and treatment details (i.e. types and dates of surgery, chemotherapy, and/or radiation received), along with disease status and survival, will be captured in Medidata Rave via the parent protocol and will be available for analysis of the ancillary. Provider-assessed adverse events will also be captured via the parent protocol in Medidata Rave, using case report forms commonly used across the NCTN and using standard data elements.

Assessments

All items in Survey of Tobacco Use will be administered using the EASEE-PRO system. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

Timing of Assessments

Given the critical questions that remain[13] about the timing of conducting tobacco use assessments, we have carefully chosen to collect tobacco assessment data at trial enrollment, 3 and 6 month follow-up. For tobacco treatment trials, 6 month follow-up is the recommended primary outcome time point. By 6 month follow-up, most cancer treatment-related quitting activity[62], cancer treatment initiation of therapy, and FDA-approved smoking cessation medication regimens will be completed. Adverse events during treatment will have been observed.

Statistical Considerations and Analysis Plans

The analysis plans described below are planned for a combined analysis of the data from the 8 selected ECOG-ACRIN trials. Consistency in the effects over the studies would be examined in this analysis.

1. CHANGES IN SMOKING STATUS AND EXPOSURE. At baseline, combustible tobacco use (1a) will be characterized by smoking status (never smoker, former smoker, and current smoker based on Baseline STU Qs 1 and 5), other forms of tobacco use (1b) will be a composite variable determined by non-cigarette items (based on Baseline STU Q7 and Q14), and environmental tobacco smoke (ETS) level (1c) will be determined by current household and work exposure (Baseline STU Qs 15-16). At follow-up, combustible tobacco use (1a) will be examined by smoking status (Follow-up STU Qs 1 and 2), other forms of tobacco use (1b) will be determined by Follow-up STU Q10, and ETS level (1c) will be determined by 30 day household and work exposure (Follow-up STU Qs 11-12). We will examine tobacco use at baseline, 3 and 6 month follow-up, and change in status (abstinence in combustible tobacco, abstinence of other forms of tobacco use, and change

in exposure to smoke-free home and work) using summary statistics (frequency and proportion). We will explore the effects of sociodemographic and cancer treatment factors on smoking status using logistic regression (comparing smokers and non-smokers). We will also evaluate factors associated with changes in smoking status.

Rev. Add4 2. TREATMENT TOXICITY. The selected trials capture information about adverse events during treatment using NCI's Common Terminology Criteria for Adverse Events. Toxicities are measured at each treatment visit and graded according to severity, with grade 1 corresponding to mild toxicity and grade 5 signifying a lethal adverse event. We will determine each patient's worst degree toxicity across all event types and treatment visits and will compare the distribution of worst degree grades between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure using exact tests. We will also examine the distribution of worst degree grades between users with different form of tobacco use. In addition, we will explore the effects of tobacco use on dose modifications (yes vs. no) using logistic regression, with each patient's dose modification status determined across all treatment visits.

3. SYMPTOM BURDEN. Tobacco variables will be conceptualized as described in the section of CHANGES IN SMOKING STATUS AND EXPOSURE. Tobacco use status (as measured at baseline, 3 and 6 month follow-up) will be compared to physical and psychological symptom burden (as measured at each corresponding time points). At 3 and 6 month follow-up, we will also examine the association between tobacco use changes and changes in symptom burden. We will explore the effects of sociodemographic and cancer treatment factors on symptom burden using repeated measures mixed effects models. As an example of statistical power, we consider the PROMIS SF-4 depression measure. We assume that 1500 patients will be enrolled across the 8 parent studies over 13 months, and that 20% are smokers. We assume that 85% of patients will have assessments at 6 months. Given groups of these sizes (26 quitters and 230 still-smokers) and standard deviation of 4.08 for the PROMIS SF-4 depression scale, there will be 83% power to detect a difference in change scores of 2.5 between groups using a two-sample t-test with Type I error of 5%. The minimally important difference for this instrument is 2.2.[79]

4. CESSATION PATTERNS AND TREATMENT. At baseline we will explore pre-treatment combustible tobacco use patterns (STU Q6a and Q6b), quitting behaviors (STU Q13), behavioral program utilization (STU Q11) and oncology provider support (5As, STU Q12), and smoking cessation medication use (STU Q10). At follow-up we will explore post-treatment combustible tobacco use patterns (STU Q3a-Q3e), quitting behaviors (STU Q9), behavioral program utilization (STU, Q7) and oncology provider support (5As, STU Q8), and smoking cessation medication use (STU Q6). We will explore the effects of sociodemographic and cancer treatment factors on these variables. We will examine associations of quitting behaviors and behavioral and medication utilization with tobacco use status (as outlined in the section of CHANGES IN SMOKING STATUS AND EXPOSURE) at baseline and on respective 3 and 6 month tobacco outcomes. These analyses will be descriptive in nature. Summary statistics (frequency, proportions, and 95% confidence intervals) will be used.

5. TRIAL OUTCOMES. We will compare treatment duration between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure. Cumulative incidence/competing risk methods will be used to estimate time to treatment discontinuation for adverse events, disease progression, completion per protocol, or other causes. Gray's test will be used to test for differences in the cumulative incidence distributions.[78] Differences in the distribution of reasons for discontinuation of treatment will be examined using exact tests. Relative dose intensity is defined as the ratio of actually delivered dose intensity to the planned dose intensity. The effects of tobacco use and

exposure on relative dose intensity (≥ 90% vs. < 90%) will be explored using logistic regression. Differences in the primary endpoint and important secondary endpoints will be examined using log rank test and exact test (as appropriate).

Data collected in the tobacco use project will support a range of analyses. Precise estimates of power will depend on the prevalence of smoking at baseline among study participants, the proportion whose smoking status changes, and the duration and adequacy of follow-up.

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