EMORY UNIVERSITY INVESTIGATOR-SPONSORED CLINICAL STUDY PROTOCOL

A phase II trial of pembrolizumab and cabozantinib in patients with RM SCCHN

PROTOCOL NUMBER: **Winship 4234-17**

STUDY DRUG: Cabozantinib (XL184)

IND NUMBER: 137,920

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SYNOPSIS

TITLE

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CLINICAL PHASE

Phase II

RATIONALE

Recent studies suggest that mechanisms of resistance to EGFR inhibition include escape signaling through other HER receptor members (HER3 through its ligand or through its heterodimerization with HER2) as well as MET expression. MET amplification may lead to resistance to EGFR through upregulation of other HER members such as HER3. In SCCHN, elevated VEGF levels have been implicated as a poor prognostic indicator of increased risk of recurrent disease in addition to radio-resistance. Activated MET signaling can lead to cell motility and scattering, angiogenesis, proliferation, branching morphogenesis, invasion, and metastasis.

Pembrolizumab is a checkpoint inhibitor that has recently been approved by the FDA for treating patients with recurrent/metastatic (RM) SCCHN who have failed platinum based therapy. In light of the fact that pembrolizumb seems to be effective in a patient population that has failed EGFR based therapy, it would make sense to combine pembrolizumab with targeted agents possibly helpful in overcoming the resistance mechanisms to EGFR, such as MET and VEGF inhibitors. The current approval for pembrolizumab in advanced SCCHN requires failure from platinum based therapy and does not require failure from EGFR based therapy such as cetuximab;

Cabozantinib is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis. Its role has been clearly established in well differentiated thyroid cancer however it has not been evaluated in SCCHN. Given the recent approval of pembrolizumab for platinum failing patients with RM disease, a combination trial of cabozantinib with pembrolizumab is a rational approach in this patient population.

OBJECTIVES

The objectives of this study are:

Primary Objectives:

Run in phase: To determine the safety and tolerability of pembrolizumab and cabozantanib in patients with recurrent and/or metastatic SCCHN

Phase II: To estimate the overall response rate (ORR) of patients with RM SCCHN who receive the combination of pembrolizumab and cabozantanib

Secondary Objectives:

- To estimate the progression free survival of patients treated with the combination of pembrolizumab and cabozantanib

- To further define the toxicities associated with these regimens in patients with SCCHN.

Exploratory Objectives:

- To identify potential biomarkers related to response to combination of pembrolizumab and cabozantanib in patients with recurrent and/or metastatic HNSCC.
    - Evaluate whether markers of angiogenesis, hypoxia, Met or pMet expression, or inflammatory activation can predict response to the combination or PFS.
    - Evaluate circulating cell free DNA (cfDNA) in plasma and its association with response to the combination or PFS.
    - Evaluate potential neoantigens in the tumor DNA, their expression, and their association with response to the combination or PFS.
    - Evaluate peripheral blood mononuclear cells (PBMC) for immune monitoring and their association with response to the combination or PFS.
- To determine a quantitative radiomics based on CT and/or PET images as a prognostic biomarker in recurrent or metastatic HNSCC.
- To determine a computational pathology (or pathomics) based prognostic marker from standard digitized H&E images of the tumor in recurrent or metastatic HNSCC.

STUDY DESIGN

Run in phase:

Pembrolizumab will be initiated in Cycle 1 at the standard dose of 200 mg Q 3 weeks.

A run in phase of cabozantinib at 40 mg/day will be performed for the first 6 patients, beginning in Cycle 1. If the combination is well tolerated the trial will complete accrual at this dose level. If the combination is not well tolerated, with 2 DLTs observed in the first 6 patients, the dose of cabozantinib will be decreased to 20 mg/day which will be the dose used for the rest of the study.

Phase II:

Pembrolizumab will be administered at the standard dose of 200 mg Q 3 weeks. Cabozantinib will be given at the dose determined in the run in phase. Both agents will be initiated on Day 1 of Cycle 1 and will continue in combination.

NUMBER OF SUBJECTS

The sample size will be up to 34 subjects in which the first 6-9 patients will be in the safety run-in phase with an interim futility assessment after 20 patients were treated.

TARGET POPULATION

Cancer patients will be eligible for enrollment as defined by the inclusion and exclusion criteria as follows:

Inclusion Criteria

1. The subject has a histologic or cytologic diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, paranasal sinuses, hypopharynx, nasopharynx or larynx. Squamous cell carcinoma of unknown primary in cervical lymph node can be included only if HPV status is positive.
2. Patients must have refractory, recurrent or metastatic disease, which is deemed to be inoperable.
3. In case patients received prior systemic therapy within the definitive or metastatic setting, disease progression must be documented following prior therapy; this can be in the recurrent or metastatic setting or in the concurrent setting.
4. Measurable disease per RECIST 1.1 as determined by the investigator;
5. A maximum of one prior radiotherapy regimen, curative or palliative, to the head and neck is allowed. If the radiation is combined with chemotherapy, a minimum of 4 months must elapse between the end of radiotherapy and registration. If the radiation is given alone, a minimum of 8 weeks must elapse between the end of radiotherapy and registration. A minimum of 3 weeks must elapse between prior radiation to other areas and registration. Treatment areas should be healed with no sequelae from RT that would predispose to fistula formation
6. The subject has had an assessment of all known disease sites eg, by computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone scan or PET/CT scan as appropriate, within 28 days before the first dose of cabozantinib;
7. The subject is ≥ 18 years old on the day of consent;
8. Life expectancy of greater than 3 months.
9. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
10. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy;
11. The subject has organ and marrow function and laboratory values as follows within 7 days before the first dose of cabozantinib:
    a. The ANC ≥ 1000/mm^3 without colony stimulating factor support;
    b. Platelets ≥ 100,000/mm^3;
    c. Hemoglobin ≥ 9 g/dL;
    d. Bilirubin ≤ 1.5 × the ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;
    e. Serum albumin ≥ 2.8 g/dl;
    f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:
        i. Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);
        ii. Female: Multiply above result by 0.85;
    g. ALT and AST ≤ 2.0 × ULN;
    h. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis;
    i. UPCR ≤ 1;
    j. Serum phosphorus, calcium, magnesium and potassium ≥ LLN.
12. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document;

13. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s);
14. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.
15. A male participant must agree to use a contraception as detailed in this protocol during the treatment period and for at least during the active treatment plus an additional 90 days (a spermatogenesis cycle) for study treatments with evidence of genotoxicity at any dose] after the last dose of study treatment and refrain from donating sperm during this period.

Exclusion Criteria

1. Patients who have HPV negative squamous cell carcinoma of unknown primary in cervical lymph node.
2. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 4 weeks, or nitrosoureas/mitomycin C within 6 weeks before the first dose of study treatment;
3. Prior treatment with cabozantinib or pembrolizumab; or any prior immunotherapy for treating squamous cell carcinoma of the head and neck;
4. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;
5. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) – such as VEGF inhibitors (examples, but not restricted to, sorafenib, sunitinib) within 14 days before the first dose of study treatment;
6. The subject has received any other type of investigational agent within 28 days or 5 half-lives, whichever is shorter, before the first dose of study treatment;
7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment;
8. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test $\geq 1.3 \times$ the laboratory ULN within 7 days before the first dose of study treatment;
9. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel);
   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, 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 ;

10. The subject has experienced any of the following:
    a. clinically-significant GI bleeding within 6 months before the first dose of study treatment;
    b. hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment;
    c. any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment.
11. The subject has radiographic evidence of cavitating pulmonary lesion(s);
12. The subject has tumor invading or encasing any major blood vessels;
13. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib;
14. The subject has uncontrolled, significant inter-current or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including:
        i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening;
        ii. Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;
        iii. Any history of congenital long QT syndrome;
        iv. Any of the following within 6 months before the first dose of study treatment:
            - unstable angina pectoris;
            - clinically-significant cardiac arrhythmias;
            - stroke (including transient ischemic attack (TIA), or other ischemic event);
            - myocardial infarction;
    b. GI disorders particularly those associated with a high risk of perforation or fistula formation including:
        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
        ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,
        Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization. Also no pre-existing fistula of head and neck area. No pre-existing ONJ
    c. Other clinically significant disorders that would preclude safe study participation;
15. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible;

16. QTcF > 500 msec within 1 month before the first dose of study treatment:
    a. Three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.
17. Pregnant or lactating females;
18. Inability to swallow intact tablets or inability to take pembrolizumab or cabozantinib
19. Previously identified allergy or hypersensitivity to components of the study treatment formulations;
20. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease-free for 1 year post diagnosis. Patients with a prior history of squamous cell or basal carcinoma of the skin or in situ cervical cancer must have been curatively treated.
21. Patients with known history of interstitial lung disease or idiopathic pneumonitis.

ESTIMATED LENGTH OF SUBJECT PARTICIPATION

Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression.

ESTIMATED STUDY DATES

December 2017 (first study screening visit) to December 2019 (last study follow-up visit)

INVESTIGATIONAL REGIMEN DOSE/ROUTE/DURATION

Cabozantinib is supplied as 20-mg tablets.

COMBINATION DRUG(S)

Pembrolizumab.

SAFETY ASSESSMENTS

Safety will be monitored on an ongoing basis. Laboratory testing (chemistry, hematology tests) will be performed every 3 weeks for the first 9 weeks followed by assessments every 6 weeks. Other safety evaluations including EKGs and urinalysis will be performed at regular intervals.

Adverse event seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

TUMOR ASSESSMENTS

Tumors will be assessed by RECIST v1.1 response criteria by CT/MRI or PET CT scan at a frequency of every 9 weeks.

BIOMARKER ASSESSMENTS

Tumor samples will be collected from all patients through archival tissue or biopsies performed from at least one site of disease prior to the first dose administration of therapy. Tumor samples collected through these biopsies will be compared with the historical samples and will also be analyzed to explore the biomarkers that could predict response to cabozantinib. Optional end of

treatment tumor biopsy (or at the time of progression) is allowed at both Emory Winship Cancer Institute and Moffitt Cancer Center. Patients will need to be off cabozantinib for at least 2 weeks before the biopsy

Baseline biopsies or surgical specimens from trial participants will be analyzed for the following:

- Tumor pVEGFR2/VEGFR2, pMet/Met, pSTAT3/STAT3, and PD-L1 protein expression as well as markers of hypoxia, antigen presenting cells, T cells, and B cells among the tumor infiltrating immune cells using multiplex immunohistochemistry (IHC).
- Tumor DNA whole exome sequencing and RNA sequencing to determine potential neoantigens and their expression.

Blood samples will be collected at screening, at 9 weeks on treatment, at 6 months on treatment, and end of treatment (or disease progression whichever is sooner).

- Plasma biomarkers will include HGF, IL-6, IL-8, VEGF, and IFN-γ determined by ELISA analyses.
- Circulating cell free DNA (cfDNA) in plasma will be determined by DNA sequencing.
- Peripheral blood mononuclear cells (PBMC) will be evaluated by flow cytometry for immune monitoring.

For a quantitative radiomics, CT and/or PET images will also be collected. For quantitative pathomics, digitized H&E images will also be collected.

STATISTICAL METHODS

The sample size will be up to 34 subjects in which the first 6 patients will be in the safety run-in phase with an interim futility assessment after 20 patients were treated.

The ORR for this patient population is reported as 18% with pembrolizumab as a single agent. We estimate that the ORR will improve to about 35% with the combined treatment. We expect to accrue patients for 2 years and follow up for additional 12 months. The sample size will be 34 by a one-arm design with null hypothesis as ORR <=0.15 vs. its one-sided alternative. If the number of responses is <= 9 out of 34, the trial will be claimed as not promising. The design yields a type 1 error of 0.05 and a power of 80% when the true response rate is 35%. An interim look after 20 patients will take place, and if <= 4 responses are observed, the trial will stop earlier and claim a futility.

Statistical analysis for biomarker studies: The ORR will be calculated with 95% confidence interval by Binomial distribution. The median PFS will be estimated by Kaplan-Meier method along with 95% confidence interval. The ability of biomarkers to predict ORR will be estimated by Chi-square test and/or logistic regression model, and association with PFS will be assessed by the Kaplan Meier method, Log-rank test, and Cox model, and the frequency of adverse events and serious adverse events will be summarized accordingly.

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AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
BP	blood pressure
BUN	blood urea nitrogen
CHF	congestive heart failure
CrCl	creatinine clearance
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESC	Exelixis Safety Committee
ESMO	European Society of Medical Oncology
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GI	gastrointestinal
GGT	γ-glutamyl transferase
GnRH	gonadotropin-releasing hormone
ICH	International Conference on Harmonisation
IME	important medical event
INR	International Normalized Ratio
IRB	Institutional Review Board
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LMWH	low molecular weight heparin
LLN	lower limit of normal

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PD	progressive disease
PE	pulmonary embolism
PI	principal investigator
PPE	palmar-plantar erythrodysesthesia
PT	prothrombin time
PTT	partial thromboplastin time
qd	once daily
ONJ	osteonecrosis of the jaw
QTc	corrected QT interval
QTcF	QTc calculated by the Friderica formula
RBC	red blood cell
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SBP	systolic blood pressure
TFT	thyroid function test
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein/urine creatinine ratio
VEGF(R)	vascular endothelial growth factor (receptor)

1 BACKGROUND AND RATIONALE

1.1 Background:

SCCHN:

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common malignancy worldwide, representing a major international health problem. In the United States, close to 59,000 new cases of oral cavity, pharyngeal, and laryngeal cancers were estimated in 2015 accounting for 3.3% of new cancers and close to 12,000 deaths (1). Despite advances in multimodal therapy, the survival rates and functional outcomes of patients remain limited with an overall 5-year survival rate that is still close to 50% (1). Novel strategies are urgently needed particularly in patients with recurrent or metastatic disease. The majority of patients with SCCHN are diagnosed with locally advanced regional disease, and in more than 50 percent of cases, the disease is incurable and relapses locally or at distant sites (2-4). Patients with relapsed or metastatic SCCHN have a poor prognosis and limited therapeutic options. Therapeutic advances, such as the use of multi-modality therapies, have significantly improved survival of advanced stage SCCHN patients over the past 10-15 years (5-7). However, still 30-40% of patients have recurrences or distant metastases (8, 9). There has been very little improvement in survival in this group of patients. Chemotherapeutic agents employed in the management of recurrent and/or metastatic SCCHN include methotrexate, taxanes and platinum-based regimens with response rates in the range of 10-40% (10-12). Unfortunately, the duration of response is limited (2-4 months) and a survival advantage has not been shown beyond the median survival of 6-10 months (13, 14).

EGFR in SCCHN:

The human epidermal growth factor receptor (EGFR) family consists of four types of trans-membrane tyrosine kinase receptors, HER1 (EGFR, ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). The general structure of ErbB members includes an extracellular ligand-binding region, an α-helical trans-membrane segment, a cytoplasmic tyrosine-kinase-containing domain, and a C-terminal phosphorylation tail (15, 16). ErbB members are widely expressed in epithelial, mesenchymal, and neuronal tissues and regulate cell division, proliferation, differentiation, and other normal cellular processes (17, 18). The ErbB network is key to important signaling pathways and has been preserved throughout evolution.

The epidermal growth factor receptor (EGFR) is a 170 kDa membrane-anchored protein tyrosine kinase that has been implicated in tumorigenesis. Ligands such as transforming growth factor alpha or EGF activate the EGFR, resulting in its dimerization or heterodimerization with other

receptors that are closely related such as Her2/neu. Phosphorylation of these receptors through their tyrosine kinase domains leads to the recruitment of downstream effectors and activation of proliferation and cell-survival signals (19). This process appears to be overactive in malignancy (20).

Although expressed in non-malignant cells, the EGFR is highly expressed in a variety of tumors, and its expression is correlated with poor response to treatment and poor survival (21). EGFR activation has been shown to promote tumor proliferation, angiogenesis, metastases and invasion (22). Abnormal EGFR signaling is reportedly correlated with advanced disease, poor response to chemotherapy and poor prognosis (23, 24). Human malignancies use several mechanisms that activate the EGF pathway, including overproduction of ligands, overproduction of receptors or constitutive activation of receptors (25, 26). EGFR is expressed in many normal epithelial tissues, and overexpression occurs in many types of tumors including esophageal (92%), head and neck (90%) and colorectal (72%) cancer (27, 28).

The EGFR is expressed in more than 80% of SCCHN (29). Ligand binding, resulting in homodimerization or heterodimerization with other HER family members, causes phosphorylation of the tyrosine kinase domain and cell proliferation. The EGFR-specific monoclonal antibody drug cetuximab decreases tumor cell line growth, and increases apoptosis of SCCHN cells (30). *In vitro* and xenograft studies have shown that cetuximab decreases tumor cell proliferation (31-34).

The combination of cetuximab with radiation therapy for the treatment of locally advanced SCCHN disease significantly improved loco-regional control and median overall survival compared to radiation therapy alone (35). In addition, for patients with recurrent metastatic disease, cetuximab plus platinum-based chemotherapy doublet (cisplatin or carboplatin) improved survival as well as response rate when compared to platinum based chemotherapy alone (36). These results led to the approval of cetuximab for SCCHN both in the concurrent and metastatic settings. Since the approval of cetuximab, efforts have focused on combining EGFR inhibitors with systemic cytotoxic therapies with the goal of improving outcome for patients with locally advanced as well as metastatic SCCHN. None of these efforts have led yet to the adoption of a novel standard of care in first line recurrent or metastatic SCCHN. Despite the success, the overall response rate to cetuximab as a single agent does not exceed 13% with a response duration less than 70 days (37). In addition, a number of patients frequently display primary resistance to EGFR monoclonal antibodies; acquired resistance may also emerge over time (38, 39). Possible mechanisms for *de novo* and acquired resistance to cetuximab include mutations in the KRAS, BRAF and NRAS genes (38), a secondary mutation (S492R) in the

extracellular domain of EGFR receptor (38, 39), overexpression of the MET proto-oncogene (c-Met) (40), and in SCCHN, the expression of the in-frame deletion mutation of EGFR variant III (41).

Despite the fact that cetuximab is the only approved targeted agent in SCCHN, the clinical response to cetuximab therapy in this disease is fairly meager (42). Possible mechanisms of resistance to EGFR based therapy may include up-regulation of EGFR (43), resistance through dimerization with other HER members such as HER2 and HER3 and its ligand neuregulin (NRG), as well as nuclear translocation of EGFR (42, 44). In addition, mutations in the extracellular EGFR domain such as EGFRvIII (45) have been reported in SCCHN. Intracellularly, downstream signaling pathways may be constitutively activated as a mechanism to overcome EGFR inhibition; such pathways include the Ras/Raf/ MEK/MAPK and the PI3K/AKT/mTOR pathways (46-49).

Recently, an increasing body of literature has suggested that resistance to anti-EGFR therapy arises frequently through activation of alternative signaling pathways that bypass the original target (50, 51). Compensatory HER3 signaling and sustained PI3K/AKT activation are associated with sensitivity and resistance to anti-EGFR targeted therapies, especially in SCCHN (50-53). Unlike other HER receptors, HER3 has diminished intracellular kinase activity but has known ligands. These characteristics make HER3 an obligate heterodimerization partner for HER2 (53).

MM-121 (SAR256212) is a fully human IgG2 antibody that directly binds to the extracellular domain of HER3 (54, 55) and induces receptor downregulation. We have explored the activity of MM-121 as a single agent and in combination with cetuximab in preclinical models of SCCHN. Our findings indicate that HER3 is active in the majority of SCCHN cell lines, and that a combination of EGFR and HER3 inhibition with cetuximab and MM-121 provides improved antitumor activity relative to either inhibitor alone. Of note is that the combination inhibited signaling *in vitro* and *in vivo* through both ERK and PI3K/AKT pathways (56). These findings provide a rationale to target HER3, HER2 and HER1 in order to overcome resistance to cetuximab.

Recent data reported at the American Society of Clinical Oncology (ASCO 2014) have suggested that the use of HER3 inhibitors in different tumor types such as ovarian, breast and lung carcinoma has clinical activity based on a certain biomarker profile mostly centered around heregulin (HRG) expression in primary tumor samples. In general, a high NRG expression has correlated with improved outcome when HER3 inhibition was added to the standard systemic therapy in these tumor types. We also reported in the same meeting that HRG is associated with worse overall survival in a retrospective database of patients with SCCHN treated at our institution (Figure 1) (57, 58). It has however not been possible to further develop HER3 inhibition in SCCHN in light of the negative clinical trials in other disease sites and lack of interest from sponsors to develop such a concept; we therefore have chosen to use a pan HER inhibitor instead of a specific HER3 inhibitor in combination with cetuximab in patients who have failed cetuximab based therapy. Our focus on MET stems from the fact that there is a clear correlation between failure from EGFR-based therapy and upregulation of other HER pathways as well as MET. NRG is the ligand for HER3 signaling and has been implicated in the resistance to a number of cytotoxic therapies including taxanes and other anti-cancer agents in preclinical models (59, 60).

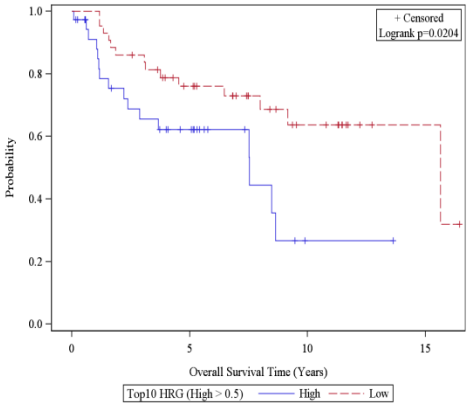

Figure 1: Association between HRG expression and OS in a retrospective database of patients with SCCHN treated at Emory

The HER3 ligand HRG was shown to be over-expressed to a greater degree in SCCHN cell lines compared to other cell lines (61). When we compared the expression of HER3 and HRG in different types of tumors including squamous cell and non-squamous cell cancers using data from TCGA, heregulin expression was higher in SCCHN compared to other tumor types (Figure 2) (57). We have also explored the levels of EGFR, HER2, HER3, and HRG and their clinical associations in a retrospective tissue repository of 96 patients with a diagnosis of oropharyngeal HPV positive and negative SCCHN. EGFR, HER2, and HER3 levels were measured by qIHC and HRG mRNA was measured by RNA ISH. p16 status was determined by IHC and HPV status was confirmed by HPV DNA ISH. The correlations between each protein level and clinical characteristics and their effects on disease-free survival (DFS) or overall survival (OS) were also assessed, and our data were presented at ASCO 2014 (62). Strikingly, a high HRG level was correlated with a worse overall survival in both HPV positive and negative SCCHN (57).

MET and its role in resistance to HER inhibition in SCCHN:

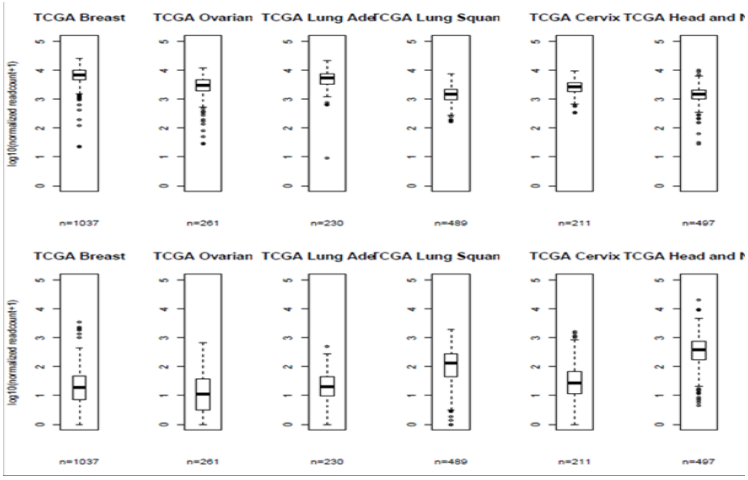

Figure 2: HER3 and HRG expression in different tumor types (TCGA data).

Activation of c-Met signaling can lead to angiogenesis, proliferation, enhanced cell motility, invasion, and eventual metastasis. c-Met is a disulfide linked a-b heterodimeric membrane RTK that has been previously identified as a protooncogene and is expressed in both normal and malignant cells (63-65). c-Met has high affinity to scatter-factor/ hepatocyte growth factor (HGF), which is its only known ligand (for review see references (66-69)). Mature c-Met is composed of disulfide bound α- and β-subunits. The extracellular α-subunit contains the ligand binding domain and the β-subunit holds the juxtamembrane and tyrosine kinase domains. Binding of HGF triggers dimerization and transphosphorylation at the C-terminus of the receptor. In addition, c-Met is able to interact with EGFR, HER2, and HER3 through dimerization (70-72). The human Met (HGF receptor) gene is located on chromosome 7 band 7q21–q31 and spans more than 120 kb in length (73, 74). HGF is a member of the plasminogen-related growth factor (PRGFs) family, thus is sometimes also referred to as PRGF-1. The gene encoding HGF spans 70 kb on chromosome 7q21.1 and is initially produced as pro-HGF, which is subsequently cleaved by a protease to HGF (75, 76).

MET receptor tyrosine kinase and its ligand HGF regulate a variety of cellular functions, many of which can be dysregulated in human cancers. Activated MET signaling can lead to cell motility and scattering, angiogenesis, proliferation, branching morphogenesis, invasion, as well as metastasis (77). Activation of HGFR can occur through binding to its ligand, HGF, overexpression/amplification, mutation, and/or decreased degradation. Amplification of HGFR can occur *de novo* or in resistance to therapy (78). In pre-clinical studies of SCCHN cell lines and tissue analysis, 84% of SCCHN samples showed MET overexpression, whereas 18 of 20 SCCHN cell lines (90%) expressed MET. HGF overexpression was present in 45% of SCCHN. In addition, MET inhibition abrogated MET signaling, cell viability, motility/ migration *in vitro*, and tumor angiogenesis *in vivo* (79). There does not seem to be a clear pattern of MET expression as a function of HPV status; Met expression and gene amplification were not associated with survival outcomes in oropharyngeal SCC patients, whereas HGF may be a

potential prognostic marker in HPV-negative disease (80). HER family members have increased activity in cetuximab-resistant SCCHN and NSCLC cells and MET expression seems to be increased in these cells as well (44). MET amplification leads to resistance to EGFR inhibition by activating ERBB3 signaling; In addition, concurrent inhibition of MET and EGFR suppresses growth of HCC827 GR cells and leads to down-regulation of ERBB3/PI3K/AKT signaling, further supporting the rationale for combining EGFR inhibition with MET inhibition (81).

Compensatory c-Met signaling and sustained RAS/RAF/MEK/ERK and PI3K/AKT activation have been associated with sensitivity and resistance to anti-EGFR agents in different tumor types (40, 82, 83). Increasing *c-Met* copy numbers and mutations in the kinase domain have been reported in SCCHN (69, 84, 85). These mutations were significantly correlated with lymph node and distant metastasis (86). Examining SCCHN tissues by immunohistochemistry (IHC) revealed overexpression and activation of c-Met in 85% and 66% of cases, respectively (84). Nisa *et al*., has summarized c-Met expression and its correlation with clinico-pathological features of SCCHN from 14 publications in a review article (67). Furthermore, activated c-Met signaling was detected in cancer stem-like cells in SCCHN and shown to contribute to resistance to chemoradiation therapies (87, 88). Taken together, c-Met plays an important role in the development and progression of cancers, including SCCHN.

Similar to resistance to EGFR targeted therapy, accumulated evidence demonstrates that activation of EGFR/HER3 pathways is responsible for resistance to c-Met targeted therapy (71, 72, 89-91).

Immune checkpoint inhibitors in SCCHN:

Targeted immunotherapy has resulted in improved survival and durable objective responses in different solid tumors and offers a rationale for use in SCCHN (92); PD-L1 expression is observed in close to 68% of SCCHN patients regardless of HPV status (93, 94). Furthermore immune checkpoint inhibitors (CPIs) such as the PD-1 inhibitors nivolumab and pembrolizumab were recently noted to have a significant clinical activity in heavily pre-treated patients with SCCHN regardless of HPV status (95)(96).

The FDA granted accelerated approval for pembrolizumab based on results from the Keynote-012 trial in 174 patients with recurrent/metastatic SCCHN who had disease progression on or after platinum-containing chemotherapy. In the first arm, patients with PD-L1-postive HNSCC received pembrolizumab at 10-mg/kg (n = 60). In the second group, patients received pembrolizumab at 200 mg every 3 weeks regardless of PD-L1 status (n = 132). The objective

response rate (ORR) was 16%, complete response rate of 5%, and responses lasting for 6 months or longer observed in 82% (23/28) of the responding patients. The ORR and duration of response were similar regardless of human papillomavirus (HPV) status (96). Safety data were evaluated in 192 patients with SCCHN receiving at least one dose of pembrolizumab 10 mg/kg every 2 weeks or 200 mg every 3 weeks. The most common (greater than or equal to 20%) adverse reactions were fatigue, decreased appetite, and dyspnea. A more recent analysis reported ORR of 18% and 6-month PFS and OS rates of 23% and 59%, respectively (97).

Full FDA approval for pembrolizumab is contingent upon confirmatory results from a larger study. Currently, the phase III KEYNOTE-040 study is comparing pembrolizumab with methotrexate, docetaxel, or cetuximab in 466 patients with recurrent or metastatic head and neck cancer. The primary completion date for this study is January 2017, and the study has fully accrued. (NCT02252042). In a second phase III study, pembrolizumab is being explored as a frontline treatment for patients with recurrent or metastatic HNSCC. The PD-1 inhibitor is being compared with platinum-based chemotherapy plus 5-FU and cetuximab or in combination with platinum-based therapy and 5-FU. This study plans to enroll 780 patients, with an estimated primary completion date of November 2017 (NCT02358031).

These studies support the use of PD-1 inhibitors in a heavily pre-treated patient population who are at high risk of recurrence and disease related mortality such as patients with recurrent platinum and cetuximab refractory disease who cannot be cured with local therapies.

More recent results from the KN048 revealed that response to Pembrolizumab in the first line setting is close to 18%; Pembrolizumab in combination with chemotherapy resulted in superior overall survival to platinum based regimen for patients with recurrent or metastatic disease regardless of PD-L1 status and was superior to chemotherapy for patients with PD-L1 positive disease (CPS score >1) (Burtness B et al, ESMO 2018)

1.2 Cabozantinib (XL184)

1.2.1 Pharmacology

Cabozantinib is a multi-targeted inhibitor of RTKs. Cabozantinib inhibits several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization, namely MET, VEGFR2 (also known as KDR), AXL, and RET. Other recognized targets include ROS1, TRKA, TRKB, TIE2, TYRO3, MER, VEGFR1, VEGFR3, KIT and FLT-3. Similar to other drugs targeting RTKs, cabozantinib binds in a fully reversible manner to a region of the kinase

domain (including the ATP-binding site) which forces the kinase activation loop into a pseudo-inactive conformation, thereby inhibiting subsequent catalytic activity.

Data from pharmacodynamic experiments have shown that cabozantinib inhibits MET and VEGFR2 in vivo. Treatment with cabozantinib results in anti-angiogenic effects in xenograft tumors and is associated with pro-apoptotic effects. These effects translate into significant tumor growth inhibition or tumor regression after cabozantinib treatment in multiple tumor models including MTC, breast cancer, lung carcinoma, and GB (Yakes et al. 2011). Data from the RIP-Tag2 mouse model of neuroendocrine pancreatic cancer suggest that dual inhibition of MET and VEGFR2 with cabozantinib leads to potent antitumor efficacy, including protection from metastatic tumor escape, which translates into survival advantages.

Cabozantinib showed no adverse effects on neurobehavioral or respiratory-system function in rats, and no significant changes in cardiovascular or electrocardiographic parameters (including QTc) in telemeterized dogs at plasma exposures (AUC values) ≥ 10-fold higher clinically-relevant plasma exposures. No direct inhibition of hERG channel activity (IC50 > 30 μM) was observed for cabozantinib and four metabolites. Of 74 pharmacologic targets (including receptors, transporters, and enzymes) exposed to cabozantinib at 1 μM in an in vitro study of its inhibitory specificity, only the adenosine A3 receptor was inhibited > 50% (cabozantinib IC50 = 0.9 μM).

Nonclinical PK of cabozantinib was studied in mice, rats, dogs, and monkeys. Oral bioavailability was comparably high in rats (80-86%), dogs (87%) and monkeys (73%) and moderately high in mice (42-51%) when cabozantinib was formulated with an aqueous vehicle. In rats, systemic drug exposure parameters (Cmax and AUC0-t) increased less than dose-proportionally in association with single cabozantinib oral doses, and generally dose-proportionally with moderate accumulation (≤ 4-fold) following repeat daily oral dosing. In dogs, systemic drug exposure parameters increased less than dose-proportionally with increasing single cabozantinib oral doses, and generally dose-proportionally with little or no accumulation (≤ 2-fold increase) following repeat daily dosing.

Further details can be found in the Investigator's Brochure.

1.2.2 Cabozantinib Nonclinical Toxicology

Toxicity associated with oral administration of cabozantinib was characterized in definitive (GLP-compliant) single-dose and repeat-dose studies in mice, rats, and dogs; a fertility study in rats; embryotoxicity/teratogenicity studies in rats and rabbits; juvenile toxicity studies in rats; in

vitro and in vivo genotoxicity bioassays; and an in vitro phototoxicity study. Target tissues for cabozantinib-related toxicity identified in these studies include GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, kidney and skin. Histopathologic changes were also present in bone, central nervous system (CNS) tissues and liver/gall bladder. Adverse findings associated with cabozantinib administration were: (1) generally dose-related; (2) often correlative with clinical signs and/or clinical pathology parameter changes reflective of associated target tissue histopathologic findings; (3) generally reversible upon discontinuation of treatment; and (4) often observed in both rodent and non-rodent species. In definitive reproductive and developmental toxicity studies, cabozantinib reduced fertility in male and female rats, was embryotoxic in rats, produced a fetal soft-tissue malformation (small spleen) in rabbits and produced fetal external malformations (cleft palate/lip, dermal aplasia and kinked or rudimentary tail) in rats. Cabozantinib was negative in in vitro bacterial and mammalian genotoxicity, clastogenicity, and phototoxicity bioassays. The metabolite present at highest plasma concentrations in humans administered cabozantinib, EXEL-1644, was negative in an in vitro bacterial genotoxicity bioassay and caused no systemic tissue toxicity in rats dosed subcutaneously with EXEL-1644 for two weeks.

The carcinogenic potential of cabozantinib is being evaluated in an ongoing two-year bioassay in rats. No carcinogenic signal was observed in the rasH2 transgenic mouse model following cabozantinib dosing for 26 weeks.

Further details can be found in the Investigator's Brochure.

1.2.3 Clinical Experience

1.2.3.1 Clinical Summary

Details of all studies may be found in the Investigator's Brochure.

1.2.3.2 Clinical Safety Profile

A pooled analysis through 29 February 2016 included 2410 subjects with cancer who had been treated with single-agent cabozantinib in company-sponsored clinical trials. The subjects in that dataset were predominately White (83.4%) and male (77.5%) with a median age of 64.0 years; the gender distribution reflects the inclusion of CRPC studies in the pooled analysis. Summaries of safety data were also captured for several individual studies including phase 3 studies.

The severity of AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 or version 4.0, and AE and SAE PTs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 for all studies. For AEs and SAEs,

multiple occurrences of the same event in any individual subject are counted once at the highest grade reported. Events that were assessed as possibly related or probably related to cabozantinib are reported as "related," and events that were assessed as not related or unlikely related to cabozantinib are reported as "not related."

1.2.3.2.1 Adverse Events

In the pooled analysis of 2410 patients treated with single-agent cabozantinib, the most common AEs (≥ 5% incidence) reported at severity of Grade 3 and above were fatigue (15.3%), hypertension (13.7%), diarrhea (10.4%), anemia (8.3%), PPES (7.7%), asthenia (6.8%), pulmonary embolism (6.1%), and decreased appetite (5.6%).

The most frequently (≥ 20% incidence) observed AEs reported as related to cabozantinib were diarrhea (53.9%), fatigue (53.2%), decreased appetite (44.8%), nausea (44.1%), PPES (34.0%), weight decreased (27.8%), vomiting (25.4%), dysgeusia (25.1%), hypertension (25.0%), and dysphonia (21.6%).

Based on AE data available as of the data cutoff dates, 533 subjects (22.1%) in the pooled single-agent cabozantinib studies discontinued cabozantinib due to an AE (including events related to disease progression). The most frequently reported AEs (≥ 1% of subjects) that led to treatment discontinuation were fatigue (2.9%), general physical health deterioration (1.8%), asthenia (1.3%), decreased appetite (1.2%), nausea (1.0%), and diarrhea (1.0%).

Further details can be found in the Investigator's Brochure.

1.2.3.2.2 Serious Adverse Events

The most commonly reported SAEs (≥ 1% incidence), excluding events of disease progression, were pulmonary embolism (5%), vomiting (3.4%), nausea (3%), general physical health deterioration (2.9%), dehydration (2.9%), and pneumonia (2.9%).

Further details can be found in the Investigator's Brochure.

1.2.3.2.3 Deaths

As of 29 February 2016, the incidence of Grade 5 AEs from the pooled single-agent studies was 10.5% (254 subjects). The Grade 5 events that occurred at the highest frequency (≥ 1% incidence) were prostate cancer (2.9%) and general physical health deterioration (1.0%). Since prostate cancer was the progression of cancer in CRPC studies, only general physical health deterioration was assessed as related to study treatment. Thirty-three (33) of the 254 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).

Further details can be found in the Investigator's Brochure,

1.2.3.3 Clinical Pharmacokinetics

The clinical pharmacology of cabozantinib (XL184) has been characterized in studies in healthy subjects and cancer subjects evaluating in vivo drug-drug interaction potential, effect of food intake on cabozantinib plasma PK, intrinsic and extrinsic factors as covariates in a PopPK analysis, and routes of elimination and metabolite identification.

Details can be found in the Investigator's Brochure.

1.2.3.4 Clinical Activity

Cabozantinib has been evaluated in three Phase 3 clinical trials, in renal cell carcinoma (Study XL184-308 (METEOR; N=658)), medullary thyroid cancer (Study XL184-301 (EXAM; N=330)), and castration-resistant prostate cancer (Study XL184-307 (COMET-1; N=1023)).

Study XL184-308 enrolled patients with histologically or cytologically confirmed advanced RCC with a clear cell component, measurable disease by CT/MRI per Response Evaluation Criteria in Solid Tumors (RECIST), and who had received treatment with at least one prior VEGFR-TKI. Eligible subjects were randomized 1:1 to receive either cabozantinib (60 mg, tablet formulation) or everolimus (10 mg) which was the standard of care for the second-line setting at the time of the initiation of the study. The primary PFS analysis in the Primary Endpoint Intent-to-Treat [PITT] population (N=375) demonstrated a statistically significant improvement in PFS per IRC for subjects in the cabozantinib arm (n=187) compared with the everolimus arm (n=188): the HR adjusted for stratification factors was 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value < 0.0001). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs 3.8 months in the everolimus arm. The second interim OS analysis with 13 months of follow-up demonstrated a highly statistically significant prolongation of OS for subjects in the cabozantinib arm compared with the everolimus arm: the HR, adjusted for stratification factors was 0.66 (95% CI: 0.53, 0.83; stratified log-rank p-value 0.0003). Kaplan-Meier estimates for median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm.

Study XL184-301 enrolled 330 patients with medullary thyroid cancer with radiographically documented disease progression by modified RECIST (mRECIST) compared with a radiologic assessment performed within the previous 14 months. The estimated median PFS was 11.2

months for cabozantinib versus 4.0 months for placebo (HR 0.28; 95% CI, 0.19 to 0.40; p < .001). The estimated median OS for the cabozantinib arm was 26.6 months versus 21.1 months for the placebo arm (HR = 0.85; 95% CI 0.64, 1.12; p = 0.2409). The subgroup analysis of subjects with a RET M918T mutation revealed a larger improvement in OS for the cabozantinib arm: the median OS was 44.3 months for the cabozantinib arm versus 18.9 months for the placebo arm (HR = 0.60; 95% CI 0.38, 0.94; p = 0.0255 not adjusted for multiple subgroup analyses.

Study XL184-307 enrolled 1023 subjects with advanced CRPC with bone metastases. The prespecified primary analysis of the primary endpoint (OS) was based on an ITT analysis of all randomized subjects. The analysis included 614 events (578 were required) and did not demonstrate a statistically significant improvement in OS for subjects in the cabozantinib arm compared with the prednisone arm: the adjusted HR was 0.90 (95% CI: 0.76, 1.06; stratified logrank p-value 0.213). The Kaplan-Meier estimates for median duration of OS were 11.0 months in the cabozantinib arm and 9.8 months in the prednisone arm, an estimated 1.2 month difference in the medians. The secondary efficacy endpoint was the proportion of subjects with a BSR per IRC at Week 12. BSR was defined as a ≥ 30% decrease in total bone-scan lesion area compared with baseline without soft-tissue disease progression. The analysis demonstrated a statistically significant improvement in the cabozantinib arm compared with the prednisone arm (42% vs 3%; stratified Cochran-Mantel-Haenszel [CMH] p-value < 0.001). The median duration of BSR was 5.8 vs 1.8 months. Median PFS per Investigator was 5.6 months in the cabozantinib arm and 2.8 months in the prednisone arm. The HR adjusted for randomization stratification factors was 0.48 (95% CI 0.40, 0.57; stratified logrank p-value < 0.0001).

Further details can be found in the Investigator's Brochure.

1.2.3.5 Translational Medicine

In RCC, tumor MET status was assessed as a biomarker. Subgroup analyses demonstrated benefits for treatment with cabozantinib over everolimus for subjects irrespective of baseline MET status.

In MTC, exposure to cabozantinib resulted in significant changes in levels of the circulating biomarkers placental growth factor (PlGF), VEGF, soluble VEGFR2 (sVEGFR2), and erythropoietin (EPO). Calcitonin (CTN) and carcinoembryonic antigen (CEA) levels and doubling times in subjects with MTC have been found to correlate with tumor burden and risk of progressive disease (PD), respectively (Giraudet et al. 2007). There were clear treatment-related reductions in both markers in the majority of subjects with MTC in Study XL184-001 treated

with cabozantinib. In the placebo-controlled Phase 3 Study XL184-301, from baseline to Week 12, the cabozantinib arm displayed significant decreases in CTN (mean of -45.2%) compared with increases in the placebo arm (mean of +57.3%; $P < 0.001$). Changes in CEA levels from baseline to Week 12 showed a similar trend (-23.7% in the cabozantinib arm compared with +88.7% in the placebo arm; $P < 0.001$). A generally linear relationship was observed when changes in CTN and CEA from baseline to Week 12 (up to approximately 200% increases) were compared with changes in target lesion size. In the Phase 3 Study XL184-301, archival tumor samples to determine RET mutational status in tumors and a whole blood sample to determine hereditary RET status were collected. The subgroup analysis of subjects with a RET M918T mutation revealed a larger improvement in OS for the cabozantinib arm: the median OS was 44.3 months for the cabozantinib arm versus 18.9 months for the placebo arm.

In CPRC, circulating biomarker analyses have focused on markers of bone turnover, including the C-terminal cross-linked telopeptides of type I collagen (CTx) and N-terminal cross-linked telopeptides of type I collagen (NTx), which are markers of osteoclast activity and bone resorption, and bone-specific alkaline phosphatase (BSAP), a marker of osteoblast activity and bone formation. In a Phase 3 comparator-controlled study (XL184-307), treatment with cabozantinib (60 mg qd) decreased these biomarkers to a greater extent than in the prednisone arm based on best change from baseline at Week 6 or Week 12 (BSAP: -10% cabozantinib, 11% prednisone; NTx: -24%, 0%; CTx: -12%, 0%). When assessing circulating tumor cells (CTCs) in the same study, a higher percentage of subjects in the cabozantinib arm with ≥ 5 CTCs/7.5 mL blood at baseline converted to < 5 cells post-baseline (cabozantinib 33%, prednisone 6%). Conversely, a lower percentage of subjects in the cabozantinib arm with < 5 CTCs/7.5 mL blood at baseline converted to ≥ 5 cells as best post-baseline result (cabozantinib 5%, prednisone 19%).

Further details can be found in the Investigator's Brochure.

1.3 Rationale

Rationale for targeted therapy in SCCHN focusing on checkpoint inhibitors and MET inhibition:

Based on the aforementioned studies, it is clear that mechanisms of resistance to EGFR inhibition include escape signaling through other HER receptor members (namely HER3 through its ligand or through its heterodimerization with HER2) as well as MET expression. It is clear that MET amplification may lead to resistance to EGFR through upregulation of other HER members such as HER3 (81). In SCCHN, elevated VEGF levels have been implicated as a poor prognostic indicator of increased risk of recurrent disease in addition to radio-resistance (98, 99).

Activated MET signaling can lead to cell motility and scattering, angiogenesis, proliferation, branching morphogenesis, invasion, as well as metastasis (77).

Pembrolizumab is a checkpoint inhibitor that has recently been approved by the FDA for treating patients with RM SCCHN who have failed platinum based therapy. In light of the fact that pembrolizumb seems to be effective in a patient population that has failed EGFR based therapy, failed platinum based therapy as well as patients who have not had systemic therapy, it would make sense to offer this agent in all of these clinical scenarios; it would also make sense to combine pembrolizumab with targeted agents that are possibly helpful in overcoming the resistance mechanisms to EGFR, such as MET and VEGF inhibitors and be good therapeutic partners with Pembrolizumab.

Cabozantinib is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis. Its role has been clearly established in medullary thyroid cancer however it has not been evaluated in SCCHN. Given the recent approval of pembrolizumab for platinum failing patients with RM disease, as well as its approval in the first line setting, a combination trial of cabozantinib with pembrolizumab is a rational approach in this patient population.

There may be possible cooperative effects between pembrolizumab and cabozantinib based on cabozantinib's role in supporting a more immune permissive environment. It was recently shown that a suppressive tumor microenvironment plays a major role in the immunosuppression observed in patients with SCCHN; this is now better corroborated through biomarker studies suggesting that an inflamed T cell phenotype in the microenvironment contributed to a higher response to single agent pembrolizumab (Abstract #6009, ASCO 2017). Since cabozantinib produces a more immune permissive environment (Cabozantinib IB version 13, section 4.2.2), its combination with a checkpoint inhibitor such as pembrolizumab is welcomed.

In this protocol we will be starting with a cabozantinib dose of 40 mg daily instead of 60 mg daily, which is the dose approved for renal cell carcinoma. The rationale is based on unpublished information obtained from investigators indicating a poor tolerance to the combination of high dose cabozantinib at 60 mg with PD-1 inhibitors.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The objectives of this study are as follows:

Primary Objectives:

To estimate the overall response rate (ORR) of patients with RM SCCHN who receive the combination of pembrolizumab and cabozantinib.

Secondary Objectives:

- To estimate the progression-free survival (PFS) of patients treated with the combination of pembrolizumab and cabozantinib.
- To further define the toxicities associated with these regimens in patients with SCCHN.

Exploratory Objectives:

- To identify potential biomarkers related to response to the combination of pembrolizumab and cabozantinib in patients with RM SCCHN. Specifically, to evaluate whether markers of angiogenesis, hypoxia, Met or pMet expression, or inflammatory activation can predict response to the combination or PFS.
- To gather exploratory clinical data on a potentially predictive set of biomarkers (potential biomarkers include MET expression by FISH, NGS and IHC/IHF of cMET, pMET, HGF, HER2, HER3 and heregulin mRNA level).
- To evaluate circulating cell free DNA (cfDNA) in plasma and its association with response to the combination or PFS.
- To evaluate potential neoantigens in the tumor DNA, their expression, and their association with response to the combination or PFS.
- Evaluate peripheral blood mononuclear cells (PBMC) for immune monitoring and their association with response to the combination or PFS.
- To determine a quantitative radiomics based on CT and/or PET images as a prognostic biomarker in recurrent or metastatic HNSCC.
    - To determine a computational pathology (or pathomics) based prognostic marker from standard digitized H&E images of the tumor in recurrent or metastatic HNSCC.
-

Endpoints

Primary Endpoint

ORR: The proportion of subjects with partial response (PR) or complete response

(CR) as defined by RECIST v1.1 response criteria.

Secondary Endpoints

PFS: The duration from date of treatment start to the date of objectively documented progression or death due to any cause, whichever status is recorded first.

2.2 Study Design

2.2.1 Overview of Study Design

All patients will require measurable disease by RECIST 1.1 and will need documentation of disease progression after platinum based therapy; archival tissue will need to be submitted; if archival tissue is not possible a fresh biopsy is mandated.

Run-in phase:

Pembrolizumab will be initiated in Cycle 1 at the standard dose of 200 mg Q 3 weeks for one cycle.

A run in phase of cabozantinib at 40 mg/day will be performed for the first 6 patients, beginning in Cycle 1. If the combination is well tolerated (<2 DLTs in the first cycle), the trial will complete accrual at this dose level. If the combination is not well tolerated, with 2 DLTs in the first treatment cycle observed in the first 6 patients, the dose of cabozantinib will be decreased to 20 mg/day which will be the dose used for the rest of the study.

DLT Criteria

Adverse events (AEs) will be graded in accordance to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (v4.0). Dose-limiting toxicity (DLT) is defined as any of the following treatment-<u>related</u> AEs occurring during the DLT Evaluation Period, which will be during the first cycle of combined pembrolizumab and cabozantinib.

- <u>Treatment-Related Non-Hematologic AEs:</u>

    1. Any related ≥ Grade 3 AE which is unexpected in severity and/or duration compared to the known safety profiles of cabozantinib and pembrolizumab when used as single agents, and that cannot be managed by dose modification (reduction or interruption) and adequate supportive care, and requires permanent discontinuation of cabozantinib and/or pembrolizumab.

2. Inability to take ≥ 75% of the total planned cabozantinib dose for the DLT Evaluation Period because of a treatment-related AE leading to dose reductions and/or interruptions

For the AEs described in Section 3.3.2 - 3.3.2.19, the specific AE management guidelines in this section should be followed to determine the need for dose reductions and dose interruption.

- Treatment-Related Hematologic AEs:

    1. Grade 3 neutropenia of ≥ 7 days duration or any Grade 4 neutropenia

    2. ≥ Grade 3 febrile neutropenia;

    3. All other hematologic toxicities of Grade 4 (except anemia as described in Section 3.3.2.4)

A subject will be replaced if the subject does not have a DLT but is not fully evaluable for DLT due missing more than 25% in total of the dosing days due to progressive disease or for reasons other than cabozantinib-related toxicity.

Each subject's course will consist of three periods:

- A Pre-Treatment Period in which subjects are consented and undergo screening assessments to be qualified for the study (Section 16.o);

- A Treatment Period in which subjects receive study treatment and undergo study assessments (Section 16.o);

- A Post-Treatment Period in which subjects no longer receive study treatment but undergo follow-up study assessments and contacts (Section 16.o).

Phase II:

Pembrolizumab will be administered at the standard dose of 200 mg Q 3 weeks. Cabozantinib will be given at the dose determined in the run in phase. Both agents will be initiated on Day 1 of Cycle 1 and will continue in combination for the rest of the study.

Patients will be evaluated every 3 weeks on the study with a physical exam, clinic visit. CT scans MRIs or PET/CT will be required for staging every 9 weeks.

2.3 Treatment Assignment

It is the responsibility of the investigator to assign a subject number before treating each subject with cabozantinib.

2.4 Blinding and randomization

Not applicable.

2.5 Study Sites

This study will be conducted at up to 2 sites: Emory Winship Cancer Institute and Moffitt Cancer Center.

2.6 Registration

Pre-registration: Emory: Pre-registration must be completed and sent to the Central Subject Registrar and to the Office of Clinical Research. After receipt of the pre-registration form and confirmation of a valid, signed informed consent form/HIPAA authorization form, the Winship Clinical Trials office will assign a patient study number.

Participating site(s): After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship Clinical Trial Office within 48 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form. The Winship Clinical Trials office will assign a patient study number to these patients.

Patient study number assignment/confidentiality: Subjects will be assigned a coded designation according to the site at which the subject signs consent. Actual names, contact information and relationship to this code will be kept secure in the Winship Clinical Research Office.

Registration: Participating site(s): The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator or designee (fax 404-778-5033) within 14 days after pre-registration but no later than 2 business days from scheduled treatment visit. Eligibility will be confirmed by a clinical principal or co-investigator and the Multi-site Coordinator or designee within 2 business days of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria. Once eligibility is confirmed, then patient will be registered and scheduled for appropriate appointments.

2.7 Withdrawals

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

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

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study
- Specific conditions described in the Management of Adverse Events Sections 3.3.2 and 3.3.2.1;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (eg, male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator / Sponsor;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;
- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- The minimum dose of study treatment will be 20 mg once daily (qd). Subjects who cannot tolerate 20 mg qd will have study treatment discontinued;

- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator

3 TREATMENTS

3.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

3.1.1 Investigational Treatment

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

3.1.2 Cabozantinib Tablets

Exelixis internal number: XL184

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round. The components of the tablets are listed in Table 3-1.

Table 3-1: Cabozantinib 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

3.2 Dose, Schedule and Route

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

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

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

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 3.3 below.

3.3 Cabozantinib Dose Modifications, Interruptions, and Discontinuation

Subjects will be monitored for AEs from the time of signing informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment.) Subjects will be instructed to notify their physician immediately at the onset of any AE. Causality assessment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.4.0.

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

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.
- Dose modification criteria for cabozantinib are shown in Table 3-3. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.
  The assigned starting dose for cabozantinib is 40 mg/day. 1 dose reduction level of cabozantinib is permitted to 20 mg/day (seeTable 3-2).
- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 3-3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.
- Dose interruptions for reason(s) other than related AEs (eg, surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Table 3-2: Dose Reductions of Cabozantinib

Guidelines for the management of specific AEs are provided in Section 3.3.2.

Assigned dose	First Dose Level Reduction
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd

When cabozantanib or pembrolizumab are discontinued for reasons deemed to be related to one or the other agent, the protocol calls for the discontinuation of both agents until and when the toxicities have reached a tolerable level (as specified in the dose modification sections) at which time both agents will be re-initiated. Patients who have interruption of both agents for more than 6 consequential weeks will be removed from the study; response assessment for these patients will still be assessed if available; in addition to assessment of OS and PFS based on the intent to treat analysis principle.

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

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

AE, adverse event.

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 3.3.2. For re-treatment criteria of study treatment after a dose hold see Section 3.3.1.1.

[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

Please refer to Sections 3.3.2.2 – 3.3.2.19 for the expected adverse events and management guidelines for cabozantinib.

3.3.1.1 Cabozantinib Dose Reinstitution and Reescalation

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

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 3-2 for the schedule of dose reductions).

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

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

3.3.2 Warnings and Precautions and Guidelines for the Management of Adverse Events

The most frequent adverse events experienced by ≥ 20% of subjects treated with cabozantinib were diarrhea, fatigue, nausea, decreased appetite, vomiting, weight decreased, PPES, constipation, hypertension, dysgeusia, dysphonia, and asthenia.

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib include anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lipase increased, lactate dehydrogenase (LDH) increased, neutropenia, ALP increased, hyponatremia, and leukopenia. Mild to moderate QTc interval prolongation (10-15ms) has also been observed with a QT interval calculated by the Fridericia formula (QTcF) not exceeding 500 ms.

Subjects may also experience medically important but less frequent adverse events including arterial and venous thrombotic AEs (eg, DVT, pulmonary embolism [PE], transient ischemic attack [TIA], and myocardial infarction [MI]), severe hemorrhagic events, proteinuria, wound healing complications, GI perforation, abscesses including intra-abdominal and pelvic abscess,

GI and non-GI fistulae formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Cabozantinib treatment should be permanently discontinued for the following adverse events: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, malignant hypertension, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw (ONJ), and RPLS.

Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections. Each dose reduction of cabozantinib should be to one dose level lower that the current dose. Dose reductions of more than one dose level are acceptable per Investigator judgment. All AEs should also be managed with supportive care at the earliest signs of toxicity. Adverse reactions are presumed to be attributable to study drug. Adverse events classified as "not related" are defined as AEs that are, without question, not associated with the study treatment and definitely attributable to another cause.

The predicted effective plasma half-life of cabozantinib is 55 hours. Thus, when initiating therapy with cabozantinib, it will take most subjects 2 to 3 weeks to reach steady state. If AEs attributable to cabozantinib occur within the initial 3-week period of dosing, early intervention with dose modifications may be justified for AEs that, if worsened, could potentially be dangerous or debilitating, because without a dose adjustment, systemic exposure of cabozantinib might be expected to increase after the onset of the AE.

Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea and vomiting. In addition, earlier onset for events of dehydration was observed in subjects with CRPC when compared with subjects with other tumor types.

3.3.2.1 Guidelines for Management of Potential Adverse Events

Sections 3.3.2.2 – 3.3.2.19 present management guidelines or warnings/precautions for the following cabozantinib treatment-emergent adverse events/serious adverse events of particular interest.

- Gastrointestinal disorders (diarrhea, nausea and vomiting, dehydration [prostate cancer studies], stomatitis and mucositis)
- Hepatobiliary disorders (elevated ALT and AST)

- Hematological disorders
- Fatigue, anorexia, and weight loss
- Skin disorders (palmar-plantar erythrodysesthesia syndrome [PPES] and rash)
- Wound healing and surgery
- Hypertension
- Thromboembolic events (venous and arterial)
- Proteinuria
- QTc prolongation
- Hypophosphatemia
- Thyroid function disorders
- Hemorrhagic events
- Osteonecrosis of the jaw (ONJ)
- Angioedema
- Musculoskeletal and connective tissue disorders
- Respiratory, thoracic, and mediastinal disorders

Please refer to the Investigator's Brochure for additional practice guidelines and management recommendations for these and other AEs potentially related to cabozantinib treatment (e.g. intra-abdominal and pelvic abscess; nervous system disorders; infections and infestations; and respiratory thoracic and mediastinal disorders) use in specific populations, and overdose and first aid measures for accidental cabozantinib exposure.

As with all investigational products, unknown AEs may occur. Subjects should be monitored closely for all AEs. As with other agents in development, additional AEs are unknown.

3.3.2.2 Gastrointestinal Disorders

The most common non-hepatobiliary GI AEs reported in clinical studies with cabozantinib regardless of causality are diarrhea, nausea, decreased appetite, vomiting, constipation, stomatitis and abdominal pain.

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. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal

agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 3-3.

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

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care in accordance to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists. When therapy with antiemetic agents does not control the nausea or vomiting to tolerable levels, study treatment should be temporarily interrupted or dose reduced per Table 3-3.

Dehydration may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

Stomatitis and Mucositis

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

During treatment with cabozantinib good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered per Table 3-2 and Table 3-3.

3.3.2.3 Hepatobiliary Disorders

Elevations of ALT, AST, and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more

frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin.

Subjects on this study may enter with increased ALT/AST serum levels up to 2 × ULN. Dose reductions of study treatment should be considered in any subject who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A subject who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (see Table 3-2) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In subjects with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In subjects who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and cabozantinib treatment interrupted. Reinstitution of study treatment after recovery of ALT, AST, and bilirubin to Grade 1 or baseline level is at the discretion of the investigator.

3.3.2.4 Hematological Disorders

Hematological toxicities (ie, neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia.

Complete blood counts with differentials and platelets should be performed regularly. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. Results of such tests are to be forwarded to the local laboratory data management vendor.

Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.

3.3.2.5 Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated in accordance to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Refer to Table 3-3 for general management guidelines.

Anorexia and weight loss should be managed in accordance to local standard of care including nutritional support. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced per Table 3-2 and Table 3-3.

3.3.2.6 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blisters, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30, avoidance of exposure of hands and feet to hot water, removal of calluses, protection of pressure-sensitive areas of hands and feet, and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (eg, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment guidelines for PPE related to study treatment are presented in Table 3-4.

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

Table 3-4: Management of Treatment-Emergent Hand-Foot Syndrome (PPES)

CTCAE v.4.0 Grade	Action To Be Taken
Grade 1	Study treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, study treatment 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	Study treatment may be continued if PPES is tolerated. Study treatment should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND clobetasol 0.05% cream 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 study treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with clobetasol 0.05% cream 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.

3.3.2.7 Wound Healing and Surgery

VEGFR inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed before starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib. If possible, cabozantinib treatment should be stopped for at least 28 days prior to major surgery.

3.3.2.8 Hypertension

Hypertension is a common class effect of drugs that inhibit VEGF pathways and has been reported among subjects treated with cabozantinib.

Treatment guidelines for hypertension deemed related to cabozantinib are presented in Table 3-5. Blood pressure should be monitored in a constant position at each visit (either sitting or supine). In general, subjects with known hypertension should be optimally managed before study entry. Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes after the first measurement. Other than for hypertension requiring immediate

therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.

Cabozantinib should be discontinued in subjects with hypertensive crises or hypertensive encephalopathy.

Table 3-5: 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 study 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 study treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt study 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, study treatment should be dose reduced further or interrupted • Study 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 study treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency[c]	• Discontinue study treatment

BP, blood pressure.

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

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

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

3.3.2.9 Thromboembolic Events

Thromboembolic complications are frequent in cancer patients due to procoagulant changes induced by the malignancy or anticancer therapy including inhibitors of VEGF pathways. Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the Investigator's Brochure). Subjects who develop a PE or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (eg, low molecular weight heparin [LMWH]) is established. LMWH are the preferred management for thrombotic events, warfarin is not recommended. Cabozantinib treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator/Sponsor. During anticoagulation treatment, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding which may require additional or more frequent laboratory tests in accordance to institutional guidelines. If there are any signs of clinically significant bleedings, cabozantinib treatment should be permanently discontinued.

Arterial thrombotic events (eg, transient ischemic attack, myocardial infarction) have been observed in studies with cabozantinib. Subjects should be evaluated for preexisting risk factors for arterial thrombotic events such as diabetes mellitus, hyperlipidemia, hypertension, coronary artery disease, history of tobacco use, and cardiac or thromboembolic events that occurred before initiation of study treatment. Cabozantinib treatment should be discontinued in subjects who develop an acute myocardial infarction, cerebral infarction or any other clinically relevant arterial thromboembolic complication.

3.3.2.10 Proteinuria

Proteinuria is an anticipated AE with the inhibition of VEGF pathways and has been observed in cabozantinib clinical studies, and nephrotic syndrome has been reported with cabozantinib and other inhibitors of VEGF pathways. Management guidelines are provided in Table 3-6.

Cabozantinib should be permanently discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with hypoalbuminemia and peripheral edema [hyperlipidemia and thrombotic disease may also be present]) or any other relevant renal disease.

Table 3-6: Management of Treatment-emergent Proteinuria

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

UPCR, urine protein/creatinine ratio.

3.3.2.11 Corrected QTc Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms.

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

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

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

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

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

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms or increase of > 60 ms above baseline is not confirmed according to protocol procedures
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

3.3.2.12 Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Other causes of hypophosphatemia should be ruled out and/or these causes treated in accordance to standard of care. Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (dairy items, meats, beans) and/or oral phosphate supplements in accordance to standard clinical practice guidelines.

Clinically relevant hypophosphatemia should be managed in accordance to the dose modification guidelines as outlined in Table 3-2 and Table 3-3 or as clinically indicated.

3.3.2.13 Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib therapy and other tyrosine kinase inhibitors as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent (100). Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 3-2 and Table 3-3.

3.3.2.14 Hemorrhagic Events

Hemorrhagic events have been reported with cabozantinib. In order to mitigate risk of severe hemorrhage, subjects should be evaluated for potential bleeding risk factors before 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 of the lung with cavitary lesions or tumor lesions which invades, encases, major blood vessels. The anatomic location and characteristics of tumor as well as the medical history must be carefully reviewed in the selection of subjects for treatment with cabozantinib;
- Recent or concurrent radiation to the thoracic cavity;
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis;
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia);
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis;
- History of clinically significant hemoptysis.

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

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

3.3.2.15 GI Perforation/Fistula and Non-GI Fistula Formation

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

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

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

After starting cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula are present.

Discontinue cabozantinib treatment in subjects who have been diagnosed with GI perforation/fistula.

Non-GI fistula formation: Complications from radiation therapy has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (ie, radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 3 months of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

Discontinue cabozantinib treatment in subjects who have been diagnosed with non-GI fistula.

3.3.2.16 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in subjects treated with cabozantinib. Additional risk factors for ONJ have been identified including the use of bisphosphonates and denosumab, chemotherapy, corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw 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 ONJ.

Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib therapy. 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 held 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.

3.3.2.17 Angioedema

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

3.3.2.18 Musculoskeletal and Connective Tissue Disorders

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

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

A diagnosis of reversible posterior leukoencephalopathy syndrome requires permanent discontinuation of cabozantinib.

3.3.2.19 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation (Section 0) and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

3.4 Concomitant Medications and Therapies

3.4.1 Anticancer Therapy

Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (eg, palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

Pembrolizumab Drug information:

Brand Names: US

Keytruda

Dosing: Adult

Head and neck cancer, squamous cell, recurrent or metastatic:

IV: 200 mg once every 3 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

No dosage adjustment necessary. In a pharmacokinetic study, no difference in clearance was noted for patients with eGFR ≥15 mL/minute/1.73 m^2.

Dosing: Hepatic Impairment

*Hepatic impairment **prior** to treatment initiation:*

Mild impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment necessary.

Moderate (total bilirubin >1.5 to 3 times ULN and any AST) to severe (total bilirubin >3 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

*Hepatotoxicity **during** treatment:*

Note: For patients with baseline grade 2 ALT or AST abnormalities due to liver metastases, permanently discontinue if AST or ALT increases by ≥50% (relative to baseline) and persists at least 1 week.

AST or ALT >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN: Withhold treatment; may resume therapy upon recovery to grade 0 or 1 toxicity. Also administer corticosteroids (prednisone 0.5 to 1 mg/kg/day [or equivalent] followed by a taper).

AST or ALT >5 times ULN or total bilirubin >3 times ULN: Permanently discontinue. Also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed a taper).

Ocular toxicity: Optic neuritis which could manifest as a sudden onset of vision loss, loss of color vision, pain when moving eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).

Dosing: Adjustment for Toxicity

Withhold treatment for any of the following (may resume upon recovery to grade 0 or 1 toxicity):

Colitis, moderate (grade 2) or severe (grade 3); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Endocrinopathies:

Hyperglycemia, severe (Grade 3); also administer antihyperglycemics.

Hyperthyroidism, severe (grade 3) or life threatening (grade 4); manage with thionamides and beta-blockers as appropriate.

Hypophysitis, grade 2 (symptomatic); also administer corticosteroids (followed by a taper) and hormone replacement therapy if appropriate.

Hypoparathyroidism (Low levels of parathyroid hormone) (may occur rarely (<1%) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in fingertips, toes or lips

Nephritis, grade 2; also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Pneumonitis, moderate (grade 2); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Other treatment-related toxicity, severe or grade 3; may require corticosteroids (based on severity). Upon improvement to grade 0 or 1, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at grade 0 or 1 following corticosteroid taper. May consider other systemic immunosuppressants if not controlled by corticosteroids (based on limited data).

Withhold (may resume upon recovery to grade 0 or 1 toxicity) or discontinue for:

Hyperthyroidism, severe (grade 3) or life-threatening (grade 4); manage with thionamides and beta-blockers as appropriate.

Hypophysitis, severe (grade 3) or life-threatening (grade 4); also administer corticosteroids and hormone replacement as appropriate.

Permanently discontinue for:

Adverse reactions that are life-threatening, persistent grade 2 or 3 adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy) that does not recover to grade 0 or 1 within 12 weeks after the last pembrolizumab dose, or any recurrent severe or grade 3 treatment-related adverse reaction. Also administer corticosteroids (may consider other systemic immunosuppressants if not controlled by corticosteroids [based on limited data]).

Colitis, life-threatening (grade 4); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Immune mediated adverse reactions: Discontinue permanently if unable to reduce corticosteroid dose to prednisone ≤10 mg/day (or equivalent) within 12 weeks.

Infusion-related reaction, grade 3 or 4.

Nephritis, severe (grade 3) or life-threatening (grade 4); also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Pneumonitis, severe (grade 3), life-threatening (grade 4), or moderate (grade 2) that recurs; also administer corticosteroids (prednisone 1 to 2 mg/kg/day [or equivalent] followed by a taper).

Dosage Forms: US

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Keytruda: 100 mg/4 mL (4 mL) [contains polysorbate 80]

Solution Reconstituted, Intravenous [preservative free]:

Keytruda: 50 mg (1 ea) [contains polysorbate 80]

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM417493.pdf, must be dispensed with this medication.

Administration

IV: Infuse over 30 minutes through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter. Do not infuse other medications through the same infusion line. Would allow a 10 minutes window of infusion duration.

Use

Melanoma, unresectable or metastatic: Treatment of unresectable or metastatic melanoma.

Non-small cell lung cancer, metastatic: Treatment of metastatic non-small cell lung cancer in patients with PD-L1-expressing tumors (as determined by an approved test) who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression (on approved EGFR- or ALK-directed therapy) prior to receiving pembrolizumab.

Head and neck cancer, squamous cell, recurrent or metastatic: Treatment of recurrent or metastatic squamous cell carcinoma of the head and neck in patients with disease progression on or after platinum-containing chemotherapy.

Adverse Reactions Significant

Incidence of adverse reactions include unapproved dosing regimens.

>10%:

Cardiovascular: Peripheral edema (10%)

Central nervous system: Fatigue (43% to ≤44%)

Dermatologic: Pruritus (12% to 28%), skin rash (18% to 24%; immune-mediated <1%)

Endocrine & metabolic: Hyperglycemia (48% to 49%; grades 3/4: 3% to 6%), hyponatremia (37% to 38%), hypoalbuminemia (32% to 37%), hypertriglyceridemia (23% to 33%), decreased serum bicarbonate (22%), hypocalcemia (21%), hypercholesterolemia (20%)

Gastrointestinal: Decreased appetite (20% to 25%), nausea (18% to 22%), constipation (15% to 22%), diarrhea (15% to 20%), abdominal pain (13%), vomiting (12% to 13%)

Hematologic & oncologic: Anemia (12% to 44%; grades 3/4: ≤10%), lymphocytopenia (40%; grades 3/4: 9%)

Hepatic: Increased serum alkaline phosphatase (26%), increased serum AST (20% to 24%; grades 3/4: 1% to 2%), increased serum ALT (21%; grades 3/4: 2%)

Neuromuscular & skeletal: Weakness (10% to ≤44%), arthralgia (14% to 15%)

Respiratory: Cough (18% to 29%), dyspnea (23%)

Miscellaneous: Fever (12% to 14%)

1% to 10%:

Cardiovascular: Pulmonary embolism (≥2%)

Central nervous system: Peripheral neuropathy (2%)

Endocrine & metabolic: Hypothyroidism (immune-mediated; 7% to 8%), hyperthyroidism (immune-mediated; 2% to 3%; grade 2: <1%; grade 3: <1%)

Gastrointestinal: Colitis (immune-mediated; ≤2%; grade 2: <1%, grade 3: <1%)

Neuromuscular & skeletal: Back pain (10%)

Respiratory: Pneumonitis (2% to 4%; grade 2: ≤1%; grade 3: ≤1%; grade 4: <1%), pleural effusion (≥2%), pneumonia (≥2%)

<1% (Limited to important or life-threatening): Adrenocortical insufficiency (immune-mediated), antibody development, arthritis (immune-mediated), bullous pemphigoid (immune-mediated), chronic inflammatory demyelinating polyradiculoneuropathy, diabetic ketoacidosis, exfoliative dermatitis (immune-mediated), Guillain-Barré syndrome (immune-mediated), hemolytic anemia (immune-mediated), hepatitis (including autoimmune hepatitis), hypophysitis, infusion-related reaction, interstitial nephritis (with renal failure), Lambert-Eaton syndrome (immune-mediated), myasthenia gravis (immune-mediated), myositis (immune-mediated), nephritis (autoimmune), optic neuritis (immune-mediated), pancreatitis (immune-mediated), partial epilepsy (immune-mediated; in a patient with inflammatory foci in brain parenchyma), rhabdomyolysis (immune-mediated), serum sickness (immune-mediated), severe dermatitis, type 1 diabetes mellitus, uveitis (immune-mediated), vasculitis (immune-mediated)

New identified risk of myelitis has been added to the safety profile of Pembrolizumab

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to pembrolizumab or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may

occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than onone body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

- Diabetes mellitus: Type 1 diabetes mellitus has occurred (including diabetic ketoacidosis). Monitor closely for hyperglycemia and other signs/symptoms of diabetes. Insulin therapy may be required; if severe hyperglycemia is observed (Grade 3), administer antihyperglycemics and withhold pembrolizumab treatment until glucose control has been accomplished.
- Gastrointestinal toxicity: Immune-mediated colitis has occurred, including cases of grade 2 to 4 colitis. The median time to onset of colitis was 3.4 months (range: 10 days to ~10 months) and the median duration was 1.4 months (range: 1 day to ~7 months) in patients with melanoma. In patients with NSCLC, the median time to onset was 1.6 months (range: ~1 to ~2 months) and the median duration was 16 days (range: 1 to ~6 weeks). In some melanoma patients, colitis was managed with high-dose systemic corticosteroids for a median duration of 6 days (range: 1 day to 5.3 months), followed by a corticosteroid taper. Most patients with colitis experienced complete resolution. May require treatment interruption, systemic corticosteroid therapy, and/or permanent discontinuation. Monitor for signs and symptoms of colitis; administer systemic corticosteroids for grade 2 or higher colitis.
- Hepatotoxicity: Immune-mediated hepatitis occurred (grades 2 to 4 hepatitis). The median onset for hepatitis was 26 days (range: 8 days to 21.4 months); the median duration was 1.2 months (range: 8 days to 4.7 months). Hepatitis resolved in most patients. Administer corticosteroids (prednisone 0.5 to 1 mg/kg/day [or equivalent] for grade 2 hepatitis, and prednisone 1 to 2 mg/kg/day [or equivalent] for grade 3 or higher, each followed by a taper), and withhold or discontinue therapy based on the severity of liver enzyme elevations. The median duration of high-dose corticosteroid therapy was 5 days (range: 1 to 14 days) followed by a taper. Monitor for liver function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation.

- Hypophysitis: Immune-mediated hypophysitis occurred (grades 2, 3, and 4). In patients with melanoma, the median time to onset was 3.3 months (range: 1 days to 7.2 months) and the median duration was 2.7 months (range 12 days to 12.7 months). The time to onset in NSCLC (1 patient) was 3.7 months. Monitor for signs/symptoms of hypophysitis (eg, hypopituitarism, adrenal insufficiency). May require treatment interruption, systemic corticosteroids and hormone replacement therapy (as clinically indicated), and/or permanent discontinuation.
- Infusion-related reactions: Infusion-related reactions (including severe and life-threatening cases) have occurred. Monitor for signs/symptoms of a reaction (eg, rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever). Interrupt infusion and permanently discontinue for severe (grade 3) or life-threatening (grade 4) infusion-related reactions.
- Nephrotoxicity: Immune-mediated nephritis has occurred. The onset for autoimmune nephritis in melanoma patients was 5.1 months (range: 12 days to 12.8 months) and the median duration was 1.1 months (range: 3 days to 3.3 months). Grade 2 or higher nephritis should be managed with systemic corticosteroids (prednisone initial dose of 1 to 2 mg/kg/day [or equivalent], followed by a taper). The median duration of corticosteroid use was 15 days (range: 3 days to 1.6 months), followed by a taper. Nephritis resolved in some patients. Monitor for renal function changes. May require treatment interruption, systemic corticosteroids (for grade 2 or higher toxicity), and/or permanent discontinuation.
- Pulmonary toxicity: Immune-mediated pneumonitis has been observed, including fatal cases. For patients with melanoma, the median time to development was 4.3 months (range: ~2 days to ~19 months) and the median duration was 2.6 months (range: 2 days to ~15 months). Some patients required initial management with high-dose systemic corticosteroids, the median duration of initial corticosteroid therapy was 8 days (range: 1 to 34 days) followed by a corticosteroid taper. Pneumonitis completely resolved in nearly two-thirds of melanoma patients. For patients with NSCLC, the median time to development was 1.7 months (range: 4 days to ~13 months) and the median duration was 1.2 months (range: 5 days to ~12 months). Some NSCLC patients had complete resolution of pneumonitis. May require treatment interruption, corticosteroid therapy (prednisone 1 to 2 mg/kg /day [or equivalent] followed by a taper, for grade 2 or higher pneumonitis), and/or permanent discontinuation. Monitor for signs and symptoms of pneumonitis; if pneumonitis is suspected, evaluate with radiographic imaging and administer systemic corticosteroids for grade 2 or higher pneumonitis. For NSCLC, pneumonitis occurred more frequently in patients with a history of asthma, COPD, or prior thoracic radiation.

- Thyroid disorders: Immune-mediated hyperthyroidism and hypothyroidism have occurred. The median onset for hyperthyroidism was 1.4 to 1.8 months (range: 1 day to ~22 months), and the median duration was 1.7 to 4.5 months (range: 1 day to ~13 months). Hyperthyroidism resolved in over two-thirds of melanoma patients. Hypothyroidism occurred with a median onset of 3.3 to 4.2 months (range: 5 days to 19 months) and median duration of 5.4 to 5.84 months (range: 6 days to 24.3 months), and occurred in some patients with no prior history of thyroid disorders. Hypothyroidism was generally managed with long-term thyroid hormone replacement therapy, although some patients only required short-term replacement therapy. Hypothyroidism did not require systemic corticosteroid therapy or discontinuation. Thyroid disorders may occur at any point in pembrolizumab therapy. Monitor for changes in thyroid function (at baseline, periodically during treatment and as clinically indicated) and for signs/symptoms of thyroid disorders. Administer thionamides and beta-blockers for hyperthyroidism as appropriate; may require treatment interruption and/or permanent discontinuation. Isolated hypothyroidism may be managed with replacement therapy (without corticosteroids and treatment interruption).
- Other immune-mediated toxicities: Other clinically relevant immune-mediated disorders have been observed, including rash, exfoliative dermatitis, bullous pemphigoid, uveitis, arthritis, vasculitis, myositis, Guillain-Barré syndrome, pancreatitis, hemolytic anemia, serum sickness, myasthenia gravis, and partial seizures (in a patient with inflammatory foci in brain parenchyma). If an immune-mediated adverse event is suspected, evaluate appropriately to confirm or exclude other causes; withhold treatment and administer systemic corticosteroids based on severity of reaction. Upon resolution to grade 0 or 1, initiate corticosteroid taper (continue tapering over at least 1 month). When reaction remains at grade 1 or less during taper may reinitiate pembrolizumab. Immune-mediated adverse reactions that do not resolve with systemic corticosteroids may be managed with other systemic immunosuppressants (based on limited data). Discontinue permanently for severe or grade 3 immune-mediated adverse event that is recurrent or life-threatening.

Pregnancy Implications

Animal reproduction studies have not been conducted. Immunoglobulins are known to cross the placenta; therefore fetal exposure to pembrolizumab is expected. Based on the mechanism of action, pembrolizumab may cause fetal harm if administered during pregnancy; an alteration in the immune response or immune mediated disorders may develop following in utero exposure.

Women of reproductive potential should use highly effective contraception during therapy and for at least 4 months after treatment is complete.

Breast-Feeding Considerations

It is not known if pembrolizumab is excreted into breast milk. The manufacturer recommends that breast-feeding be discontinued during therapy and for 4 months following the final dose. Immunoglobulins are excreted in breast milk; therefore pembrolizumab may be expected to appear in breast milk.

Monitoring Parameters

PD-L1 expression status in patients with NSCLC; liver function tests (AST, ALT, and total bilirubin); renal function; thyroid function (at baseline, periodically during treatment and as clinically indicated); glucose; signs/symptoms of colitis, hypophysitis, thyroid disorders, pneumonitis, infusion reactions.

3.4.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the case report forms.

3.4.3 Allowed Therapies

- Antiemetics and antidiarrheal medications are allowed prophylactically in accordance to standard clinical practice if clinically indicated;
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);
- Drugs used to control bone loss (eg, bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require Sponsor approval;
- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice;

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* at the time of first dose are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 6 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* after first dose are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 3.3.2.9.

    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction);

    - For restrictions on oral anticoagulants see Section 3.4.4.

- 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.

Potential drug interactions with cabozantinib are summarized in Section 3.4.5.

3.4.4 Prohibited or Restricted Therapies

The following therapies are prohibited while the subject is on study:

- Any investigational agent or investigational medical device;

- Any drug or herbal product used specifically for the treatment of SCCHN;

- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines);

- Any other systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides) and local anticancer treatment such as surgery, ablation, or embolization.

The following therapies should be <u>avoided</u> if possible, while the subject is on study:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;

- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence and/or progression associated with erythropoietin(101);

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;

- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, because this could significantly increase the exposure to cabozantinib;

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 3.4.5.

3.4.5 Potential Drug Interactions

<u>Cytochrome P450 (CYP):</u> Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked

effect on the area under the plasma drug concentration time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

In addition, cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

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

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

Other Interactions:

Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. Subjects should fast (with the exception of water) for at least 2 hours before taking their dose of cabozantinib. After the 2-hour fast, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose.

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 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.

3.5 Compliance

Drug accountability and subject compliance will be assessed with drug dispensing and return records.

3.6 Study Drug Accountability

The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled and destroyed in accordance with applicable state and federal regulations.

4 STUDY POPULATION

4.1 Inclusion Criteria

A subject must fully meet all of the following criteria to be eligible for the study:

1. The subject has a histologic or cytologic diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, paranasal sinuses, hypopharynx, nasopharynx or larynx. Squamous cell carcinoma of unknown primary in cervical lymph node can be included only if HPV status is positive.

2. Patients must have refractory, recurrent or metastatic disease, which is deemed to be inoperable.

3. In case patients received prior systemic therapy within the definitive or metastatic setting, disease progression must be documented following prior therapy; this can be in the recurrent or metastatic setting or in the concurrent setting.

4. Measurable disease per RECIST 1.1 as determined by the investigator;

5. A maximum of one prior radiotherapy regimen, curative or palliative, to the head and neck is allowed. If the radiation is combined with chemotherapy, a minimum of 4 months must elapse between the end of radiotherapy and registration. If the radiation is given alone, a minimum of 8 weeks must elapse between the end of radiotherapy and registration. A minimum of 3 weeks must elapse between prior radiation to other areas and registration. Treatment areas should be healed with no sequelae from RT that would predispose to fistula formation.

6. The subject has had an assessment of all known disease sites eg, by computerized tomography (CT) scan, magnetic resonance imaging (MRI), bone scan or PET/CT as appropriate, within 28 days before the first dose of cabozantinib;

7. The subject is ≥ 18 years old on the day of consent;

8. Life expectancy of greater than 3 months.

9. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;

10. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy;

11. The subject has organ and marrow function and laboratory values as follows within 7 days before the first dose of cabozantinib:

    a. The ANC ≥ 1000/mm^3 without colony stimulating factor support;

    b. Platelets ≥ 100,000/mm^3;

    c. Hemoglobin ≥ 9 g/dL;

    d. Bilirubin ≤ 1.5 × the ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;

    e. Serum albumin ≥ 2.8 g/dl;

    f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used:

        i. Male: CrCl (mL/min) = (140 - age) × wt (kg) / (serum creatinine × 72);

        ii. Female: Multiply above result by 0.85;

    g. ALT and AST ≤ 2.0 × ULN;

    h. Lipase < 2.0 x the upper limit of normal and no radiologic or clinical evidence of pancreatitis;

    i. UPCR ≤ 1;

    j. Serum phosphorus, calcium, magnesium and potassium ≥ LLN.

12. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document;

13. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s);

14. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

15. A male participant must agree to use a contraception as detailed in this protocol during the treatment period and for at least during the active treatment plus an additional 90 days (a spermatogenesis cycle) for study treatments with evidence of genotoxicity at any dose] after the last dose of study treatment and refrain from donating sperm during this period.

- **Exclusion Criteria**

A subject who meets any of the following criteria is ineligible for the study:

1. Patients who have HPV negative squamous cell carcinoma of unknown primary in cervical lymph node.

2. The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg, cytokines or antibodies) within 4 weeks, or nitrosoureas/mitomycin C within 6 weeks before the first dose of study treatment;

3. Prior treatment with cabozantinib or pembrolizumab; or any prior immunotherapy for treating squamous cell carcinoma of the head and neck;

4. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before the first dose of study treatment. Systemic treatment with radionuclides within 6 weeks before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible;

5. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before the first dose of study treatment;

6. The subject has received any other type of investigational agent within 28 days or 5 half-lives, whichever is shorter, before the first dose of study treatment;

7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment;

8. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test $\geq 1.3 \times$ the laboratory ULN within 7 days before the first dose of study treatment;

9. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel);

   Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects 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.

10. The subject has experienced any of the following:

    a. clinically-significant GI bleeding within 6 months before the first dose of study treatment;

    b. hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment;

    c. any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment.

11. The subject has radiographic evidence of cavitating pulmonary lesion(s);

12. The subject has tumor invading or encasing any major blood vessels;

13. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib;

14. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders including:

        i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening;

        ii. Concurrent uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment;

        iii. Any history of congenital long QT syndrome;

        iv. Any of the following within 6 months before the first dose of study treatment:

            - unstable angina pectoris;
            - clinically-significant cardiac arrhythmias;
            - stroke (including transient ischemic attack (TIA), or other ischemic event);
            - myocardial infarction;

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

        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,

Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization. Also no pre-existing fistula of head and neck area. No pre-existing ONJ.

c. Other clinically significant disorders that would preclude safe study participation;

15. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. Minor surgery (including uncomplicated tooth extractions) within 28 days before the first dose of study treatment with complete wound healing at least 10 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible;

16. QTcF > 500 msec within 1 month before the first dose of study treatment:

    a. Three ECGs must be performed for eligibility determination. If the average of these three consecutive results for QTcF is ≤ 500 msec, the subject meets eligibility in this regard.

17. Pregnant or lactating females;

18. Inability to swallow intact tablets or inability to take pembrolizumab or cabozantinib

19. Previously identified allergy or hypersensitivity to components of the study treatment formulations;

20. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease-free for 1 year post diagnosis. Patients with a prior history of squamous cell or basal carcinoma of the skin or in situ cervical cancer must have been curatively treated.

21. Patients with known history of interstitial lung disease or idiopathic pneumonitis.

16. STUDY ASSESSMENTS AND PROCEDURES

- **Pre-Treatment Period**

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is

performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

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

- History and physical
- ECOG performance status
- Tumor measurement
- Blood analysis: CBC and differential, blood chemistries, blood or urine pregnancy test if appropriate
- Urine analysis, liver function tests
- Tumor biopsy (fresh biopsy if paraffin blocks are not available); If tumor blocks cannot be provided 20 unstained slides are requested; if 20 slides cannot be provided due to tumor sample size a minimum of 10 unstained slides are required;
- Blood sample for research purposes
- Radiology: CT scan of neck, chest, abdomen, pelvis

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

- **Treatment Period**

During the Treatment Period subjects will receive cabozantinib with pembrolizumab until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 2.6. Subjects should be instructed to immediately inform the principal investigator (PI) of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

The following schedule of assessments applies to all subjects

Table 5-1). More frequent assessments should be obtained if clinically indicated.

Table 16-1: Study Assessments

	Study Treatment Period		Post-Treatment Period		
Test[a]	**Pre-therapy (Day -14 to 0)**	**Day 1 of each cycle (21 days) while on study drugs[n]**	**30 - 37 Days after last dose**	**At one year [b]**	**End of follow up at 2 years [b]**
History and Physical	X	X	X (and every 3 months)[b]	X	X
Weight and ECOG PS	X	X	X (and every 3 months)[b]	X	X
Tumor Measurement	X[a]	X (every 9 weeks)		X [m]	
CBC and diff [d]	X	X[c]	X (and after 3 months)	X	X
Chemistries (Na, CL, CO2, K, BUN, blood glucose[e] Creatinine, Ca, Mg, Phos), Urine analysis	X	X[c,e]	X (and after 3 months)	X	X
Liver function panel[f]	X	X[c]	X (and every 3 months)	X	X
PT, PTT, INR	X	X[c]	X	X	
TSH	X	X[c]	X (and every 3 months)	X	X
12-lead ECG	X[L]	X[L]			
Tissue for Research Purposes (paraffin embedded)[g]	X				
Blood for Research Purposes	X[k]				
Toxicity Assessment[h]	X	X			
Radiology: CT-neck, chest, abdomen, and pelvis for tumor measurements[i]	X	X (every 9 weeks)		X	
Blood or Urine B-HCG[j]	X				

[a].a range of 4 days before or after the scheduled scans and screening tests is allowed – for scans , a 28 days period is allowed to obtain scans before initiation of therapy)

[b]. Once the patient has fully recovered from the study drug-related toxicities or the patient enrolls in a hospice, the follow up can be done by a phone call if the patient is off the study drugs.

[c] Laboratory testing will be performed every 3 weeks for the first 9 weeks followed by assessments every 6 weeks. CBC with diff, liver function panel and blood chemistries (excluding T3, T4, TSH, GGT, LDH, Amylase, Lipase; PT, PTT/INR) will continue to be done every 3 weeks with each new cycle following the first 9 weeks of therapy.

[d]. CBC and diff includes: WBC, ANC, HCT, HGB, PLT, % lymphocytes, % monocytes, % neutrophils, other Differential (labs need to be done within 7 days of start of therapy)

[e]. GGT, Amylase, Lipase, LDH can be performed every 3 cycles

[f]. Liver function panel includes: Alk Phos, Total Bilirubin, SGOT (AST), SGPT (ALT), Total Protein.(Labs need to done within 7 days of start of therapy)

[g]. If tumor paraffin blocks are not available, fresh biopsy will be obtained before the first treatment. If fresh biopsy is indicated, one core (or punch) will be collected in formalin and the second core (or punch) will be collected in liquid nitrogen. Optional end of treatment tumor biopsy (or at the time of progression) is allowed at Emory University and Moffitt Cancer Center. If fresh biopsy is indicated, one core (or punch) will be collected in formalin and the second core (or punch) will be collected in liquid nitrogen.

[h] Toxicity assessment: Common Toxicity Criteria (CTC) version 4.0 will be used. All toxicity grades (including grade 1) should be captured on the case report forms. All toxicities that occurred during treatment should be followed until resolution.

[i] Tumor measurement: The same type of scan should be used for repeat measurements. (CT, MRI or PET/CT are acceptable) ; A PET CT can be exchangeable with a CT scan for the purpose of tumor measurements ; A CT of the pelvis at screening can be omitted if a prior PET CT scan does not show pelvic involvement within 3 months from enrollment; CT scans (tumor measurements) during treatment (i.e. after baseline) should be obtained every 9 weeks from C1D1

[j] Pregnancy test should be done in woman of child bearing age who are sexually active and may potentially be pregnant. Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. All WOCBP MUST have a negative pregnancy test within 7 days prior to first receiving investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

[k] Blood for research before therapy, 9 weeks into therapy, at 6 months, and end of treatment (or at the time of progression whichever is sooner).

[L] Screening EKG in triplicate at eligibility. On treatment routine EKGs at each cycle for 3 cycles, and then every 9 weeks thereafter

[M] Only for select patients who have lack of prior progression at one year

[N] - A 2 days window for infusion of Pembrolizumab is allowed for logistic reasons- Every effort should be made to avoid interruption in Cabozantinib administration as a result of changes in Pembrolizumab schedule. A 2 day window for clinical labs and history & physical is also allowed for logistical reasons.

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

Regular tumor assessments should be performed in accordance to the guidelines in Section o to determine if PD is present.

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

- **Post-Treatment and End on Treatment Period**

Subjects will return to the study site 30 to 37 days after their last dose of cabozantinib, pembrolizumab or both to complete end-of-study assessments.

At the end of 24 months of treatment on the combination of pembrolizumab and cabozantinib, patients who are in continued response and who in the opinion of the investigators can continue to benefit from therapy will be given the options of either terminating therapy, or continuing on the combination with the use of the EASE program overlooked by Exelixis ; This program will provide commercial cabozantinib to patients who wish to continue therapy for an additional 12 months of treatment; patients who continue on the EASE program will be followed as per standard of care at the respective institutions.

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

- **Laboratory Assessments**

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hematocrit • platelet count • RBC count • hemoglobin • ESR • reticulocytes	
Serum chemistry		
• albumin • ALP • amylase • ALT • AST • bicarbonate • BUN • chloride	• creatinine • GGT • Glucose • ionized calcium or total and corrected calcium • lactate dehydrogenase • lipase	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• Glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Other		
• TSH, Free T3 and T4 • Pregnancy text (urine or serum) for women of child-bearing potential • Blood for research studies		• PT/INR or PTT • 24 hour urine collection for protein

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate ; GGT, γ-glutamyltransferase; INR, International Normalized Ratio; PT, prothrombin time; PTT partial thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; UPCR, urine protein/creatinine ratio; WBC, white blood cell.

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring)

are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE.

- **Tumor Assessment**

Response Criteria (RECIST 1.1)

For subjects who have measurable disease at baseline, this is a summary of overall response status calculation.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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).

17. SAFETY

Adverse Events and Laboratory Abnormalities

Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been given an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Pre-existing medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 3.3.

All untoward events that occur after informed consent through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

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

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;

- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (eg, evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

Serious Adverse Events

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

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

- Result in death;
- Is immediately life-threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
- Results in persistent or significant disability or incapacity:
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

- **Serious Adverse Event Reporting**

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this should be documented to the extent that information is available.

- Investigator shall notify sponsor within twenty-four (24) hours of making such discovery by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form;
- Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make

a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

- For multicenter studies the Investigator must notify the IND/CTA Sponsor by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form within 24 hours to allow the IND/CTA Sponsor to submit the SAE report form to Exelixis no later than 2 business days.

- This report must be submitted by sponsor to Exelixis at e-mail: drugsafety@exelixis.com or fax 650-837-7392, even if it is not felt to be drug related;

- Pregnancy (for a subject or for the partner of a subject), although not itself an SAE, should also be reported on a pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities;

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

    - all SAEs that occur after informed consent and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure);

    - any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment;

    - although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

- **Regulatory Reporting**

All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities, Emory IRB, and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;
- The final MedWatch Form or CIOMS-1 form must be submitted by the sponsor to Exelixis within one to two business days of submission to the FDA or applicable regulatory agency (including confirmation of date that the report was submitted) to allow Exelixis time to cross-report to Exelixis' IND. E-mail: drugsafety@exelixis.com; Fax 650-837-7392.

- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Sponsor reporting responsibilities.

- **Other Safety Considerations**
  - **Laboratory Data**

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

- **Pregnancy**

If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

- **Medication Errors/Overdose**

Any study drug administration error or overdose that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis or designee.

- **Follow-Up of Adverse Events**

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

18. STATISTICAL CONSIDERATIONS

- **Analysis Population**

- **Safety Population**

The safety population will consist of all subjects who receive any amount of study treatment.

- **Safety Analysis**

Safety will be assessed by evaluation of AEs. All safety analyses will be performed using the safety population.

- **Adverse Events**

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v4.0. Listings of AEs will be provided.

- **Sample Size**

The sample size will be up to 34 evaluable subjects in which the first 6 patients will be in the safety run-in phase with an interim futility assessment after 20 patients were treated.

(Evaluable subjects based on the primary endpoint are defined as subjects who received therapy on study and had at least one follow up scan after initiation of study treatment)

The ORR for this patient population is reported as 18% with pembrolizumab as a single agent. We estimate that the ORR will improve to about 35% with the combined treatment. We expect to accrue patients for 2 years and follow up for additional 12 months. The sample size will be 34 by a one-arm design with null hypothesis as ORR <=0.15 vs. its one-sided alternative. If the number of responses is <= 9 out of 34, the trial will be claimed as not promising. The design yields a type 1 error of 0.05 and a power of 80% when the true response rate is 35%. An interim look after 20 patients will take place, and if <= 4 responses are observed, the trial will stop earlier and claim a futility.

Statistical analysis for biomarker studies: The ORR will be calculated with 95% confidence interval by Binomial distribution. The median PFS will be estimated by Kaplan-Meier method along with 95% confidence interval. The ability of biomarkers to predict ORR will be estimated by Chi-square test and/or logistic regression model, and association with PFS will be assessed by the Kaplan Meier method, Log-rank test, and Cox model, and the frequency of adverse events and serious adverse events will be summarized accordingly. The performance of predictability of biomarker for clinical outcomes will be described by AUC for binary outcome ORR and Uno's C-statistics for PFS with 95% CI and ranked accordingly.

19. OTHER ANALYSES

Tumor samples will be collected from all patients through archival tissue or biopsies performed from at least one site of disease prior to the first dose administration of therapy. Tumor samples collected through these biopsies will be compared with the historical samples and will also be analyzed to explore the biomarkers that could predict response to cabozantinib. Optional end of treatment tumor biopsy (or at the time of progression) is allowed at both Emory Winship Cancer Institute and Moffitt Cancer Center.

Baseline biopsies or surgical specimens from trial participants will be analyzed for the following:

- Tumor pVEGFR2/VEGFR2, pMet/Met, pSTAT3/STAT3, and PD-L1 protein expression as well as markers of hypoxia, antigen presenting cells, T cells, and B cells among the Tumor infiltrating immune cells using multiplex immunohistochemistry (IHC).
- Tumor DNA whole exome sequencing and RNA sequencing to determine potential neoantigens and their expression.

Blood samples will be collected at screening, at 9 weeks on treatment, at 6 months on treatment, and end of treatment (or disease progression whichever is sooner).

- Plasma biomarkers will include HGF, IL-6, IL-8, VEGF, and IFN-γ determined by ELISA analyses.
- Circulating cell free DNA (cfDNA) in plasma will be determined by DNA sequencing.
- Peripheral blood mononuclear cells (PBMC) will be evaluated by flow cytometry for immune monitoring.

For detailed tissue collection and processing information, please see **LAB MANUAL**.

20. DATA QUALITY ASSURANCE

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

OnCore: The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and assigned dose cohort. All data must be entered no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The Multi Site Coordinator (MSC) will provide OnCore training and request access to the appropriate staff at the participating site.

21. STUDY COMMITTEES

This study will be under the purview of the Winship Data and Safety Monitoring Committee (DSMC). The committee monitors the research charts of patients enrolled to all investigator-initiated studies at the Winship Cancer Institute (Winship DSMC will only monitor Emory patients). Approximately 10% of charts are reviewed on these studies. The monitoring report will be reviewed by the DSMC and will be forwarded to the sponsor. Audits/inspections may also be conducted by the FDA in the case of studies using drugs covered by an IND or devices covered by an IDE.

The DSMC reports, and recommends corrective action if needed, to the PI. The Monitoring Committee may initiate an external audit of any trial at any time if it determines such action to be necessary. The Monitoring Committee will review all internally audited trials annually. The Monitoring Committee is responsible for oversight. If deficiencies are discovered during the annual review, the Monitoring Committee will first inform the PI. If the deficiencies cannot be corrected, the Monitoring Committee will involve the PI's direct supervisor and may refer the protocol to the Medical Director for corrective action including possible termination of the trial. The Medical Director has the authority to terminate trials for cause.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed.

Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

22. ETHICAL ASPECTS

o Local Regulations

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

o Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed

consent discussion. After the subject has orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

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

- **Institutional Review Board/Ethics Committee**

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

- **Future Use of Patient Samples**

Tumor and blood samples will be collected from all patients and used for biomarker studies. Unused samples will be stored in the Winship tissue bank with consent from participants.

23. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications may be made and will be prepared, reviewed, and approved by representatives of the sponsor.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (eg, change in monitor or change of telephone number).

24. CONDITIONS FOR TERMINATING THE STUDY

Exelixis reserves the right to terminate the study, and investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and

consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

25. STUDY DOCUMENTATION AND RECORDKEEPING

o Investigator's Files and Retention of Documents

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

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

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

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

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Exelixis to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

o Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important

when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

- **Audits and Inspections**

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

- **Case Report Forms**

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

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

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

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

26. MONITORING THE STUDY

Winship internal monitors will monitor the Emory sites and the Multi-site coordinator will monitor all other non-Emory sites.

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

The Emory Winship Cancer Institute (Winship) clinical trial office will serve as the coordinating center for this study. The sponsor will review responses and toxicity and report these to the regularly scheduled meetings of the DSMC of the Emory Winship Cancer Institute. Each participating site is expected to have its own data monitoring and safety plan (DMSP) with regard to forwarding information to their IRBs. If the data reveals a change in the risk/benefit ratio, the investigator will notify the IRB and the PI.

The PI and co-investigators will review the data and forward any changes or protocol amendments to the IRBs. All serious adverse events will be reported immediately to the IRB. All study participant information will be kept in a confidential manner by the assigning of a random number to each study participant. All data will be kept confidential as per institutional guidelines and policies. Any breach of confidentiality is a serious matter and conflicts with institutional policies and will be reported to the IRB. A cumulative summary of all adverse events occurring on this study and a report of the data safety and monitoring plan will be submitted to the IRBs with the annual renewal reports.

Monitoring plan of Subsite(s):

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet, which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail monthly. Teleconferences will be conducted weekly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. A record of the teleconferences will be kept in the regulatory binder. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy and the PI at Emory will communicate with participating sites via email as needed. This communication will also be maintained in the regulatory binder. Chart reviews will be performed on selected cases by the participating site staff to confirm that the data collection is accurate.

Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (annually once onsite and three times remotely) until subject follow-up is terminated. In situations where the one annual onsite monitoring visit cannot be completed at non-Emory sites due to institutional restrictions, the visit will still occur, however, it will be completed remotely. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

27. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

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

28. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Exelixis, Inc. for review at least sixty (60) days before submission and also comply with any provisions regarding publication that are agreed to between the PI's institution (eg, institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined in accordance to guidelines established by the International Committee of Medical Journal Editors.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

ECOG, Eastern Cooperative Oncology Group