CLINICAL STUDY PROTOCOL

A Phase 2, Multicenter Study of Tesevatinib in Subjects with Non-Small Cell Lung Cancer, EGFR Activating Mutation, Prior Treatment with a Tyrosine Kinase Inhibitor, and Brain Metastases or Leptomeningeal Metastases

Protocol Number: KD019-206

Study Drug: Tesevatinib (KD019)

Sponsor: Kadmon Corporation, LLC
450 East 29th Street
New York, NY 10016

Medical Monitor: Sanjay Aggarwal, MD
Kadmon Corporation, LLC
55 Cambridge Parkway
Cambridge, MA 02142

Date of Protocol: Original: 16 July 2015
Amendment 1: 09 February 2016
Amendment 2: 10 May 2016
Amendment 3: 08 August 2017
Amendment 4: 03October 2017

1 PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

All serious adverse events (SAEs)* occurring in subjects while on-study or within 30 days of receiving study drug regardless of relationship, must be promptly reported (within 24 hours) by telephone, email, or telefax to the sponsor (or designee).

Emergency Contact Information

For SAE/SUSAR reporting:	**For any other questions or to contact the medical monitor:**
APCER Life Sciences, LLC. Fax: 646-430-9549 In the event of an issue with the fax line, forward the SAE/SUSAR via email to: ClinicalSAEReporting@kadmon.com	Sanjay Aggarwal, MD Vice President Clinical Development, Medical Monitor Kadmon Corporation 55 Cambridge Parkway Cambridge, MA 02142 Mobile Phone: 857-253-8642 E-mail: sanjay.aggarwal@kadmon.com

SAE AND SUSAR CRITERIA

* A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 15.3.1 Serious Adverse Events for additional information):

- Death
- Life-threatening adverse drug event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/ incapacity
- A congenital anomaly/birth defect
- An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

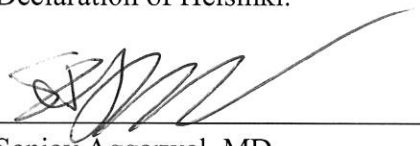
Some serious events will not be reported as SAEs, including:

- Disease progression
- Death due to disease progression occurring more than 30 days after the last dose of study drugs
- Medical or surgical procedures when the condition that leads to the procedure is an adverse event (AE)
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen
- Situations for which an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions)

** A suspected unexpected serious adverse reaction (SUSAR) is any untoward and unintended responses to an investigational product related to any dose administered, of which the nature, or severity, is not consistent with the applicable product information (see also Section15.3.2 of this document; Suspected Unexpected Serious Adverse Reactions). All suspected adverse reactions related to an investigational medicinal product which occur in the concerned trial and that are both unexpected and serious are subject to expedited reporting.

2 SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.



06-OCT-2017

Sanjay Aggarwal, MD
Kadmon Medical Monitor

Date of Signature
(DD MM YYYY)

3 INVESTIGATOR SIGNATURE

I have read this protocol, including all appendices, and I agree to conduct the study in compliance with all applicable regulations (including 21 CFR Part 312). I will also make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kadmon Corporation, LLC. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I am aware that, prior to the commencement of this study, the Institutional Review Board must approve this protocol and the informed consent document associated with the clinical facility where the study will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol. I agree to provide all subjects with a signed and dated copy of their informed consent document, as required by the Food and Drug Administration (FDA) and ICH regulations. I further agree to report to Kadmon any adverse events (AEs) in accordance with the terms of this protocol and FDA regulation 21 CFR 312.64.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD MM YYYY)
Name of Investigator (please print)	

4 SYNOPSIS

Study title	A Phase 2, Multicenter Study of Tesevatinib in Subjects with Non-Small Cell Lung Cancer, EGFR Activating Mutation, Prior Treatment with a Tyrosine Kinase Inhibitor, and Brain Metastases or Leptomeningeal Metastases
Clinical phase	Phase 2
Number of study centers	10-15
Study background	Tesevatinib (formerly known as KD019) is an orally administered tyrosine kinase inhibitor that has been documented to inhibit multiple molecular drivers of tumor growth, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), sarcoma (Src), and vascular endothelial growth factor receptor 2 (VEGFR2). Tesevatinib is a highly potent inhibitor of the EGFR activating mutations that, when present, drive the growth of non-small cell lung cancers (NSCLCs). When measured in HCC827 cells, which are human lung cancer cells with an EGFR exon 19 deletion, the IC_{50} for inhibition of EGFR phosphorylation for tesevatinib (0.6 nM) was very similar to that for erlotinib (0.8 nM). The IC_{50} for inhibition of proliferation in the same cell line was 3.5 nM for tesevatinib and 4.6 nM for erlotinib. Thus tesevatinib and erlotinib have similar potency in vitro against a cell line with an activating EGFR mutation. Tesevatinib has been evaluated in two single-agent Phase 1 studies in subjects with advanced solid tumors (Studies XL647-001 and XL647-002), in two single-agent Phase 2 studies in subjects with NSCLC (Studies XL647-201 and XL647-203), and in a Phase 3 study (Study KD019-301) in NSCLC that only enrolled 8 patients. Tesevatinib is also being evaluated in a Phase 1/2 study in subjects with HER2+ metastatic breast cancer, and in a Phase 1/2 study in subjects with autosomal dominant polycystic kidney disease (ADPKD). The single-agent tesevatinib Phase 1 study (XL647-002) concluded that the maximum tolerated dose (MTD) for daily dosing of tesevatinib was 300 mg daily because two subjects who received 350 mg daily had Grade 3 QT interval, corrected (QTc) prolongation (> 500 ms). However, when these were later reviewed by a central cardiology review, they were both downgraded to Grade 2. In one case, the site QTc reading was confounded by a new right bundle branch block and, in the other case, by bradycardia. Due to these complicating issues, the MTD for daily administration of tesevatinib was evaluated further in combination with trastuzumab in the ongoing study in patients with HER2+ breast cancer. The MTD of 300 mg daily was recently confirmed in the breast cancer study. This study and others have also determined that tesevatinib has a prolonged half-life of approximately 60 hours. The other single-agent tesevatinib Phase 1 study (XL647-001) evaluated a schedule of 5 days of tesevatinib administered every 2 weeks. This study initially used a powder-in-capsule preparation of tesevatinib. At 7 mg/kg, the only two subjects treated both had Grade 3 diarrhea. In one subject (11032), the Grade 3 diarrhea occurred on Day 4 of the study and diarrhea resolved on Day 8. In the other subject (11034), the Grade 3

	diarrhea occurred on Day 7 and diarrhea resolved on Day 25. The next lowest dose, 4.68 mg/kg, was determined to provide similar exposure to 350 mg given as formulated tablets, which was called the MTD for this schedule. However, this study was performed from 2004-2007 when aggressively treating diarrhea due to EGFR inhibitors was not necessarily routine. It is unknown whether 350 mg administered for 5 days every 2 weeks would be considered to be the MTD if subjects had aggressive diarrhea management. The first of the two single-agent Phase 2 studies in NSCLC (Study XL647-201) enrolled treatment naïve patients with advanced stage NSCLC who were Asian, female, or with minimal or no smoking history. There were 41 subjects enrolled in an intermittent dosing schedule and 14 enrolled in a daily dosing schedule. Subjects in the intermittent cohort received tesevatinib at a dose of 350 mg for 5 days every 2 weeks. Subjects in the daily dosing cohort received tesevatinib administered at a dose of 300 mg daily. Retrospective sequencing of tumor samples identified 14/41 subjects with EGFR mutations. The confirmed partial response (PR) rate in subjects with EGFR mutations was 57% (8/14), and an additional 3 subjects with EGFR mutations had unconfirmed PRs. Response rates were similar in the daily and intermittent tesevatinib schedules. Patients with PRs were those whose tumors had Exon 19 deletions as well as those with the L858R mutation. One subject in this study who is on the intermittent schedule has had a long-term response lasting nearly five years and is still receiving tesevatinib therapy. In the second single-agent tesevatinib study in NSCLC (Study XL647-203), tesevatinib was administered daily at a dose of 300 mg/day to 41 subjects with NSCLC who had disease progression after treatment with other EGFR inhibitors (erlotinib or gefitinib). The most frequently reported adverse events (AEs) were diarrhea, nausea, cough, dry skin, and electrocardiogram (ECG) QTc prolongation. Two (2) of the 41 subjects experienced QTc(F) > 500 msec confirmed by a central cardiology review. (All subjects in all tesevatinib studies with QTc prolongation have been asymptomatic.) Eleven subjects (11; 28%) required a dose reduction for toxicity, most commonly for diarrhea (27%) and rash (18%). Whether EGFR-related diarrhea or rash were treated aggressively is not clear. There were 12 subjects with documented T790M EGFR mutations, none of whom had a response to tesevatinib treatment. The Phase 3 study (KD019-301) was a double-blind, randomized, and controlled trial of KD019 vs erlotinib in subjects with Stage IIIB/IV non-small cell lung cancer who had progressed after first- or second-line chemotherapy. The study was closed early due to slow enrollment after 8 subjects were entered. One subject who carried an EGFR activating mutation had a partial response to tesevatinib for eight cycles before progressing. A Phase 1b/2a study (KD019-204) of the combination of trastuzumab and tesevatinib is ongoing in subjects with HER2+ metastatic breast cancer. The Phase 1 portion of the study used a 3+3 design that is commonly used in oncology studies. The Phase 1 portion of the study has determined that 300 mg daily of tesevatinib in combination with trastuzumab is the MTD dose, as the two subjects treated with 350 mg daily had Grade 3 events considered to be at least possibly related to tesevatinib (one had Grade 3 diarrhea not recovering to Grade 1 by seven days, and the other had Grade 3 QTc prolongation confirmed by central reading).

	A Phase 1b/2a study (KD019-101) of tesevatinib in patients with ADPKD is ongoing. Subjects with ADPKD, in whom the drug will be administered chronically for years, did not tolerate the Grade 2 acneiform skin rash that occurred in 2/5 patients at 150 mg daily. In addition there were 2/8 patients receiving tesevatinib at a dose of 100 mg daily who had asymptomatic prolongation of the QTc duration (one Grade 3 and one Grade 2). Doses of 50 mg daily are being evaluated further.
Study rationale	Subjects with NSCLC with activating EGFR mutations have a high response rate to tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib or afatinib. However, these are not curative therapies and tumors inevitably develop resistance.[1,2] The central nervous system (CNS) is a sanctuary site, as gefitinib, erlotinib and afatinib penetrate poorly into the brain. These drugs penetrate even more poorly into the cerebrospinal fluid (CSF), with CSF levels documented to be approximately 1% of plasma levels for gefitinib and afatinib and 2.5%–13% for erlotinib.[3,4,5] Disease progression after initial gefitinib or erlotinib treatment involves the CNS in approximately 28% of patients, and includes leptomeningeal metastases (LM) in 8%.[6] Progression with LM occurs more commonly in patients with previous brain metastases than in patients without previous brain metastases.[6] Patients with brain metastases (BMs) generally present with neurologic symptoms, which can include headache, confusion, and seizures. Patients with LM also present with neurologic symptoms, which often include headaches or cranial neuropathies or pain, but can be highly varied. Despite the frequency of progression in the CNS, there are no approved treatments for the treatment of BM or of LM in patients with NSCLC and activating EGFR mutations. Radiation therapy, either Whole-Brain Radiotherapy (WBRT) or stereotactic radiosurgery (SRS), is often used to control symptoms of BMs. However, these treatments are rarely curative, and are not without side effects. WBRT is associated with early occurring fatigue and all too often with neurocognitive decline. In patients who received WBRT after SRS there is a significant decline of learning and memory function at 4 months compared to patients receiving only SRS. SRS is associated with fewer side effects, but has a higher recurrence rate when used without WBRT as the entire brain is not irradiated. There are few effective therapies to control LM. Intrathecal methotrexate is sometimes used, although response rates are low and time to disease progression is short. In patients with NSCLC with activating EGFR mutations, high doses of gefitinib or erlotinib have been used to treat patients with BM and LM with some degree of effectiveness.[2,8,9] However, response rates are low and the time to disease progression is generally short with this treatment as well. Diagnosis of BM is generally obtained by magnetic resonance imaging (MRI) of the brain. The diagnosis of LM is more complex. Diagnosis of LM is most definitive when cytologic evaluation of CSF specimens detects malignant cells. However, single CSF analysis has a false negative rate of approximately 50%, and thus cytologic diagnosis of LM often requires several separate CSF samples.[10] MRI findings (such as subarachnoid nodules, enhancement in basal cisterns, and enhancement/clumping of nerve roots) are diagnostic, but normal CNS imaging does not exclude a diagnosis of LM. Antibodies to EpCam, an epithelial cell adhesion molecule, have been utilized to identify rare tumor cells such as circulating tumor cells in the blood. The same approach to rare cell capture has been utilized in the analysis of tumor cells in CSF. In one study of patients with LM, cytology had a sensitivity of 67%, MRI had a sensitivity of 73%, and EpCam based

	identification of CSF tumor cells had a sensitivity of 100%.[11] Cell-free DNA is present in patients with activating EGFR mutations and BM, and can be utilized to evaluate the EGFR mutations that are present.[12] Evaluation of cell-free DNA in the CSF may provide a method independent of cytological analysis for evaluation of the course of patients with LM. Approximately 50% of erlotinib-resistant, EGFR-mutant patients harbor a T790M EGFR mutation, which gefitinib, erlotinib, and afatinib do not inhibit.[1,2] IC_{50}s for one cell line with the T790M EGFR mutation were 10.4 μM for gefitinib, 16.1 μM for erlotinib, and 0.9 μM for tesevatinib.[13] Despite having an IC_{50} against cells with the T790M EGFR mutation that is much lower than that for gefitinib or erlotinib, tesevatinib was not effective in treating NSCLC patients with the T790M EGFR mutation in the XL647-203 study.[14] However, patients with BM and LM occurring while receiving erlotinib therapy have been documented to have a much lower frequency (10%) of T790M mutation in the CNS than is the case for patients with progression in non-CNS locations (38%).[15] This presumably occurs because erlotinib and afatinib and gefitinib penetrate poorly into the CNS, and thus tumor cells in the CNS can grow in the presence of the low levels of TKI that are present. Tesevatinib effectively penetrates into the brain, with levels in mice and rats with intact blood-brain barriers (BBB) the same or higher than plasma levels. Tesevatinib has levels in the choroid plexus and meninges in rats that are 10 times the plasma levels, suggesting that tesevatinib may penetrate well into CSF and may be an effective treatment for leptomeningeal metastases adhering to the inner surface of meninges. Preliminary data from the initial patients enrolled in this study demonstrate that tesevatinib can achieve brain and leptomeningeal exposures with clinically significant effects. Radiological data are available from one of the 6 initial patients enrolled in the study. A 36 year old female patient was enrolled with symptoms of Grade 1 headache, anal numbness, and intermittent left leg weakness. She had a right parietal brain metastasis and leptomeningeal metastases diagnosed both by CSF cytology and by MRI. By study day 14 the headache, anal numbness, and intermittent left leg weakness were no longer present. On MRI at study day 41 there was a 57% decrease in size of the right parietal brain metastasis and no evidence of leptomeningeal metastases. Thus, there is good biologic rational to evaluate tesevatinib in subjects with NSCLC and EGFR activating mutations who have disease progression with BM or LM, or who have BM or LM at initial presentation. This study will enroll subjects with BM or LM occurring while being treated with erlotinib or afatinib or gefitinib, or with BM or LM at initial presentation.
Study objectives	**Cohort A** <u>Primary objective</u> • To evaluate the clinical activity of tesevatinib in subjects with non-small cell lung cancer (NSCLC), activating EGFR mutations, and brain metastases (BM) as measured by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 evaluated changes in BM size. <u>Secondary objectives</u>

	• To evaluate changes in Quality of Life (QOL) in subjects receiving tesevatinib for BM. • To determine the median progression-free survival (PFS), rate of CNS non-progression at 3 and 6 months, non-CNS time to progression (TTP), and CNS TTP. • To determine the median overall survival (OS). Exploratory objective • To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response. **Cohort B** Primary objective • To evaluate the clinical activity of tesevatinib in subjects with NSCLC, activating EGFR mutations, and leptomeningeal metastases (LM) as measured by improvement in Common Terminology Criteria for Adverse Events (CTCAE) v4.03 symptoms and signs. Secondary objectives • To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by decreases in NSCLC cells in the CSF using standard cytology. • To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by improvement in CNS MRI findings . • To evaluate the pharmacokinetics (PK) of tesevatinib in CSF versus plasma • To evaluate changes in QOL in subjects receiving tesevatinib for LM. • To determine the median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP. • To determine the median OS. Exploratory objective • To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response. • To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by decreases in NSCLC cells in the CSF using rare cell capture techniques. • To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM measured by decreases in CSF cell-free DNA. • To utilize CSF cell-free DNA to detect activating EGFR mutations in patients receiving tesevatinib for LM. **Cohort C** Primary objective • To evaluate the clinical activity of tesevatinib in subjects with NSCLC, activating EGFR mutations, and BM at initial presentation as measured by RECIST 1.1 evaluated changes in BM size.

	Secondary objectives • To evaluate changes in QOL in subjects receiving tesevatinib for BM. • To determine the median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP in subjects with NSCLC, activating EGFR mutations, and BM at initial presentation. • To determine the median OS. Exploratory objectives • To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response.
Study design	This is a multicenter, Phase 2 study to assess the activity of tesevatinib in subjects with NSCLC and activating EGFR mutations and BM or LM. **Screening and Study Treatment** After completion of the screening assessments and confirmation of study eligibility, tesevatinib will be orally administered to all subjects at a dose of 300 mg once daily. Tumor response, both in the CNS and outside the CNS, will be assessed after the second cycle of treatment and then at the end of every two cycles of treatment thereafter. Subjects will usually receive treatment with tesevatinib only until disease progression occurs, however treatment beyond progression is permissible in certain circumstances (See Duration of Treatment). Measuring response in LM is complex.[10] Subjects with LM entering the study will be required to have MRI evidence of LM or cytological evidence of LM or both. Thus in subjects with LM, response will be measured by symptom improvement, disappearance of signs of LM on MRI and/or by improvement in cytological results. Subjects will undergo safety evaluations, including physical examination, vital sign measurements, hematology, serum chemistry, urinalysis and ECG. MRI/computed tomography (CT) will be performed to evaluate peripheral tumor lesions. MRI will be performed to evaluate both BM and LM tumor involvement. For subjects with LM in Cohort B, lumbar puncture (LP) will be performed to evaluate CSF levels of tesevatinib, CSF malignant cell numbers by standard cytology and by rare cell capture techniques, CSF cell-free DNA, and detection of activating EGFR mutations in CSF cell-free DNA. **End of Treatment Visit** An End-of-Treatment visit is to occur within 3 days after the subject's last dose of study drug. This may occur at the visit at which disease progression is diagnosed. The subject will continue to be followed in the study for disease progression and survival. **Follow-Up Period** A follow-up visit will occur 30 days (±5 days) after the last dose of study drug. Subjects will undergo PEs; vital sign measurements; hematology, serum chemistry, and urinalysis, all performed prior to the start of any new therapy. This visit may occur prior to 30 days if a new therapy is started within 30 days of last dose of study drug. **Long-Term Follow-Up**

	After withdrawal from the active treatment portion of the study, subjects will be contacted by telephone every 8 weeks to assess survival status and any subsequent anti-cancer treatment.
Study population/Number of subjects	Up to 20 subjects with NSCLC who have progressed with BM will be enrolled in Cohort A. Up to 20 subjects who have initial presentation or progressed with LM will be enrolled in Cohort B. Up to 20 subjects with NSCLC and BM and no prior systemic therapy will be enrolled in Cohort C. Cohort A, Cohort B, and Cohort C will be open for enrollment simultaneously; when one cohort has completed enrollment the other cohorts will remain open for enrollment until enrollment in those cohorts are also complete.
Diagnosis and main criteria for inclusion	**Cohort A – Brain Metastases** **Inclusion criteria**: Subjects will be included if they meet the following criteria: 1. Age ≥ 18 years old. 2. History of NSCLC with EGFR mutation (either exon 19 deletion or L858R mutation or an EGFR activating mutation that has had a clinical response to erlotinib, afatinib, or gefitinib in the patient being enrolled). 3. Occurrence or progression of BM while receiving first line therapy (either erlotinib or afatinib or gefitinib) for at least 14 days. Patients may have received osimertinib (or other agents inhibiting the T790M EGFR mutation) as second line therapy. If BM progression occurs after osimertinib, patient will be eligible. 4. At least one measurable BM by RECIST 1.1 criteria (≥ 10mm in longest diameter). Target lesions must not have received stereotactic radiotherapy (SRS). If subject had prior WBRT, progression in any measurable BM lesion must have occurred at least 3 months after the end of WBRT. Subjects with asymptomatic brain metastases may be enrolled without prior radiation therapy to the brain. Subjects with minimally symptomatic brain metastases may be enrolled without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating investigator and in the opinion of a radiation therapy or neurosurgical consultant. 5. Subjects in Cohort A may have asymptomatic LM detected by MRI. (Subjects with symptoms or signs attributed to LM will be enrolled in Cohort B whether or not they have brain metastases) 6. No clinically significant progression outside of the CNS on most recent EGFR inhibitor therapy. 7. Eastern Cooperative Oncology Group (ECOG) Score ≤ 2. 8. No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred. 9. Adequate organ and bone marrow functions as follows: a. Serum creatinine ≤ 1.5 mg/dL b. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN). c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3×

	the ULN d. White blood count (WBC) > 3000/mm^3 e. Absolute neutrophil count ≥ 1500/mm^3 f. Platelet count > 100,000/mm^3 g. Hemoglobin > 8 g/dL 10. Serum potassium and magnesium levels above the lower limit of normal (LLN). 11. No coexisting medical problems of sufficient severity to limit compliance with the study. 12. Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study. 13. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression. a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug. b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 13 above during the treatment period and for at least 3 months after the last dose of study drug. **Exclusion criteria:** Subjects will be excluded if they meet any of the following criteria: 1. First day of dosing with tesevatinib is less than 2 weeks from the last treatment of cytotoxic chemotherapy, biological therapy, or immunotherapy and less than 6 weeks for nitrosoureas and mitomycin C. Surgical procedures must have been performed at least 2 weeks prior to the start of study treatment. Subjects must have recovered from the reversible effects of prior lung cancer treatments, including surgery and radiation therapy (excluding alopecia). 2. First day of dosing with tesevatinib is less than 4 weeks from the last radiotherapy of the brain or spinal cord/cauda equina. 3. First day of dosing with tesevatinib is less than 2 weeks from treatment with another investigational agent. 4. Treatment with erlotinib must be discontinued at least 3 days prior to first dose of tesevatinib and treatment with afatinib or other tyrosine kinase inhibitor must be discontinued at least 3 days prior to first dose of tesevatinib.

	5. Any concurrent therapy for BM other than the specified treatment in this study. 6. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine). 7. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval. 8. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction. 9. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor. 10. Has an active infectious process. 11. Female subject who is pregnant or lactating. 12. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body. 13. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate. 14. Gastrointestinal (GI) condition that interferes with drug absorption. 15. Non-malignant neurological disease that would interfere with evaluation of symptoms or signs of brain metastases. **Cohort B – Leptomeningeal Metastases** **Inclusion criteria**: Subjects will be included if they meet the following criteria: 1. Age ≥ 18 years old. 2. History of NSCLC with EGFR mutation (either exon 19 deletion or L858R mutation or, if previously treated, history of an activating EGFR mutation that has had a clinical response to erlotinib, afatinib, or gefitinib in the patient being enrolled). 3. Presentation with LM at initial presentation with no prior systemic treatment, or occurrence or progression of LM while receiving first line therapy (either erlotinib or afatinib or gefitinib) for at least 14 days. Patients may have received osimertinib (or other agents inhibiting the T790M EGFR mutation) as second line therapy. If LM progression occurs after osimertinib, patient will be eligible. 4. Presence of at least one CTCAE 4.03 symptom/sign of at least Grade 1 attributed by the investigator to leptomeningeal metastases 5. Diagnosis of LM by: a) Cytological evidence in CSF sample of LM due to NSCLC, and/or b) Findings on gadolinium-enhanced MRI

	6. No clinically significant progression outside of the CNS on most recent EGFR inhibitor therapy. 7. Concomitant brain metastases and brain metastases previously treated with radiation therapy are allowed. (Subjects with symptoms or signs attributed to LM will be enrolled in Cohort B whether or not they have brain metastases) 8. ECOG Score ≤2. 9. No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred. 10. Adequate organ and bone marrow functions as follows: a) Serum creatinine ≤ 1.5 mg/dL b) Total bilirubin ≤ 1.5 × ULN (except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN). c) ALT and AST ≤ 3× the (ULN d) WBC > 3000/mm^3 e) Absolute neutrophil count ≥ 1500/mm^3 f) Platelet count > 100,000/mm^3 g) Hemoglobin > 8 g/dL 11. Serum potassium and magnesium levels above the LLN. 12. No coexisting medical problems of sufficient severity to limit compliance with the study. 13. Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study. 14. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression. a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug. b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 14 above during the treatment period and for at least 3 months after the last dose of study drug

	Exclusion criteria: Subjects will be excluded if they meet any of the following criteria: 1. First day of dosing with tesevatinib is less than 2 weeks from the last treatment of cytotoxic chemotherapy, biological therapy, or immunotherapy, and less than 6 weeks for nitrosoureas and mitomycin C. Surgical procedures must have been performed at least 2 weeks prior to the start of study treatment. Subjects must have recovered from the reversible effects of prior lung cancer treatments, including surgery and radiation therapy (excluding alopecia). 2. First day of dosing with tesevatinib is less than 4 weeks from the last radiotherapy of the brain or spinal cord/cauda equina. 3. First day of dosing with tesevatinib is less than 2 weeks from treatment with another investigational agent. 4. Treatment with erlotinib must be discontinued at least 3 days prior to first dose of tesevatinib and treatment with afatinib or other tyrosine kinase inhibitor must be discontinued at least 3 days prior to first dose of tesevatinib. 5. Any concurrent therapy for LM other than the specified treatment in this study. 6. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine). 7. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval. 8. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction. 9. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor. 10. Has an active infectious process. 11. Female subject who is pregnant or lactating. 12. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body. 13. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate. 14. GI condition that interferes with drug absorption. 15. Non-malignant neurological disease that would interfere with evaluation of symptoms or signs of leptomeningeal metastases. 16. Contraindications to lumbar puncture: a) International normalized ratio (INR) > 1.5 b) Platelets < 50 × 109/L (Note that platelets are required to be ≥100× 109/L at

	screening) c) Therapeutic anticoagulant treatment that can't be held for 24 hours. Low dose low molecular weight heparin given for deep vein thrombosis (DVT) prophylaxis is allowed. d) CNS lesions considered to be at risk for cerebral herniation, myelocompression, or conus/cauda compression. **Cohort C – Brain Metastases at Initial Presentation** **Inclusion criteria**: Subjects will be included if they meet the following criteria: 1. Age ≥ 18 years old. 2. NSCLC with EGFR activating mutation. 3. No prior systemic treatment for NSCLC. Treatment with systemic steroids is not considered systemic treatment for NSCLC. 4. No prior radiation therapy to the CNS (brain or spinal cord) 5. At least one measurable BM by RECIST 1.1 criteria (≥ 10mm in longest diameter) in a subject with asymptomatic or minimally symptomatic brain metastases who does not require immediate surgical or radiation therapy in the opinion of the treating investigator and in the opinion of a radiation therapy or neurosurgical consultant. 6. Subjects in Cohort C may have asymptomatic LM detected by MRI. 7. ECOG Score ≤2. 8. No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred. 9. Adequate organ and bone marrow functions as follows: e) Serum creatinine ≤ 1.5 mg/dL f) Total bilirubin ≤ 1.5 × ULN (except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN). g) ALT and AST ≤ 3× the ULN h) WBC > 3000/mm^3 i) Absolute neutrophil count ≥ 1500/mm^3 j) Platelet count > 100,000/mm^3 k) Hemoglobin > 8 g/dL 10. Serum potassium and magnesium levels above the LLN. 11. No coexisting medical problems of sufficient severity to limit compliance with the study. 12. Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study. 13. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women

	without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression. a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug. b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 13 above during the treatment period and for at least 3 months after the last dose of study drug **Exclusion criteria:** Subjects will be excluded if they meet any of the following criteria: 1. Surgical procedures that were performed less than 2 weeks prior to the start of study treatment. 2. Any concurrent therapy for BM other than the specified treatment in this study. 3. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine). 4. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval. 5. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction. 6. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor. 7. Has an active infectious process. 8. Female subject who is pregnant or lactating. 9. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body. 10. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate. 11. GI condition that interferes with drug absorption. 12. Non-malignant neurological disease that would interfere with evaluation of

	symptoms or signs of brain metastases.
Dosage and administration	Tesevatinib will be administered at the dose of 300 mg once daily. Tesevatinib will be used in dosage strength of 100-mg, and 150-mg tablets. Patient diaries will be utilized to evaluate compliance. One cycle will be defined as 28 days of treatment. Tesevatinib should be taken in the morning (unless there is a subject-specific rationale to take it regularly at a different time of day) and can be administered without regard to food intake.
Duration of treatment/ Discontinuation	Duration of treatment: Subjects will be treated with study drug until disease progression or unacceptable toxicity occurs. However, subjects with limited peripheral disease progression (oligoprogressive disease) may receive local ablative (radiation therapy or surgery) while study drug is withheld for up to 28 days, and then be continued on tesevatinib. Discontinuation: Subjects who discontinue tesevatinib treatment will be followed for survival.
Concomitant medications	Concomitant treatment and medication information will be collected from the time the subject signs the informed consent form until 30 days after their last dose of study drug or until the subject starts a new treatment, and is to be reported on the appropriate case report form (eCRF). The generic name of the drug (or trade name for combination drugs) must be specified along with the reason for use, and duration of treatment. Additionally, all diagnostic, therapeutic, or surgical procedures, whether relating to malignancy or not, should be recorded in the eCRF including the date, indication, description of the procedure(s), and any clinical finding. Any medication that is considered necessary for the subject's welfare may be given at the discretion of the investigator. Ancillary treatments will be given as medically indicated. The reason for administration must be recorded on the eCRF. Any changes in documented, permitted concomitant treatment already being taken at the beginning of the clinical study must be recorded in the eCRF, noting the type of medication, the duration, and indication. Concurrent treatment with bisphosphonates or denosumab is allowed, if started prior to the start of tesevatinib administration.
Prohibited treatments	• Other investigational drugs • Concurrent anti-tumor therapies such as chemotherapy, gene therapy, biologics, tyrosine kinases inhibitors, radiation therapy, or other immunotherapy • Medications associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval, including anti-arrhythmic medications within 2 weeks prior to Day 1 of treatment in the study. • Tesevatinib is largely metabolized by CYP3A4. Therefore, taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).

	• Steroid medications are allowed • Use of proton pump inhibitors, H2 antagonists, and antacids is allowed, with restrictions • Tesevatinib is a MATE inhibitor. MATE transporter substrates and/or inhibitors should be used with caution
Safety assessments	The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03 - www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf) will be used for grading toxicities. Safety assessments will include adverse events (AEs), serious adverse events (SAEs), physical examinations (PEs), vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG scores, and ECGs. The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through 30 days after the last dose of study drug or until start of new treatment. All AEs that occur in enrolled subjects during the AE reporting period specified in the protocol must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to tesevatinib should be reported to Kadmon. Vital sign measurements, including sitting blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study. If ≥ Grade 3 CTCAE AEs occur that are determined to be at least possibly related to study drug (with the exception of asymptomatic Grade 3 elevations of amylase or lipase, Grade 3 elevation of alkaline phosphatase in a subject known to have bone metastases, Grade 3 elevation of glucose in a subject receiving systemic corticosteroids, Grade 3 creatine phosphokinase [CPK] elevation in the absence of muscle symptoms, or Grade 3 sodium values ≥126 mmol/L in a subject with diarrhea), tesevatinib will be withheld until all drug-related toxicities have resolved to ≤ Grade 1. If the QTc(F) interval increases to the level of ≥ 500 msec study drug should be withheld and appropriate investigations undertaken.
Pharmacokinetic Evaluation	For patients in Cohort B, PK samples will be drawn to evaluate tesevatinib pharmacokinetics. A plasma sample for tesevatinib PK analysis will be obtained at predose on Day 14 of Cycle 1 and at predose on Day 1 of Cycle 3. A plasma sample also will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within 4–8 hours after tesevatinib administration (i.e., at approximately the same time the CSF PK sample is obtained). CSF PK samples will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within 4–8 hours after tesevatinib administration. For all cohorts, additional samples for the preparation of plasma will be collected for tesevatinib analyses if the QTc(F) interval increases to the level of ≥ 500 msec (sample to be drawn as soon as possible after ECG performed).
Pharmacodynamic Evaluation	For all subjects, a plasma cell free DNA sample will be obtained at screening in order to correlate response with EGFR DNA mutations seen in plasma cell free DNA at screening. For subjects with LM (Cohort B), NSCLC cells in the CSF will be evaluated by both

	standard cytology and by a central rare cell detection methodology at Screening, on Day 14 of Cycle 1, and on Day 1 of Cycle 3. Samples will be evaluated for EGFR mutations (both the EGFR mutation or mutations known to be present in the tumor of a particular subject by prior investigation as well as for the T790M mutation and other EGFR mutations) as well as by immunochemistry for EGFR expression and phosphorylation.
Efficacy	For subjects with BM (Cohort A and Cohort C) efficacy will be evaluated by RECIST 1.1 criteria separately for non-CNS tumor lesions and for BMs at screening, at Cycle 2 Day 1 (for BM), at Cycle 3, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression. For subjects with LM (Cohort B), symptoms attributed to leptomeningeal disease will be evaluated at screening, Cycle 1 Day 1, at Cycle 1 Day 14, at Cycle 2 Day 1, at Cycle 3, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression. CTCAE v4.03 (www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf) will be utilized for the evaluation of symptoms and signs attributed to leptomeningeal disease. Symptom improvement is defined as a decrease in 1 grade in at least one CTCAE v4.03 symptom or sign attributed to leptomeningeal metastases without worsening of other symptoms or signs that are attributed to leptomeningeal metastases. Symptom progression is defined as an increase of 1 grade in at least one CTCAE v4.03 symptom or the appearance of new symptoms or signs of LM. Symptoms or signs attributed to leptomeningeal metastases will be followed as one component of the efficacy evaluation for Cohort B. In addition to bone scan at screening, scans of the thorax and abdomen will be performed at screening, at Cycle 3, and then every two cycles thereafter until disease progression. Radiological disease assessments by brain MRI will be performed at screening, at Cycle 2 Day 1, at Cycle 3 Day 1, and then every two cycles until disease progression. Response for peripheral disease and for BM will be evaluated according to RECIST, Version 1.1. Response will be recorded separately for non-CNS disease, for BM, and for LM. All CT and MRI scans will be collected for central review. All clinical decisions during the study will be based on local site radiology assessments, which will also be used for the primary efficacy analysis. For subjects with LM (Cohort B), NSCLC cells in the CSF will be evaluated during the study (screening, Day 14 of Cycle 1, and on Day 1 of Cycle 3) for malignant cells both by standard cytological analysis and by a rare cell detection methodology. CSF obtained at the same time points will be evaluated for protein and glucose levels. Response will be based on standard cytological analysis if cytology was positive at screening. Response categories will be complete response (CR) (no malignant cells, which must be present on 2 consecutive CSF evaluations to support response of CR), and non-PR, non-progressive disease (PD) (continued presence of malignant cells). PD will not be defined by CSF cytology. For subjects with LM (Cohort B), CSF for isolation of cell-free DNA will be collected at screening, Day 14 of Cycle 1, and on Day 1 of Cycle 3. Evaluation for EGFR mutations will be performed. Quantitation of EGFR mutations in cell-free DNA will be utilized for an exploratory efficacy analysis. LM will also be evaluated by serial MRI of the brain. For patients with positive findings of LM on MRI at screening, response categories will be CR (no evidence of

	LM on MRI), or non-PR, non-PD (continued presence of evidence of LM on MRI). PD for LM will not be defined by MRI. The response efficacy endpoints will be evaluated separately for peripheral disease, for BM, and for LM, and a summary response will also be derived (See Table 14-1). For LM, if positive CSF cytology and MRI diagnostic findings were both present at screening, CR requires the absence of LM by both modalities. Best overall response, duration of response, and duration of stable disease will be reported, based on the examples in Table 14-1. PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP, and OS also will be assessed. Subjects with limited CNS or extra-CNS disease progression (oligoprogressive disease) may receive local ablative therapy (radiation therapy or surgery) and then be continued on tesevatinib. This practice is consistent with data indicating that some patients with NSCLC on TKI therapy who have oligoprogressive disease appear to have significant periods of additional disease control with this approach.[16] Any such patients will be considered to have disease progression for analyses of PFS and for analyses of progression in the relevant (CNS or extra-CNS) compartment at the time of detection of oligoprogressive disease. Subjects with scans that are on the "borderline" of disease progression (e.g. 21% increase in sum of target lesion diameters or equivocal findings on CSF cytology or MRI) but for whom the investigator determines a clinical benefit may occur in the study. These subjects will be allowed to continue in the study after discussion with the medical monitor. If improvement is documented at the next subsequent staging time point (e.g. 17% increase in sum of target lesion diameters or stable CNS symptoms), the subject will continue on study. If worsening is documented (e.g. 30% increase in sum of target lesion diameters or worsening of CNS symptoms), the subject should be discontinued from the study, and the progression date should be the original date on which "borderline" disease progression was first documented. If stable, then they will be followed until improvement or worsening occurs.
Quality of Life	QOL will be evaluated via the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires administered at Screening, on Day 1 of Cycle 3, and on Day 1 of odd-numbered cycles thereafter.
Statistical methods	For Cohort A, assuming that 20% of subjects with BM have RECIST 1.1 response (CR or PR), the study has an approximately 80% chance of having at least 3 subjects with RECIST 1.1 response, and an over 90% chance of at least 2 subjects having a response. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments. For Cohort B, assuming that 20% of subjects with LM have improvement in at least one symptom or sign attributed to leptomeningeal metastases, the study has an approximately 80% chance of having at least 3 subjects with improvement in at least one symptom or sign attributed to leptomeningeal metastases and an over 90% chance of at least 2 subjects having improvement. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments. For Cohort C, assuming that 20% of subjects with BM have RECIST 1.1 response (CR or PR), the study has an approximately 80% chance of having at least 3 subjects with

	RECIST 1.1 response, and an over 90% chance of at least 2 subjects having a response. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments. Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 18.1 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, according to the most severe grade using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately. AEs, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by cohort and tesevatinib overall according to SOC and preferred terms. AEs will also be summarized in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome. Descriptive statistics including 95% confidence intervals for improvement in symptoms attributed to leptomeningeal metastases, clearing of NSCLC cells in the CSF, and clearing of CNS MRI findings will be presented. Exploratory evaluation of efficacy results by EGFR mutation will be performed. In addition, identical statistics for the change and percent change from Cycle 1 Day 1 tumor measurements will be presented. These analyses will be done after each two cycles of therapy, and will include peripheral (non-CNS) tumors as well as brain metastases. Summary statistics will be produced for PFS and OS. The percentage of subjects without disease progression after 3 and 6 months of dosing will also be presented separately by local and central radiograph results. Laboratory results will be classified according to NCI-CTCAE Version 4.03 and summarized by cohort. Laboratory results not corresponding to a coded term will not be graded. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of ≥ Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from Cycle 1 Day 1 to highest grade post-Cycle 1 Day 1 will be displayed. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. ECOG performance status results will be summarized by scheduled time point. Additional statistical details will be provided in a prospective statistical plan. Tesevatinib concentrations in the plasma and CSF will be summarized at each scheduled collection time point using descriptive statistics, and displayed graphically.

Table 4-1: Study Assessments for Cohort A – Brain Metastases and Cohort C - Brain Metastases at Initial Presentation

Timepoint (Study Day)	Screen	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7+	EOS Tx[k]	30-Day FU[l] (± 5d)	LTFU	UNS[m]
	-29 to -1	Day 1	Day 7 (± 3d)	Day 14 (± 3d)	Day 1 (± 3d)	Day 1 (± 3d)	Day 1 (± 3d)	Day 1 (± 3d)	Day 1 (± 3d)	Day 1 (± 3d)				
Informed Consent	X													
Medical History	X													
Demographics	X													
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Score	X	X		X	X	X	X	X	X	X	X	X		
Safety Labs[c]	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test[d]	X	X			X	X	X	X	X	X	X	X		
12-Lead ECG[e]	X	X	X	X	X	X	X	X	X	X	X			
Tumor Assessment[f]	X				X[f]	X		X		X	X			
Bone scan[g]	X													
Tesevatinib Administration[h]		X	X	X	X	X	X	X	X	X				
Plasma Cell-free DNA	X													
QOL questionnaires[i]	X					X		X		X	X			
Concomitant Medications	*To be collected from the time of informed consent through 30 days after last dose of study drug.*													
AE Monitoring[j]	*To be collected from the time of informed consent through 30 days after last dose of study drug.*													
Collect/Dispense Study Drug		X			X	X	X	X	X	X	X			
Collect/Dispense Study Drug Diary		X			X	X	X	X	X	X	X			
Follow-Up Phone Contact													X[n]	

d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; FU = follow-up; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; QOL = quality of life; UNS = unscheduled; Tx = treatment

a: At screening, PE to include height and weight. Complete PE including weight is required at all visits except for Days 7 and 14 of Cycle 1, when an abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

b: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained after the subject has been sitting for 5 minutes. On Cycle 1, Day 1, and Cycle 1, Day 14 vital signs are to be measured predose and 1 and 4 hours postdose.

c: Safety labs = hematology and clinical chemistry and urinalysis. Note that Cycle 1 Day 1 labs need not be repeated if screening visit occurred within 4 days prior to Day 1 visit. Safety labs will also be done at C2D15, C3D15, C4D15, C5D15, and C6D15; they are to be done locally and will include serum chemistry only. There will be a 3 day window for the D15 chemistry labs. Cystatin C does not need to be included in the chemistry labs done on C2D15, C3D15, C4D15, C5D15, and C6D15.

d: Pregnancy tests will be done using urine samples in women of childbearing potential. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Confirm with serum testing if urine sample is positive..

e: Supine 12-Lead ECGs will be performed at screening; Days 1, 7 and 14 of Cycle 1; on Day 1 of Cycles 2 and Day 1 of each Cycle including at End of Study Drug Treatment visit Assessment to be performed at predose, and once within 4 – 8 hours postdose for Days 1, 7 and 14 of Cycle 1. At each timepoint, repeat ECG three times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs).

f: Tumor assessment is to be performed at screening, at C2D1, on C3D1, and after every 2 cycles (beginning on Day 1 of Cycle 3 [± 7 days]). Tumor assessment should include brain MRI. Peripheral (non-CNS) tumor may be assessed with either CT or MRI, but method of assessment should be the same throughout the study. Tumor assessment on C2D1 will be limited to brain MRI.

g: Bone scans are to be performed at screening and then as clinically indicated.

h: Tesevatinib will be administered at the dose of 300 mg once daily.

i: EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires administered at screening, on Day 1 of Cycle 3, and on Day 1 of odd-numbered cycles thereafter and EOS

j: AEs are to be collected from the time of informed consent through 30 days after last dose of study drug.

k: The End-of-Study Drug Treatment visit is to occur within 3 days after the subject's last dose of study drug. This may occur at the visit at which disease progression is diagnosed. Tumor assessment does not need to be performed if it was performed in the previous 8 weeks.

l: The 30-Day Follow-Up visit should occur 30 days (±5 days) after the subjects' last dose of tesevatinib, but prior to starting on a new therapy. This may occur prior to 30 days if the new therapy is started within 30 days of last dose of study drug.

m: For unscheduled visits, study assessments are at the investigator's discretion.

n: Subjects are to be contacted by telephone every 8 weeks to assess survival status and any subsequent anti-cancer treatment.

Table 4-2: Study Assessments for Cohort B – Leptomeningeal Metastases

Timepoint (Study Day)	Screen -29 to -1	Cycle 1 Day 1	Cycle 1 Day 7 (± 3d)	Cycle 1 Day 14 (± 3d)	Cycle 2 Day 1 (± 3d)	Cycle 3 Day 1 (± 3d)	Cycle 4 Day 1 (± 3d)	Cycle 5 Day 1 (± 3d)	Cycle 6 Day 1 (± 3d)	Cycle 7+ Day 1 (± 3d)	EOS Tx[n]	30-Day FU [o] (± 5d)	LTFU	UNS[p]
Informed Consent	X													
Medical History	X													
Demographics	X													
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Score	X	X		X	X	X	X	X	X	X	X	X		
Safety Labs[c]	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test[d]	X	X			X	X	X	X	X	X	X	X		
12-Lead ECG[e]	X	X	X	X	X	X	X	X	X	X	X			
Tumor Assessment[f]	X				X[f]	X		X		X	X			
Evaluation of LM Symptoms	X	X		X	X	X		X		X	X			
Bone scan[g]	X													
Tesevatinib Administration[h]		X	X	X	X	X	X	X	X	X				
Plasma PK Sampling[i]				X		X								
Plasma Cell-free DNA	X													
CSF PK Sampling[j]				X		X								
CSF Cytology and Cell-free DNA[k]	X			X		X								
QOL questionnaires[l]	X					X		X		X	X			
Concomitant Medications	*To be collected from the time of informed consent through 30 days after last dose of study drug.*													
AE Monitoring[m]	*To be collected from the time of informed consent through 30 days after last dose of study drug.*													
Collect/Dispense Study Drug		X			X	X	X	X	X	X	X			
Collect/Dispense Study Drug Diary		X			X	X	X	X	X	X	X			
Follow-Up Phone Contact													X[q]	

CSF = cerebrospinal fluid; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; FU = follow-up; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; QOL = quality of life; UNS = unscheduled; T_x = treatment

a: At screening, PE to include height and weight. Complete PE including weight is required at all visits except for Days 7 and 14 of Cycle 1, when an abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

b: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained after the subject has been sitting for 5 minutes.. On Cycle 1, Day 1, and Cycle 1, Day 14 vital signs are to be measured predose and 1 and 4 hours postdose.

c: Safety labs = hematology and clinical chemistry and urinalysis. Note that Cycle 1 Day 1 labs need not be repeated if screening visit occurred within 4 days prior to Day 1 visit. Safety labs will also be done at C2D15, C3D15, C4D15, C5D15, and C6D15; they are to be done locally and will include serum chemistry only. There will be a 3 day window for the D15 chemistry labs. Cystatin C does not need to be included in the chemistry labs done on C2D15, C3D15, C4D15, C5D15, and C6D15.

d: Pregnancy tests will be done using urine samples in women of childbearing potential. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Confirm with serum testing if urine sample is positive.

e: Supine 12-Lead ECGs will be performed at screening; Days 1, 7 and 14 of Cycle 1; on Day 1 of Cycles 2 and Day 1 of each Cycle including at End of Study Drug Treatment visit Assessment to be performed at predose and once within 4 – 8 hours postdose for Days 1, 7, and 14 of Cycle 1. At each timepoint, repeat ECG three times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs).

f: Tumor assessment is to be performed at screening, C2D1, C3D1, and after every 2 cycles (beginning on Day 1 of Cycle 3 [± 7 days]). Tumor assessment should include brain MRI. Peripheral (non-CNS) tumor may be assessed with either CT or MRI, but method of assessment should be the same throughout the study. Tumor assessment on C2D1 will be limited to brain MRI.

g: Bone scans are to be performed at screening and then as clinically indicated.

h: Tesevatinib will be administered at the dose of 300 mg once daily.

i: A plasma sample for tesevatinib PK analysis will be obtained at predose on Day 14 of Cycle 1 and at predose on Day 1 of Cycle 3. A tesevatinib plasma sample also will be obtained on Cycle 1 Day 14, and Cycle 3 Day 1, within 4–8 hours after tesevatinib administration (at approximately the same time the CSF PK sample is obtained). Additional samples for the preparation of plasma will be collected for tesevatinib analyses if the QTc(F) interval increases to ≥ 500 msec (sample to be drawn as soon as possible after ECG performed).

j: CSF PK samples will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1 at 4-8 hours after administration of the tesevatinib dose that day.

k: NSCLC cells in the CSF will be evaluated at screening, on day 14 of Cycle 1, and on Cycle 3 Day 1 and will be evaluated for EGFR mutations (both the EGFR mutation or mutations known to be present in the tumor of a particular patient by prior investigation as well as for the T790M mutation) as well as by immunochemistry for EGFR expression and phosphorylation. Samples will be drawn both for standard cytological analysis as well as for a rare cell detection methodology. CSF for cell-free DNA isolation will be obtained at the same times (screening, on day 14 of Cycle 1 and on Cycle 3 Day1) and will be evaluated for EGFR mutations and the amount of cell-free DNA present. In cases where CSF is limiting, samples will first be sent for CSF cytology, glucose, and protein, second for CSF tesevatinib PK, third for rare cell detection, and last for cell-free DNA.

l: EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires administered at screening, on Day 1 of Cycle 3, and on Day 1 of odd-numbered cycles thereafter and EOS.

m: AEs are to be collected from the time of informed consent through 30 days after last dose of study drug.

n: The End-of-Study Drug Treatment visit is to occur within 3 days after the subject's last dose of study drug. This may occur at the visit at which disease progression is diagnosed. Tumor assessment does not need to be performed if it was performed in the previous 8 weeks.

o: The 30-Day Follow-Up visit should occur 30 days (±5 days) after the subjects' last dose of tesevatinib, but prior to starting on a new therapy. This may occur prior to 30 days if the new therapy is started within 30 days of last dose of study drug.

p: For unscheduled visits, study assessments are at the investigator's discretion.

q: Subjects are to be contacted by telephone every 8 weeks to assess survival status and any subsequent anti-cancer treatment.

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LIST OF ABBREVIATIONS

ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRF	case report form
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2
ICH	International Conference on Harmonization
ICF	informed consent form
INR	International Normalized Ratio
IRB	Institutional Review Board
LLN	lower limit of normal
LM	leptomeningeal metastases
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OS	overall survival
PD	progressive disease

PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
QD	once daily
QOL	quality of life
QTc(F)	QT interval, corrected
RECIST	Response Evaluation Criteria In Solid Tumors
RTK	receptor tyrosine kinases
SADR	suspected adverse drug reactions; also referred to as SAR
SAE	serious adverse event
SAR	suspected adverse reactions; also referred to as SADR
SOC	system organ class
Src	sarcoma
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TTP	time to progression
ULN	upper limit of normal
VEGFR2	vascular endothelial growth factor receptor 2

5 BACKGROUND AND RATIONALE

5.1 Tesevatinib

Tesevatinib (formerly known as KD019) is an orally administered tyrosine kinase inhibitor, which has been documented to inhibit multiple molecular drivers of tumor growth, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2(HER2), Src, and VEGFR2.

Tesevatinib is a highly potent inhibitor of the EGFR activating mutations that, when present, drive the growth of non-small cell lung cancers (NSCLCs). When measured in HCC827 cells, which are human lung cancer cells with an EGFR exon 19 deletion, the IC50 for inhibition of EGFR phosphorylation for tesevatinib (0.6 nM) was very similar to that for erlotinib (0.8 nM). The IC50 for inhibition of proliferation in the same cell line was 3.5 nM for tesevatinib and 4.6 nM for erlotinib. Thus tesevatinib and erlotinib have similar potency in vitro against a cell line with an activating EGFR mutation.

5.1.1 Tesevatinib Nonclinical Toxicology

Tesevatinib nonclinical toxicology has been characterized in multiple species using a variety of dosing regimens. Details are provided in the Investigator's Brochure.

5.1.2 Clinical Experience with Tesevatinib

Tesevatinib has been evaluated in two single-agent Phase 1 studies in subjects with advanced solid tumors (Studies XL647-001 and XL647-002), in two single-agent Phase 2 studies in subjects with NSCLC (Studies XL647-201 and XL647-203), and in a Phase 3 study (Study KD019-301) in NSCLC that only enrolled 8 patients. Tesevatinib is also being evaluated in a Phase 1/2 study in subjects with HER2+ metastatic breast cancer, and in a Phase 1/2 study in subjects with autosomal dominant polycystic kidney disease (ADPKD).

5.1.2.1 Phase 1

The single-agent tesevatinib Phase 1 study (XL647-002) concluded that the maximum tolerated dose (MTD) for daily dosing of tesevatinib was 300 mg daily because two subjects who received 350 mg daily had Grade 3 QTc prolongation (>500 ms). However, when these were later reviewed by a central cardiology review, they were both downgraded to Grade 2. In one case, the site QTc reading was confounded by a new right bundle branch block and, in the other case, by bradycardia. Thus, due to these complicating issues, the MTD for daily administration of tesevatinib was evaluated further in combination with trastuzumab in the ongoing study in patients with HER2+ breast cancer. The MTD of 300 mg daily was recently confirmed in the

breast cancer study. This study and others have also determined that tesevatinib has a prolonged half-life of approximately 60 hours.

The other single-agent tesevatinib Phase 1 study (XL647-001) evaluated a schedule of 5 days of tesevatinib administered every 2 weeks. This study initially used a powder-in-capsule preparation of tesevatinib. At 7 mg/kg, the only two subjects treated both had Grade 3 diarrhea. In one subject (11032), the Grade 3 diarrhea occurred on Day 4 of the study and diarrhea resolved on Day 8. In the other subject (11034), the Grade 3 diarrhea occurred on Day 7 and diarrhea resolved on Day 25. The next lowest dose, 4.68 mg/kg, was determined to provide similar exposure to 350 mg given as formulated tablets, which was called the MTD for this schedule. However, this study was performed from 2004-2007 when aggressively treating diarrhea due to EGFR inhibitors was not necessarily routine. It is unknown whether 350 mg administered for 5 days every 2 weeks would be considered to be the MTD if subjects had aggressive diarrhea management.

5.1.2.2 Phase 2

The first of the two single-agent Phase 2 studies in NSCLC (Study XL647-201) enrolled treatment naïve patients with advanced stage NSCLC who were Asian, female, or with minimal or no smoking history.[17] There were 41 subjects enrolled in an intermittent dosing schedule and 14 enrolled in a daily dosing schedule. Subjects in the intermittent cohort received tesevatinib at a dose of 350 mg for 5 days every 2 weeks. Subjects in the daily dosing cohort received tesevatinib administered at a dose of 300 mg daily. Retrospective sequencing of tumor samples identified 14/41 subjects with EGFR mutations. The confirmed partial response (PR) rate in subjects with EGFR mutations was 57% (8/14), and an additional 3 subjects with EGFR mutations had unconfirmed PRs. Response rates were similar in the daily and intermittent tesevatinib schedules. Patients with PRs were those whose tumors had Exon 19 deletions as well as those with the L858R mutation. One subject in this study who is on the intermittent schedule has had a long-term response lasting nearly five years and is still receiving tesevatinib therapy.

In the second single-agent tesevatinib study in NSCLC (Study XL647-203), tesevatinib was administered daily at a dose of 300 mg/day to 41 subjects with NSCLC who had disease progression after treatment with other EGFR inhibitors (erlotinib or gefitinib).[18] The most frequently reported adverse events (AEs) were diarrhea, nausea, cough, dry skin, and electrocardiogram (ECG) QTc prolongation. Two (2) of the 41 subjects experienced QTc(F) > 500 msec confirmed by a central cardiology review. (All subjects in all tesevatinib studies with QTc prolongation have been asymptomatic.) Eleven subjects (11; 28%) required a dose reduction for toxicity, most commonly for diarrhea (27%) and rash (18%). Whether EGFR-

related diarrhea or rash were treated aggressively is not clear. There were 12 subjects with documented T790M EGFR mutations, none of whom had a response to tesevatinib treatment.

5.1.2.3 Phase 3

The Phase 3 study (KD019-301) was a double-blind, randomized, and controlled trial of KD019 vs erlotinib in subjects with Stage IIIB/IV non-small cell lung cancer who had progressed after first- or second-line chemotherapy. The study was closed early due to slow enrollment after 8 subjects were entered. One subject who carried an EGFR activating mutation had a partial response to tesevatinib for eight cycles before progressing.

5.1.2.4 Ongoing Studies in Other Indications

A Phase 1b/2a study (KD019-204) of the combination of trastuzumab and tesevatinib is ongoing in subjects with HER2+ metastatic breast cancer (study KD019-204). The Phase 1 portion of the study used a 3+3 design that is commonly used in oncology studies. The Phase 1 portion of the study has determined that 300 mg daily of tesevatinib in combination with trastuzumab is the MTD dose, as the two subjects treated with 350 mg daily had Grade 3 events considered to be at least possibly related to tesevatinib (one had Grade 3 diarrhea not recovering to Grade 1 by seven days, and the other had Grade 3 QTc prolongation confirmed by central reading).

A Phase 1b/2a study (KD019-101) of tesevatinib in patients with ADPKD is ongoing. Subjects with ADPKD, in whom the drug will be administered chronically for years, did not tolerate the Grade 2 acneiform skin rash, which occurred in 2/5 patients at 150 mg daily. In addition, there were 2/8 patients receiving tesevatinib at a dose of 100 mg daily who had asymptomatic prolongation of the QTc duration (one Grade 3 and one Grade 2). Daily doses below 50 mg are being evaluated further.

5.2 Safety Profile of Tesevatinib

5.2.1 Tesevatinib

AEs that have been associated with tesevatinib include the following: diarrhea, skin rash, QTc(F) prolongation, elevated serum creatinine, elevated serum amylase, and interstitial lung disease (see Warnings, Precautions, and Management in Section 11.1.3).

Diarrhea: Diarrhea is an expected AE for agents like tesevatinib that have significant EGFR inhibitor activity. Grade 3 diarrhea was the dose-limiting toxicity (DLT) for both the 5 days out of 14 days schedule of tesevatinib in study XL647-001 as well as for the daily dosing of tesevatinib in the KD019-204 study of tesevatinib in patients with metastatic breast cancer. At

doses below those that cause DLT, diarrhea has generally been manageable with anti-diarrheal medications such as loperamide.

Skin Rash: Acneiform skin rash is an expected AE for agents like tesevatinib that have significant EGFR inhibitor activity. The rash characteristically involves the chest and face. Paronychial involvement, although characteristic of EGFR inhibitors, has not been seen in tesevatinib studies.

QTc(F) Prolongation: In clinical trials of tesevatinib, cases of QTc(F) prolongation have been observed.

Common Terminology Criteria for Adverse Events (CTCAE v4.03) was used to assign the severity grade for QTc(F) AEs and the criteria for each grade are presented below.

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
ProlongedQTc(F) interval	> 450–470 msec	> 470–500 msec or ≥ 60 msec above Cycle 1 Day 1	> 500 msec	> 500 msec with life threatening signs or symptoms; torsades de pointes

In the 169 subjects with malignancies treated in 4 uncontrolled studies, the majority of whom had advanced, metastatic non-small cell lung cancer, 33 (20%) were found to have QT prolongation based on machine read ECGs at some time during treatment that met the CTCAE v4.03 definition of an AE: Grade 1 [7 (4%) subjects], Grade 2 [14 (8%) subjects], and Grade 3 [12 (7%) subjects]. The majority of these subjects received ≥ 300 mg daily or 350 mg given for 5 days with 9 days off. There were no clinical findings associated with the ECG changes. There were no reports of QTc(F) prolongation in 32 healthy volunteer subjects who received a single 300 mg dose of tesevatinib.

Clinical trial data available for review encompassed Studies XL647-001, XL647-002, XL647-201, XL647-203, and XL647-004. Other studies (XL647-005) did not have data confirmed by central ECG laboratory. In terms of total exposure, 201 subjects received tesevatinib (169 subjects with cancer and 32 normal volunteers). ECGs for a total of 178 of these subjects have been reviewed by the central ECG laboratory.

No SAEs of convulsion; sudden death; ventricular tachycardia, fibrillation, or flutter, or torsades de pointes have been received for the > 250 subjects exposed to tesevatinib.

Digital ECG files from 178 subjects were supplied to a vendor (eRT) for analysis. ECGs from 60 subjects had further review by a cardiologist, including all 41 subjects in XL647-203, and an additional 19 subjects from XL647-001 (2), XL647-002 (12), and XL647-201 (5), because they were reported to have noteworthy QTc(F) prolongation on the ECG machine analysis.

Of these 60 subjects, eRT analyzed the digital files and identified 23 (38%) subjects who had no outlier findings, 5 (8%) subjects who had no QTc(F) prolongation on the digital analysis, and 2 (3%) subjects who eRT could not completely exclude as being product related, but whose prolonged QTc(F) value obtained on the machine read ECG was not felt to be measurable due to underlying RBBB or atrial fibrillation.

Of the 30 (50%) remaining subjects, eRT identified 25 with prolonged QTc(F) values of $\leq$ 60 msec, which eRT could not completely exclude as being product related. There were 3 subjects with QTc(F) > 60 msec that were felt to be possibly/probably related to drug treatment and 2 subjects who had QTc(F) values > 500 msec, which were felt to be probably related to drug treatment.

A preliminary analysis of delta QTc(F) (change from Cycle 1 Day 1 value) versus plasma concentration was carried out using pooled data from studies with intermittent 5 days on and 9 days off dosing (Study XL647-001), single doses with crossover food effects (Study XL647-004) and once-daily dosing (Studies XL647-002 and XL647-203) regimens. Concentration-matched ECGs were available from 1104 records from 125 subjects. This analysis was done using QTc(F) values obtained from the central ECG laboratory. All ECGs digitized and read at a central laboratory and QTc(F) values were Fridericia corrected. The QTc(F) versus concentration relationship was described using linear, power, and E_{max} mixed effects models using bootstrap population parameter estimates pooled across all three models (i.e., ~ 1000 bootstrap estimates per model). Analyses showed that the concentration-QTc(F) relationship appears to be consistent across Studies XL647-001, XL647-002, XL647-004, and XL647-203 (i.e., suitable for pooling, and argues against a marked time effect because XL647-004 is single dose). In these studies, QTc(F) prolongation increased with increasing plasma concentration.

In study KD019-101, subjects treated with doses of tesevatinib as low as 100 mg daily have had prolongation of QTc(F) of > 60 ms over Cycle 1 Day 1 levels. In study KD019-204, one of two subjects receiving tesevatinib at 350 mg daily in combination with trastuzumab had QTc(F) prolongation to > 500 ms, which was a DLT event for that study. Subjects in this study will be monitored carefully for QTc prolongation, and a central laboratory will review all ECGs in this study.

Elevations of Serum Creatinine: Data from study KD019-101 indicate that subjects with ADPKD receiving tesevatinib have experienced elevations of creatinine without elevations in cystatin C. For instance, the median changes from screening values for creatinine and cystatin C from all 9 subjects in the 50-mg dose cohort reveal that creatinine values were increased by 7.5% at Day 3, by 22% at Day 7, and increased by 13% at Day 28. Data after Day 28, including two subjects who have received tesevatinib for 16 months, do not indicate any significant ongoing change in creatinine. Cystatin C levels, during the same time periods, did not change, indicating that the increases in serum creatinine may not be reflective of changes in kidney function. Data from the subjects other doses of tesevatinib exhibited a similar pattern. This increase in creatinine occurs early and after approximately 7 days, does not continue to increase, similar to the increase in serum creatinine seen with cimetidine. Increases in creatinine were seen in previous clinical trials of tesevatinib. For example, increases in serum creatinine in 10% of subjects were reported in Study XL647-201. However, most of the previous studies were in subjects with malignancies, and in previous studies, cystatin C levels were not evaluated, so increases in serum creatinine that may not represent renal dysfunction were not recognized.

In order to further investigate the effects of tesevatinib on serum creatinine levels, the effects of tesevatinib on a panel of transporter molecules (including OCT2 and MATE) were evaluated in vitro. The results indicate that tesevatinib potently inhibits MATE1 and MATE2-K transporter proteins. MATE transporter proteins carry creatinine out of kidney proximal tubule cells into the tubule lumen. Inhibition of MATE transporter proteins decreases secretion of creatinine into the proximal tubule lumen and leads to an increase in serum creatinine levels. Increases in creatinine appear to be reversible. Both serum creatinine and cystatin C will be evaluated in this study in order to provide more information about any changes in creatinine that occur.

Elevations of Serum Amylase: There have been occasional cases of asymptomatic elevation of serum amylase in subjects treated with tesevatinib. In KD019-101, a study treating subjects with polycystic kidney disease at doses up to 150 mg/day, 5 subjects had amylase levels above the normal limit, 2 of which had elevated levels at screening. None had symptoms of clinical pancreatitis.

Previous oncology studies of tesevatinib have been reviewed for cases of elevated amylase or pancreatitis. Amylase was not routinely evaluated in any of these previous studies. There was only 1 treatment-emergent adverse event (TEAE) of an increased amylase level or of possible pancreatitis. This was an elevation of amylase to 922 U/L without clinical pancreatitis in a subject with Stage IV non-small cell lung cancer who received tesevatinib at a dose of 300 mg/day. On serum amylase isoenzyme analysis, the subject had an elevation in salivary

amylase. The investigator's conclusion was that the subject appeared to have an increase in amylase due to salivary amylase secretion by the tumor. To date, no subjects receiving tesevatinib have had symptoms compatible with clinical pancreatitis.

Interstitial Lung Disease: Non-fatal interstitial lung disease (ILD) has been reported in association with the use of tesevatinib in one subject with NSCLC out of >250 subjects exposed to tesevatinib.

5.3 Rationale

5.3.1 Study Rationale

Subjects with NSCLC with activating EGFR mutations (exon 19 deletions and the L858R point mutation) have a high response rate to tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib or afatinib. However, these are not curative therapies and tumors inevitably develop resistance.[1,2] The central nervous system (CNS) is a sanctuary site, as gefitinib, erlotinib and afatinib penetrate poorly into the brain. These drugs penetrate even more poorly into the cerebrospinal fluid (CSF), with CSF levels documented to be approximately 1% of plasma levels for gefitinib and afatinib and 2.5%–13% for erlotinib.[3,4,5] Disease progression after initial gefitinib or erlotinib treatment involves the CNS in approximately 28% of patients, and includes leptomeningeal metastases (LM) in 8%[6]. Progression with LM occurs more commonly in patients with previous brain metastases than in patients without previous brain metastases.[6] Patients with brain metastases (BMs) generally present with neurologic symptoms, which can include headache, confusion, and seizures. Patients with LM also present with neurologic symptoms, which often include headaches or cranial neuropathies or pain, but can be highly varied.

Despite the frequency of progression in the CNS, there are no approved drug treatments specifically for the treatment of BM or of LM in patients with NSCLC and activating EGFR mutations. Radiation therapy, either Whole Brain Radiotherapy (WBRT) or stereotactic radiosurgery (SRS) is often used to control symptoms of BMs. However, these treatments are rarely curative, and are not without side effects. WBRT is associated with early occurring fatigue and all too often with neurocognitive decline. In patients who received WBRT after SRS there is a significant decline of learning and memory function at 4 months compared to patients receiving only SRS.[7] SRS is associated with fewer side effects when used alone, but a higher recurrence rate as the entire brain is not irradiated. There are few effective therapies to control LM. Intrathecal methotrexate is sometimes used, although response rates are low and time to disease progression is short. In patients with NSCLC with activating EGFR mutations, intermittent high doses of gefitinib or erlotinib have been used to treat patients with BM and LM

with some degree of effectiveness.[2,8,9] However, response rates are low and the time to disease progression is generally short with this treatment as well.

Diagnosis of BM is generally obtained by magnetic resonance imaging (MRI) of the brain. The diagnosis of LM is more complex. Diagnosis of LM is most definitive when cytologic evaluation of CSF specimens detects malignant cells. However, single CSF analysis has a false negative rate of approximately 50%, and thus cytologic diagnosis of LM often requires several separate CSF samples.[10] MRI findings (such as subarachnoid nodules, enhancement in basal cisterns, and enhancement/clumping of nerve roots) are diagnostic, but normal CNS imaging does not exclude a diagnosis of LM. Antibodies to EpCam, an epithelial cell adhesion molecule, have been utilized to identify rare tumor cells such as circulating tumor cells in the blood. The same approach to rare cell capture has been utilized in the analysis of tumor cells in CSF. In one study of patients with LM, cytology had a sensitivity of 67%, MRI had a sensitivity of 73%, and EpCam based identification of CSF tumor cells had a sensitivity of 100%.[11] Cell-free DNA is present in patients with activating EGFR mutations and BM, and can be utilized to evaluate the EGFR mutations that are present.[12] Evaluation of cell-free DNA in the CSF may provide a method independent of cytological analysis for evaluation of the course of patients with LM.

Approximately 50% of erlotinib-resistant, EGFR-mutant patients harbor a T790M EGFR mutation, which gefitinib, erlotinib, and afatinib do not inhibit.[1,2] IC_{50}s for one cell line with the T790M EGFR mutation were 10.4 μM for gefitinib, 16.1 μM for erlotinib, and 0.9 μM for tesevatinib.[13] Despite having an IC_{50} against cells with the T790M EGFR mutation that is much lower than that for gefitinib or erlotinib, tesevatinib was not effective in treating NSCLC patients with the T790M EGFR mutation in the XL647-203 study.[14] However, patients with BM and LM occurring while receiving erlotinib therapy have been documented to have a much lower frequency (10%) of T790M mutation in the CNS than is the case for patients with progression in non-CNS locations (38%).[15] This presumably occurs because erlotinib and afatinib and gefitinib penetrate poorly into the CNS, and thus tumor cells in the CNS can grow in the presence of the low levels of TKI that are present.

Tesevatinib effectively penetrates into the brain, with levels in mice and rats with intact blood-brain barriers (BBB) the same or higher than plasma levels. Tesevatinib has levels in the choroid plexus and meninges in rats that are 10 times the plasma levels, suggesting that tesevatinib may penetrate well into CSF and may be an effective treatment for leptomeningeal metastases adhering to the inner surface of meninges.

Preliminary data from the initial patients enrolled in this study demonstrate that tesevatinib can achieve brain and leptomeningeal exposures with clinically significant effects. Radiological data are available from one of the 6 initial patients enrolled in the study. A 36 year old female patient was enrolled with symptoms of Grade 1 headache, anal numbness, and intermittent left leg weakness. She had a right parietal brain metastasis and leptomeningeal metastases diagnosed both by CSF cytology and by MRI. By study day 14 the headache, anal numbness, and intermittent left leg weakness were no longer present. On MRI at study day 41 there was a 57% decrease in size of the right parietal brain metastasis and no evidence of leptomeningeal metastases.

Thus, there is good biologic rational to evaluate tesevatinib in subjects with NSCLC and EGFR activating mutations who have disease progression with BM or LM, or have BM or LM at initial presentation. This study will enroll subjects with BM or LM occurring while being treated with erlotinib or afatinib or gefitinib, or with BM or LM at initial presentation.

5.3.2 Rationale for Dosage Selection

Tesevatinib administered as a single-agent at a dose of 300 mg daily has shown clinically significant activity in lung cancer studies. In study XL647-201, the confirmed partial response (PR) rate in subjects with EGFR mutations was 57% (8/14), and an additional 3 subjects with EGFR mutations had unconfirmed PRs (Section 5.1.2.2).

5.4 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki. In addition, the investigator agrees to adhere to the protocol and to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

The appropriate Institutional Review Boards (IRBs) must approve the protocol and any amendments and the subject informed consent form (ICF) prior to implementation.

Voluntary written informed consent must be obtained from every subject prior to participation in this clinical study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study

personnel where sanctions have been invoked based upon scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

5.4.1 Good Clinical Practice

The principal investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50 (1998) and 21 CFR, part 56, (1998) are followed.

Since this is a covered clinical trial, the principal investigator is adhered to 21 CFR, part 54, (1998). A covered clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or Food and Drug Administration (FDA) relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Kadmon or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the principal investigator and any sub-investigator. The principal investigator and sub-investigator agree to notify Kadmon of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

6 STUDY OBJECTIVES

Cohort A

Primary objective

- To evaluate the clinical activity of tesevatinib in subjects with non-small cell lung cancer (NSCLC), activating EGFR mutations, and brain metastases (BM) as measured by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 evaluated changes in BM size.

Secondary objectives

- To evaluate changes in Quality of Life (QOL) in subjects receiving tesevatinib for BM.
- To determine the median progression-free survival (PFS), rate of CNS non-progression at 3 and 6 months, non-CNS time to progression (TTP), and CNS TTP.
- To determine the median overall survival (OS).

Exploratory objective

- To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response.

Cohort B

Primary objective

- To evaluate the clinical activity of tesevatinib in subjects with NSCLC, activating EGFR mutations, and leptomeningeal metastases (LM) as measured by improvement in Common Terminology Criteria for Adverse Events (CTCAE) v4.03 symptoms and signs.

Secondary objectives

- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by decreases in NSCLC cells in the CSF using standard cytology.
- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by improvement in CNS MRI findings .
- To evaluate the pharmacokinetics (PK) of tesevatinib in CSF versus plasma
- To evaluate changes in QOL in subjects receiving tesevatinib for LM.
- To determine the median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP.
- To determine the median OS.

Exploratory objectives

- To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response.

- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by decreases in NSCLC cells in the CSF using rare cell capture techniques.
- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM measured by decreases in CSF cell-free DNA.
  To utilize CSF cell-free DNA to detect activating EGFR mutations in patients receiving tesevatinib for LM.

Cohort C

Primary objective

- To evaluate the clinical activity of tesevatinib in subjects with NSCLC, activating EGFR mutations, and BM at initial presentation as measured by RECIST 1.1 evaluated changes in BM size.

Secondary objectives

- To evaluate changes in QOL in subjects receiving tesevatinib for BM.
- To determine the median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP in subjects with NSCLC, activating EGFR mutations, and BM at initial presentation.
- To determine the median OS.

Exploratory objective

- To evaluate the correlation between EGFR DNA mutations seen in plasma cell free DNA at screening with response.

7 STUDY DESIGN

7.1 Study Sites

This study will be conducted at approximately 10 sites in the United States, and at up to 6 sites in South Korea and Taiwan.

7.2 Overview of Study Design

This is a multicenter, Phase 2 study to assess the activity of tesevatinib in subjects with NSCLC and activating EGFR mutations and BM or LM. Up to 20 subjects with NSCLC who have progressed with BM will be enrolled in Cohort A, up to 20 subjects who have LM will be enrolled in Cohort B, and up to 20 subjects who have BM at initial presentation will be enrolled in Cohort C. All three cohorts will be open for enrollment simultaneously; when one cohort has completed enrollment the other cohorts will remain open for enrollment until enrollment in all cohorts is complete.

After completion of the screening assessments and confirmation of study eligibility, tesevatinib will be orally administered to all subjects at a dose of 300 mg once daily.

Tumor response, both in the CNS and outside the CNS, will be assessed after the second cycle of treatment and then at the end of every two cycles of treatment thereafter. Subjects will usually receive treatment with tesevatinib only until disease progression occurs, however treatment beyond progression is permissible in certain circumstances (See Section 11.1.1). Measuring response in LM is complex and there are no validated methods to do so.[10]

Subjects with LM entering the study will be required to have MRI evidence of LM or cytological evidence of LM or both. Thus in subjects with LM, response will be measured by improvement in symptoms and signs attributed to leptomeningeal metastases, disappearance of signs of LM on MRI and/or by improvement in cytological results.

Subjects will undergo safety evaluations, including physical examination, vital sign measurements, hematology, serum chemistry, and urinalysis, and ECG. MRI/computed tomography (CT) will be performed to evaluate peripheral tumor lesions. MRI will be performed to evaluate both BM and LM tumor involvement. For subjects with LM in Cohort B, lumbar puncture (LP) will be performed to evaluate CSF levels of tesevatinib, CSF malignant cell numbers by standard cytology and by rare cell capture techniques, CSF cell-free DNA, and detection of activating EGFR mutations in CSF cell-free DNA.

7.3 Randomization and Blinding

This is an open-label, nonrandomized study.

8 STUDY POPULATION

8.1 Target Population

This study will be conducted in up to 60 subjects with NSCLC and activating EGFR mutations with BM at progression (n=20), LM at initial presentation or progression (n=20), or BM at initial presentation (n=20).

8.2 Inclusion Criteria – Cohort A

A subject must meet the following criteria to be eligible for entry into the study:

1) Age ≥ 18 years old.
2) History of NSCLC with EGFR mutation (either exon 19 deletion or L858R mutation or an EGFR mutation that has had a clinical response to erlotinib, afatinib, or gefitinib in the patient being enrolled).
3) Occurrence or progression of BM while receiving first line therapy (either erlotinib or afatinib or gefitinib) for at least 14 days. Patients may have received osimertinib (or other agents inhibiting the T790M EGFR mutation) as second line therapy. If BM progression occurs after osimertinib, patient will be eligible.
4) At least 1 measurable BM by RECIST 1.1 criteria (≥ 10mm in longest diameter). Target lesions must not have received stereotactic radiotherapy (SRS). If subject had prior whole brain radiotherapy (WBRT), progression in any measurable BM lesion must have occurred at least 3 months after the end of WBRT. Subjects with asymptomatic brain metastases may be enrolled without prior radiation therapy to the brain. Subjects with minimally symptomatic brain metastases may be enrolled without prior radiation therapy to the brain if they do not require immediate surgical or radiation therapy in the opinion of the treating investigator and in the opinion of a radiation therapy or neurosurgical consultant.
5) Subjects in Cohort A may have asymptomatic LM detected by MRI. (Subjects with symptoms or signs attributed to LM will be enrolled in Cohort B whether or not they have brain metastases.)
6) No clinically significant progression outside of the CNS on most recent EGFR inhibitor therapy.
7) Eastern Cooperative Oncology Group (ECOG) Score ≤2.
8) No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred.

9) Adequate organ and bone marrow functions as follows:
   a) Serum creatinine ≤ 1.5 mg/dL
   b) Total bilirubin ≤ 1.5 × the upper limit of normal (ULN; except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN).
   c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3× ULN
   d) WBC > 3000/mm^3
   e) Absolute neutrophil count ≥ 1500/mm^3
   f) Platelet count > 100,000/mm^3
   g) Hemoglobin > 8 g/dL
10) Serum potassium and magnesium levels above LLN.
11) No coexisting medical problems of sufficient severity to limit compliance with the study.
12) Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study.
13) Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression.
   a) Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
   b) Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner

c) For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 13 above during the treatment period and for at least 3 months after the last dose of study drug

8.3 Exclusion Criteria – Cohort A

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

1. First day of dosing with tesevatinib is less than 2 weeks from the last treatment of cytotoxic chemotherapy, biological therapy, or immunotherapy, and less than 6 weeks for nitrosoureas and mitomycin C. Surgical procedures must have been performed at least 2 weeks prior to the start of study treatment. Subjects must have recovered from the reversible effects of prior lung cancer treatments, including surgery and radiation therapy (excluding alopecia).
2. First day of dosing with tesevatinib is less than 4 weeks from the last radiotherapy of the brain or spinal cord/cauda equina.
3. First day of dosing with tesevatinib is less than 2 weeks from treatment with another investigational agent.
4. Treatment with erlotinib must be discontinued at least 3 days prior to first dose of tesevatinib and treatment with afatinib or other tyrosine kinase inhibitor must be discontinued at least 3 days prior to first dose of tesevatinib.
5. Any concurrent therapy for BM other than the specified treatment in this study.
6. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
7. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval.
8. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction.
9. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor.

10. Has an active infectious process.
11. Female subject who is pregnant or lactating.
12. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body.
13. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate.
14. Gastrointestinal (GI) condition that interferes with drug absorption.
15. Non-malignant neurological disease that would interfere with evaluation of symptoms or signs attributed to brain metastases.

8.4 Inclusion Criteria – Cohort B

A subject must meet the following criteria to be eligible for entry into the study:

1. Age ≥ 18 years old.
2. History of NSCLC with EGFR mutation (either exon 19 deletion or L858R mutation or of an EGFR mutation that has had a clinical response to erlotinib, afatinib, or gefitinib in the patient being enrolled).
3. Presentation with LM at initial presentation with no prior systemic treatment, or occurrence or progression of LM while receiving first line therapy (either erlotinib or afatinib or gefitinib) for at least 14 days. Patients may have received osimertinib (or other agents inhibiting the T790M EGFR mutation) as second line therapy. If LM progression occurs after osimertinib, patient will be eligible.
4. Presence of at least one CTCAE 4.03 symptom or sign of at least Grade 1 attributed to leptomeningeal metastases.
5. Diagnosis of LM by:
   a) Cytological evidence in CSF sample of LM due to NSCLC, and/or
   b) Findings on gadolinium-enhanced MRI
6. No clinically significant progression outside of the CNS on most recent EGFR inhibitor therapy.
7. Concomitant brain metastases and brain metastases previously treated with radiation therapy are allowed. (Subjects with symptoms or signs attributed to LM will be enrolled in Cohort B whether or not they have brain metastases.)

8. ECOG Score ≤2.
9. No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred.
10. Adequate organ and bone marrow functions as follows:
    a) Serum creatinine ≤ 1.5 mg/dL
    b) Total bilirubin ≤ 1.5 × ULN (except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN).
    c) ALT and AST ≤ 3× ULN
    d) WBC > 3000/mm^3
    e) Absolute neutrophil count ≥ 1500/mm^3
    f) Platelet count > 100,000/mm^3
    g) Hemoglobin > 8 g/dL
11. Serum potassium and magnesium levels above the LLN.
12. No coexisting medical problems of sufficient severity to limit compliance with the study.
13. Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study.
14. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression.
    a) Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
    b) Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c)

2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner

c) For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 14 above during the treatment period and for at least 3 months after the last dose of study drug

8.5 Exclusion Criteria – Cohort B

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

1. First day of dosing with tesevatinib is less than 2 weeks from the last treatment of cytotoxic chemotherapy, biological therapy, or immunotherapy, and less than 6 weeks for nitrosoureas and mitomycin C. Surgical procedures must have been performed at least 2 weeks prior to the start of study treatment. Subjects must have recovered from the reversible effects of prior lung cancer treatments, including surgery and radiation therapy (excluding alopecia).

2. First day of dosing with tesevatinib is less than 4 weeks from the last radiotherapy of the brain or spinal cord/cauda equina.

3. First day of dosing with tesevatinib is less than 2 weeks from treatment with another investigational agent.

4. Treatment with erlotinib must be discontinued at least 3 days prior to first dose of tesevatinib and treatment with afatinib or other tyrosine kinase inhibitor must be discontinued at least 3 days prior to first dose of tesevatinib.

5. Any concurrent therapy for LM other than the specified treatment in this study.

6. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).

7. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval.

8. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction.

9. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor.

10. Has an active infectious process.

11. Female subject who is pregnant or lactating.

12. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body.

13. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate.

14. GI condition that interferes with drug absorption.

15. Non-malignant neurological disease that would interfere with evaluation of symptoms or signs attributed to leptomeningeal disease.

16. Contraindications to lumbar puncture:

    a) International normalized ratio (INR) > 1.5

    b) Platelets < 50×10^9/L (Note that platelets are required to be $\geq 100 \times 10^9$/L at screening)

    c) Therapeutic anticoagulant treatment that can't be held for 24 hours. Low dose low molecular weight heparin given for deep vein thrombosis (DVT) prophylaxis is allowed.

    d) CNS lesions considered to be at risk for cerebral herniation, myelocompression, or conus/cauda compression

8.6 Inclusion Criteria – Cohort C

Subjects will be included if they meet the following criteria:

1. Age ≥ 18 years old.
2. NSCLC with EGFR mutation (either exon 19 deletion or L858R mutation or an EGFR mutation).
3. No prior systemic treatment for NSCLC. Treatment with systemic steroids is not considered systemic treatment for NSCLC.

4. No prior radiation therapy to the CNS (brain or spinal cord)
5. At least one measurable BM by RECIST 1.1 criteria (≥ 10mm in longest diameter) in a subject with asymptomatic or minimally symptomatic brain metastases who does not require immediate surgical or radiation therapy in the opinion of the treating investigator and in the opinion of a radiation therapy or neurosurgical consultant.
6. Subjects in Cohort C may have asymptomatic LM detected by MRI.
7. ECOG Score ≤2.
8. No history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma-in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been surgically treated and have not recurred.
9. Adequate organ and bone marrow functions as follows:
    a. Serum creatinine ≤ 1.5 mg/dL
    b. Total bilirubin ≤ 1.5 × ULN (except in patients diagnosed with Gilbert's disease where bilirubin must be ≤ 3 × ULN).
    c. ALT and AST ≤ 3× ULN
    d. WBC > 3000/mm^3
    e. Absolute neutrophil count ≥ 1500/mm^3
    f. Platelet count > 100,000/mm^3
    g. Hemoglobin > 8 g/dL
10. Serum potassium and magnesium levels above the LLN.
11. No coexisting medical problems of sufficient severity to limit compliance with the study.
12. Willing and able to sign written informed consent and be able to comply with the study protocol for the duration of the study.
13. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. 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, anti-estrogens, or ovarian suppression.

a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.

b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner

c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 13 above during the treatment period and for at least 3 months after the last dose of study drug

8.7 Exclusion Criteria – Cohort C

Subjects will be excluded if they meet any of the following criteria:

1. Surgical procedures that were performed less than 2 weeks prior to the start of study treatment.
2. Any concurrent therapy for BM other than the specified treatment in this study.
3. Taking any medication known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers (including anti-epileptic agents such as phenytoin). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
4. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval.
5. Has evidence of active heart disease such as myocardial infarction within the 3 months prior to study entry; symptomatic coronary insufficiency congestive heart failure; moderate or severe pulmonary dysfunction.
6. History of torsades de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 bpm), heart block (excluding first degree block, being PR interval only), or

congenital long QT syndrome. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor.

7. Has an active infectious process.
8. Female subject who is pregnant or lactating.
9. Known contraindication to MRI, such as cardiac pacemaker, shrapnel, or ocular foreign body.
10. Has marked prolongation of QTc(F) interval at screening or Cycle 1 Day 1 (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate.
11. GI condition that interferes with drug absorption.
12. Non-malignant neurological disease that would interfere with evaluation of symptoms or signs of brain metastases.

9 STUDY ASSESSMENTS AND PROCEDURES

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. Screening assessments should be performed within 28 days before the first dose of study drug is administered on Day 1. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria for each cohort.

Study Day 1 is defined as the date the subject takes the first dose of study drug, with subsequent study days numbered sequentially thereafter.

If significant changes from Cycle 1 Day 1 are noted during the course of the study, additional unscheduled clinic visits may be undertaken by the investigator, or requested by the sponsor, in order to determine both the relevance of the finding(s) and the duration of the event(s).

9.1 Procedures to be Performed

9.1.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures that are not standard of care procedures, are to be performed until the subject has signed and dated an IRB/IEC-approved ICF.

9.1.2 Demographics and Medical History

A complete medical history will be taken. Information to be documented includes demographic information, prior and ongoing medical illnesses and conditions, and surgical procedures (not related to the primary diagnosis).

9.1.3 Complete and Symptom-Directed Physical Examinations

On days in which a complete physical examination is required, the investigator should perform a thorough examination of all body systems (exception: genitourinary and reproductive should be symptom-directed). On days in which a limited physical examination is required, the investigator should inquire about signs/symptoms, general appearance, eyes, heart and pulses, lungs, abdomen (liver/spleen), kidneys, and neurological (symptom directed). Interval history should be recorded at all study visits.

9.1.4 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (Celsius/Fahrenheit).

Please note that blood pressure measurements are to be performed using appropriate technique (per guidelines of the American Heart Association). Specifically, subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized. Record cuff size, arm used, and subject's position (if not seated).

9.1.5 ECOG Performance Status

Subject's performance status will be assessed using the ECOG performance status tool (see Appendix B).

9.1.6 Hematology, Serum Chemistries, and Urinalysis

Samples for laboratory assessments (hematology, serum chemistries, and urinalysis) are to be collected. A central laboratory will perform hematology, serum chemistry, and urinalysis tests and results will be provided to the investigator. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Laboratory panels are defined as listed in Table 9-1. In addition to central laboratory testing, a local laboratory will perform serum chemistry tests on Day 15 of each cycle from Cycle 2 through Cycle 6 for additional safety data. The local laboratory will perform all the serum chemistry tests included in Table 9-1 with the exception of Cystatin C.

Table 9-1: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
• Red blood cell count • WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • mean corpuscular volume (MCV) • mean corpuscular hemoglobin (MCH) • mean corpuscular hemoglobin concentration (MCHC)	• albumin • amylase • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • creatine phosphokinase • phosphorous • potassium • random glucose • sodium • total & direct bilirubin • total protein • magnesium • cystatin C	• appearance • color • pH • specific gravity • ketones • leukocytes • protein • glucose • bilirubin • urobilinogen • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)

Other
• Fasting triglycerides[a]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; MCH = mean corpuscular hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume

[a] To be drawn in the event that amylase increases to > 1.5 × ULN.

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g. dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the AE electronic case report form (eCRF) page. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated lab values) must be reported as an SAE (see Section 15.3.11).

9.1.7 Pregnancy Test

Urine pregnancy tests are to be performed for females of childbearing potential. Positive urine tests are to be confirmed with serum pregnancy testing.

9.1.8 12-Lead Electrocardiogram (ECG)

Supine 12-Lead ECGs will be performed at screening; Days 1, 7 and 14 of Cycle 1; on Day 1 of Cycles 2 and Day 1 of each Cycle including at End of Study Drug Treatment visit. Assessment to

be performed at predose, and once within 4 – 8 hours postdose for Days 1, 7 and 14 of Cycle 1 ECGs are to be performed before any blood sample collection when possible.

ECGs are to be repeated three times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs).

During the study, all ECGs will be digitally analyzed by a validated ECG laboratory. This central vendor will place ECG machines at sites under contract with Kadmon. ECGs will be transmitted electronically to the central vendor for analysis. Reports, including clinical alerts resulting from the analysis of the ECGs, will be provided back to sites. Sites will be trained on the use of the ECG machines, and instructions for performing ECG assessments will be provided in the ECG manual.

The QT interval will be corrected using Fridericia's formula[1]:

$$QT_F = \frac{QT}{RR^{1/3}}$$

Refer to Appendix C for sample calculation.

Prior to enrollment, all subjects must demonstrate an average screening QTc(F) value of ≤ 470 msec by central digital analysis. Immediate clinical management of subjects will initially be based on results of machine-read ECGs at the sites. However, the central digital analysis will prevail as it becomes available. In addition, the central digital analysis will be used for any AE and SAE documentation.

An increase in QTc(F) interval (by central digital analysis) to a value > 60 msec above Cycle 1 Day 1 or to the level of ≥ 500 msec requires further monitoring. After collection of a PK blood sample and discussion with the medical monitor (if ≥ 500 msec) on appropriate management, the subject may be removed from the trial (see guidelines in Section 11.1.3.3).

Abnormalities in the ECG that lead to a change in subject management (e.g. requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF. If ECG

[1] Adapted from: Fridericia LS (1920). "The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease." *Acta Medica Scandinavica* (53): 469–486.

abnormalities meet criteria defining them as serious, they must be reported as SAE (see Section 15.3.11).

9.1.9 Bone Imaging

Bone scans are to be performed at Screening. Additional scans are to be performed as clinically indicated.

9.1.10 Lumbar Puncture (LP) – Cohort B Only

For subjects with LM, CSF will be collected via LP for PK analysis on Cycle 1 Day 14 and on Cycle 3 Day 1 at approximately 4–8 hours after administration of the tesevatinib dose that day.

NSCLC cells in the CSF will be evaluated by both standard cytology and by a central rare cell detection methodology at screening, on Day 14 of Cycle 1 and on Day 1 of Cycle 3. Samples will be evaluated for EGFR mutations (both the EGFR mutation or mutations known to be present in the tumor of a particular subject by prior investigation as well as for the T790M mutation and other EGFR mutations) as well as by immunochemistry for EGFR expression and phosphorylation.

9.1.11 Pharmacokinetics – Cohort B Only

For subjects with LM (Cohort B), PK samples will be drawn to evaluate tesevatinib pharmacokinetics. Plasma samples for tesevatinib PK analysis will be drawn predose of tesevatinib on Day 14 of Cycle 1; and predose of tesevatinib on Day 1 of Cycle 3. Plasma samples also will be drawn on Cycle 1 Day 14 and on Cycle 3 Day 1 at 4–8 hours after administration of the tesevatinib dose that day (at as close to the same time as the CSF PK sample is obtained as possible).

For all cohorts, additional samples for the preparation of plasma will be collected for tesevatinib analyses if the QTc(F) interval increases to the level of ≥ 500 msec (sample to be drawn as soon as possible after ECG performed).

9.1.12 Tesevatinib Administration

Tesevatinib will be administered at the dose of 300 mg once daily. Tesevatinib will be used in dosage strength of 100-mg, and 150-mg tablets. Patient diaries will be utilized to evaluate compliance. One cycle will be defined as 28 days of treatment.

Tesevatinib should be taken in the morning (unless there is a subject-specific rationale to take it regularly at a different time of day) and can be administered without regard to food intake.

9.1.13 Tumor Assessments

In addition to bone scan at screening, CT scans of the thorax and abdomen will be performed at screening, after Cycle 2, and then every two cycles thereafter until disease progression. Radiological disease assessments by brain MRI will be performed at screening, at Cycle 2 Day 1, at Cycle 3 Day 1, and after every two cycles until disease progression. Response for peripheral disease and for BM will be evaluated according to RECIST, Version 1.1. Response will be recorded separately for non-CNS disease, for BM, and for LM. All CT and MRI scans will be collected for central review. All clinical decisions during the study will be based on local site radiology assessments, which will also be used for the primary efficacy analysis.

For subjects in cohort B, symptoms or signs attributed to leptomeningeal metastases will be followed. Symptoms attributed to leptomeningeal metastases will be evaluated at screening, at Cycle 1 Day 1; at Cycle 1, Day 14; at Cycle 2 Day 1, at Cycle 3 Day 1, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression, as well as at the End of Drug Treatment visit.

9.1.14 Quality of Life Questionnaires

QOL will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires administered at screening, on Day 1 of Cycle 3, on Day 1 of odd-numbered cycles thereafter, and at the EOS visit. Samples of the questionnaires are located in Appendix G and Appendix H.

9.1.15 Study Diary

Subjects will be required to keep a study drug diary in which they will record the date and time that each dose of tesevatinib is taken as well as any missed doses. Diaries will be reviewed at each visit during the treatment periods.

9.1.16 Prior and Concomitant Medications

All concomitant medications will be recorded from the time the subject signs the informed consent form through 30 days after the last dose of study drug.

9.1.17 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form throughout their participation in the study, including a period of 30 days after the subject's last dose of study drug, unless a new treatment has been started. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to tesevatinib also should be reported to Kadmon.

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor.

9.2 Schedule of Visits

9.2.1 Screening Visit

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history including demographics
- Complete physical examination, including height and weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status
- Hematology, serum chemistry and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (repeat three times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection when possible)
- Tumor assessment (brain MRI, thoracic and abdominal CT/MRI)
- Bone scan (additional scans to be performed as clinically indicated)
- Plasma cell free DNA
- Leptomeningeal metastasis symptom assessment – (Cohort B only)
- CSF collection for Rare Cell Capture and Cell-Free DNA (Cohort B)
- QOL Questionnaires
- AE assessment
- Baseline concomitant medications

9.2.2 Cycle 1, Day 1

Results of clinical and laboratory evaluations, including ECGs, must be reviewed prior to dosing to confirm that the subject continues to meet eligibility criteria. At the Day 1 Visit, the following procedures and evaluations will be performed:

- Complete physical examination, including weight
- Vital sign measurements (predose and 1 and 4 hours postdose) (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status

- Leptomeningeal metastasis symptom assessment –(Cohort B only)
- Clinical laboratory tests (hematology and serum chemistry panel) (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
- Urinalysis (need not be repeated if screening visit occurred within 4 days prior to Day 1 visit)
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours post dose prior to any blood sample collection) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tesevatinib administration
- Concomitant medications
- AE assessment
- Dispense study drug diary
- Dispense study drug

9.2.3 Cycle 1, Day 7

At the Day 7 visit (± 3 days), the following evaluations will be performed:

- Limited physical examination
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- Hematology, serum chemistry and urinalysis
- Supine 12-Lead ECG (to be performed predose and 4-8 hours postdose); perform ECG before any blood sample collection) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tesevatinib administration
- Concomitant medications
- AE assessment

9.2.4 Cycle 1, Day 14

At the Day 14 visit (± 3 days), the following evaluations will be performed:

- Limited physical examination
- Vital sign measurements (predose and at 1 and 4 hours postdose) (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status;
- Leptomeningeal metastasis symptom assessment – Cohort B only
- Hematology, serum chemistry and urinalysis

- Supine 12-Lead ECG (to be performed predose and 4-8 hours postdose); perform ECG before any blood sample collection) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Plasma PK samples predose and 4-8 hours postdose (at approximately the same time the CSK PK sample is drawn) – Cohort B Only
- Tesevatinib administration
- CSF Sampling for PK and CSF Cytology and cell-free DNA at 4-8 hours postdose – Cohort B Only
- Concomitant medications
- AE assessment

9.2.5 Cycle 2, Day 1

At the Cycle 2, Day 1 visit (± 3 days), the following procedures and evaluations will be performed:

- Physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status
- Leptomeningeal metastasis symptom assessment – Cohort B only
- Hematology, serum chemistry and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (to be performed predose prior to any blood sample collection) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tumor assessment - brain MRI only
- Tesevatinib administration
- Concomitant medications
- AE assessment
- Perform drug accountability, review subject diary, and collect old and dispense new study drug

9.2.6 Cycle 3, Day 1

At the Day 1 visit of Cycle 3 (± 3 days), the following procedures and evaluations will be performed:

- Physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)

- ECOG Performance status
- Leptomeningeal metastasis symptom assessment – Cohort B only
- Hematology, serum chemistry and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (to be performed predose) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tumor assessment (brain MRI, thoracic and abdominal CT/MRI) to be obtained after every 2 cycles beginning on Day 1 of Cycle 3 (± 7 days) and odd numbered cycles thereafter
- Plasma PK samples predose and 4-8 hours postdose (at approximately the same time the CSK PK sample is drawn) – Cohort B Only
- Tesevatinib administration
- CSF Sampling for PK and CSF Cytology and cell-free DNA at 4-8 hours postdose – Cohort B Only
- QOL Questionnaires (to be obtained after every 2 cycles [beginning on Day 1 of Cycle 3])
- Concomitant medications
- AE assessment
- Perform drug accountability, review subject diary, and collect old and dispense new study drug

9.2.7 Cycle 4, Day 1

At the Day 1 visit of Cycle 4 (± 3 days), the following procedures and evaluations will be performed:

- Physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status
- Hematology, serum chemistry and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (to be performed predose) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tesevatinib administration
- Concomitant medications
- AE assessment

- Perform drug accountability, review subject diary, and collect old and dispense new study drug

9.2.8 Cycles 5+, Day 1

Subjects will return to the clinic on Day 1 of each subsequent cycle (every 28 ± 3 days) and the following procedures will be performed:

- Physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status
- Leptomeningeal metastasis symptom assessment – Cohort B only. (to be obtained every 2 cycles [beginning on Day 1 of Cycle 3])
- Hematology, serum chemistry, and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (to be performed predose) (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tumor assessment (brain MRI, thoracic and abdominal CT/MRI); (to be obtained every 2 cycles [beginning on Day 1 of Cycle 3])
- Tesevatinib administration
- QOL Questionnaires (to be obtained every 2 cycles [beginning on Day 1 of Cycle 3])
- Concomitant medications
- AE assessment
- Perform drug accountability, review subject diary, and collect old and dispense new study drug

9.2.9 Day 15 on Cycle 2 through Cycle 6

At the Day 15 visit of Cycles 2, 3, 4, 5, and 6 (± 3 days), the following procedure and evaluation will be performed:

- Serum chemistry (Cystatin C does not need to be tested)

9.2.10 End-of-Study Drug Treatment Visit

Subjects are to return to the study site within 3 days after the subject's last dose of study drug to complete all end-of-study drug treatment assessments as described below. This may occur at the visit at which disease progression is diagnosed.

- Complete physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status

- Leptomeningeal metastasis symptom assessment – Cohort B only.
- Hematology, serum chemistry, and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Supine 12-Lead ECG (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Tumor assessment (brain MRI, thoracic and abdominal CT/MRI) (only required if one hasn't been performed in the previous 8 weeks)
- Quality of Life Questionnaire
- Concomitant medications
- AE assessment
- Final return and accounting of study drug

9.2.11 30-Day Follow-Up

The 30-Day Follow-Up should occur 30 days (± 5 days) after the subjects' last dose of tesevatinib, but prior to starting new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug.

- Complete physical examination, including weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature)
- ECOG Performance status
- Hematology, serum chemistry, and urinalysis
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Concomitant medications
- AE assessment

9.2.12 Follow-Up Phone Contact

Beginning 8 weeks after the 30-Day Follow-Up Visit, subjects are to be contacted by telephone every 8 weeks to assess survival status and any subsequent anti-cancer treatment.

9.2.13 Unscheduled/AE Resolution Visits: To Occur as Needed

If additional visits are needed (e.g. for resolution of an AE), the following procedures and evaluations may be performed as needed:

- Complete physical examination, including weight;
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, temperature);
- ECOG Performance status

- Hematology, serum chemistry and urinalysis;
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing);
- Supine 12-Lead ECG (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs];
- Tesevatinib administration (if appropriate)
- AE assessment;
- Concomitant medications;
- Perform drug accountability, review subject diary, and collect old and dispense new study drug (if appropriate).

10 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, in the event that a subject is withdrawn from the study, every effort will be made by the investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason for termination must be clearly documented on the appropriate page of the eCRF. Study withdrawal should include the final assessments, as required by the protocol and every effort should be made to perform the study follow-up procedures (e.g. laboratory tests, physical examination including an evaluation of toxicity/AEs). Refer to Table 4-1 and Table 4-2.

A termination eCRF must be completed for all enrolled subjects.

10.1 Subject Withdrawal

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

10.1.1 Subject Treatment Discontinuation

- Progression of disease
- An AE requires permanent discontinuation of study drug
- Voluntary withdrawal by subject
- Noncompliance to protocol
- Subject lost to follow-up
- Termination of the study by sponsor
- Subject death
- Other

10.1.2 Subject Study Termination

- Voluntary withdrawal by subject
- Subject lost to follow-up
- Termination of the study by sponsor
- Subject death
- Other

In the event of premature discontinuation, every effort should be made to perform the end-of-study follow-up procedures. Refer to Table 4-1 and Table 4-2. If a subject dies, Kadmon will actively seek to know the date of death.

Subjects who are withdrawn from the study due to toxicity are to be followed until there is either:

- Resolution or stabilization to Cycle 1 Day 1 or Grade 1
- The subject is lost to follow-up
- The event is otherwise explained

If there is an ongoing toxicity associated with tesevatinib, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject who is lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. If a subject is unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that the subject make contact with the investigator.

Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the End-of-Study (Final) visit (see Section 9.2.9).

10.2 Study Discontinuation

Kadmon Corporation has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other studies evaluating the drug indicates a potential health hazard to subjects;
- Subject enrollment is unsatisfactory;
- Drug supply issues;
- Data recording is inaccurate or incomplete;
- Excessive subject self-withdrawal;
- Significant protocol deviations (e.g. violation of eligibility criteria, dosing errors, missing data for study endpoint analysis).

10.3 Replacements

Subjects discontinued from the trial will not be replaced.

11 STUDY DRUG

11.1 Tesevatinib (KD019)

Tesevatinib will be provided in 100-, and 150-mg tablets. Kadmon will provide each investigator with adequate supplies of tesevatinib. Study drug must be stored at controlled room temperature and inventoried according to applicable regulations.

Subjects will be provided with either a weekly or monthly supply of study drug and instructions for taking the study drug at home. After the initial 28-day cycle, study drug will be supplied on Day 1 of each subsequent cycle to those continuing on study. Unused drug must be returned to the study site at each visit for accounting and reconciliation.

Tesevatinib tablets are white to off-white round tablets that contain API in a lactose-based immediate release (IR) formulation. Tesevatinib tablets are packaged in high-density polyethylene (HDPE) bottles capped with childproof caps. The following information will be printed on the label for clinical lots of tesevatinib:

> Tesevatinib Tablets 100-mg – 32 count
> Lot Number: XXXXX.XXX Bottle #: XXXX
> Store at 20°C - 25°C (68°F - 77°F). Brief excursions permitted to 15°C to 30°C (59°F and 86°F)
> Caution: New Drug--Limited by Federal (or United States) Law to Investigational Use
>
> Tesevatinib Tablets 150-mg – 32 count
> Lot Number: XXXXX.XXX Bottle #: XXXX
> Store at 20°C - 25°C (68°F - 77°F). Brief excursions permitted to 15°C to 30°C (59°F and 86°F)
> Caution: New Drug--Limited by Federal (or United States) Law to Investigational Use

11.1.1 Tesevatinib Administration

Tesevatinib will be administered at the dose of 300 mg once daily. One cycle will be defined as 28 days of treatment.

Study drug may be taken with or without food at approximately the same time every morning (unless there is a patient-specific rationale to take it regularly at a different time of day). Subjects should drink a full glass of water (approximately 8 ounces [240 mL]) immediately after study drug administration. Grapefruit and similar (pomelo fruit, Seville oranges, etc.) products should be avoided for the duration of study treatment.

Subjects must be instructed not to make up missed doses unless the missed dose can be taken within 12 hours of the normal dosing time. Subjects should not re-take study drug doses in the event of vomiting.

Subjects will be treated with study drug until disease progression or unacceptable toxicity occurs. However, subjects with limited peripheral disease progression (oligoprogressive disease) may receive local ablative (radiation therapy or surgery) and then be continued on tesevatinib. Subjects who discontinue tesevatinib treatment will be followed for survival. (Both CNS and non-CNS disease progression are defined in Appendices A and B.)

All subjects also will be followed for a period of 30 days following their last dose of tesevatinib. Additionally, subjects will be contacted every 8 weeks to collect information on survival and other therapies.

11.1.2 Dose Modifications and Delays for Toxicity Related to Study Drug

Subjects who develop ≥ Grade 3 AE considered by the investigator to be related to study drug (with the exception of asymptomatic Grade 3 elevations of amylase or lipase, Grade 3 elevation of alkaline phosphatase in a subject known to have bone metastases, Grade 3 elevation of glucose in a subject receiving systemic corticosteroids, Grade 3 creatine phosphokinase [CPK] elevation in the absence of muscle symptoms, or Grade 3 sodium values ≥126 mmol/L in a subject with diarrhea) will have study treatment interrupted until all drug-related toxicities have resolved to ≤ Grade 1.

Tesevatinib will be withheld for any Grade 3 rash or diarrhea related toxicities. Once toxicities have resolved to ≤ Grade 1, the subject may resume study treatment at a reduced dose of 250 mg/day if the dose was 300 mg/day, or at a reduced dose of 200 mg/day if the dose was 250 mg/day. No more than two dose reductions are permitted. Subjects who require more than two dose reductions will have study drug discontinued and enter the Follow-up Period.

Subjects for whom toxicity persists beyond 28 days despite dose interruption may resume study treatment only with permission from the responsible medical monitor.

If study treatment is withheld, the subject should be instructed not to make up the withheld doses.

11.1.3 Tesevatinib: Warnings, Precautions, and Management

AEs that have been associated with tesevatinib include the following: diarrhea, skin rash, QTc(F) prolongation, elevated serum creatinine, elevated serum amylase and interstitial lung disease.

Unless otherwise specified, study drug may be withheld for up to 28 days at the discretion of the investigator.

11.1.3.1 Diarrhea

Diarrhea should be managed according to accepted practice (e.g. with loperamide). Subjects with severe diarrhea who are unresponsive to loperamide or other antidiarrheals or who become dehydrated may require interruption of study drug until resolution to ≤ Grade 1 in severity. If Grade 3 diarrhea occurs, the medical monitor should be consulted about study drug decreases or discontinuation. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, study drug should be discontinued, and appropriate measures should be taken to rehydrate the subject intensively via intravenous fluid administration. In addition, renal function and serum electrolytes, including potassium and magnesium, should be monitored in subjects at risk of dehydration.

11.1.3.2 Skin Rash

Skin rash should be managed according to locally accepted clinical recommendations. Study drug may be withheld up to 28 days for Grade 3 rash.

Suggestions for Rash Management (Lacouture 2011, Kiyohara 2013, www.psoriasis.org)

Papulopustular (acneiform) rash:

- Most common rash seen with EGFR inhibitors
- Typically seen in the first few weeks of treatment
- Usually peaks at Week 4–6
- Then will decrease in severity at Week 6–8
- Post-inflammatory skin changes can last for months, so prevention and reactive treatment are important

Suggestions for preventative treatment:

- Subject education prior to starting treatment on what to expect
- Gentle cleansing of skin using mild soap products
- Use of moisturizer twice daily making sure to include hands, feet and nails
- Avoid sun when possible and use of sunscreen SPF 30 or higher (preferably titanium dioxide or zinc oxide)
- Hypoallergenic makeup when possible

Suggestions for treatment once a rash appears (see Appendix F for steroid potency

chart):

- Ongoing use of treatments from 'preventative treatments' above
- Grade 1 (<10 % BSA involved, without pruritus or tenderness)
  - Topical steroids (refer to Appendix F for a steroid potency chart that categorizes brand- name topical steroid medications)
    - For face use medium potency
    - For body use strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
- Grade 2 (10%–30% BSA involved, ± pruritus/tenderness; limiting instrumental ADLs and causing psychosocial impact)
  - Topical steroids
    - For face use strong potency
    - For body use very strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
  - Systemic treatment
    - Doxycycline 100 mg BID (less renal toxic than minocycline, but can cause photosensitivity)
- Grade 3 (> 30% BSA involved, limiting ADLs)
  - Refer to dermatology
  - Topical steroids
    - All areas very strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
  - Systemic treatment
    - Doxycycline 100 mg BID
    - Oral steroids: prednisolone 10 mg once daily (QD) for 1 week or equivalent

Suggestions for once a rash reappears:

- Over the course of treatment rash may come and go
  - Hydrocortisone 1% cream with moisturizer and sunscreen twice daily, in combination with doxycycline 100mg bid
  - May need to follow guidelines above if rash worsens

If unacceptable rash recurs on reintroduction of tesevatinib at the same dose, then dose reduction of tesevatinib should be discussed with the medical monitor.

11.1.3.3 QT Interval Prolongation

Acquired long QT syndrome can lead to life-threatening ventricular arrhythmias, particularly torsades de pointes. Risk factors for occurrence of arrhythmia include hypokalemia, hypomagnesemia, bradycardia, and concurrent use of multiple medications that prolong the QTc(F) interval. In vivo observations of QTc(F) prolongation in association with use of tesevatinib have been observed, including Grade 3 QTc(F) prolongation. However, the lack of a clearly discernible pattern to such occurrence makes prediction of individual subject risk difficult. Therefore, the following are recommended:

- Tesevatinib should be administered to subjects who have normal serum potassium and serum magnesium levels;
- Tesevatinib should not be administered to subjects with pathologic bradycardia;
- Medications with potential for QTc(F) prolongation should not be used concurrently or started within 24 hours of tesevatinib administration.

Subjects should be carefully monitored for symptoms of arrhythmia (i.e., dyspnea, chest pain or tightness, palpitations, dizziness) and for episodes of syncope. An ECG should be obtained if these symptoms occur. In addition, serum potassium and magnesium must be maintained within the normal range[16] and may require additional monitoring or adjustment if subjects develop diarrhea.

11.1.3.4 Response to QTc(F) Interval Prolongation

The following guidelines should be used in the management of QTc(F) prolongation. Subjects will have ECGs performed at times designated by the protocol.

If the QTc(F) interval increases to an absolute value of $\geq$ 60 msec above Cycle 1 Day 1 (predose on Day 1) but < 500 msec and the subject is asymptomatic (does not have palpitations, dizziness, syncope, orthostatic hypotension, or a significant ventricular arrhythmia on ECG), the following actions should be taken:

- Re-check and confirm concomitant medications for any medications that may be contributing to QTc(F) prolongation. Consult medical monitor for discontinuation of any medication found;
- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated;
- Obtain blood sample (plasma) for PK analysis.

If the QTc(F) interval increases to an absolute value of ≥ 500 msec at any evaluation and if the subject is asymptomatic (does not have palpitations, dizziness, syncope, orthostatic hypotension, or a significant ventricular arrhythmia on ECG), then the following actions should be taken:

- Consult with medical monitor;
- Hold study drug;
- Re-check and confirm concomitant medications for any medications that may be contributing to QTc(F) prolongation. Consult medical monitor for discontinuation of any medication found;
- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated;
- Obtain blood sample (plasma) for PK analysis;
- Contact medical monitor to discuss appropriate management;
- **QTc(F)**: When QTc(F) is within 30 msec of Cycle 1 Day 1 or ≤ 470 msec (whichever is lower), then study drug may be restarted with one dose level reduction;
- Following dose reduction and resumption of study drug treatment, ECGs must be repeated weekly for 2 weeks, then on Day 1 of each cycle per protocol following restart of study drug;
- Study drug may be restarted at the pre-event dose level if QTc(F) values of ≥ 500 msec are not confirmed by the central lab and if there is no evidence of drug-related abnormal ECG findings. This may be done as soon as the data are confirmed.

If the QTc(F) interval increases to an absolute value of ≥ 500 msec at any evaluation, and if the subject is or has recently been symptomatic (has palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG), then the following actions should be taken:

- Consult with medical monitor;
- The subject should be hospitalized and undergo a thorough cardiology evaluation;
- Do not dose with study drug again;
- Obtain blood (plasma) for PK sample;
- Check electrolytes especially magnesium and potassium; correct abnormalities as clinically indicated;
- ECGs should be monitored until the QTc(F) returns to within 30 msec above the average Cycle 1 Day 1 value or ≤ 470 msec.

Study drug should be permanently discontinued if the cardiac/electrophysiology evaluation confirms that symptoms are the consequence of a drug-induced QTc(F) interval prolongation.

However, if the subject has objective tumor response, consideration will be given to continuing treatment with tesevatinib at a reduced dose after discussion with the medical monitor.

11.1.3.5 Elevated Serum Creatinine

Subjects with increases in serum creatinine to > 2 × ULN should be evaluated for non-renal causes of renal dysfunction, such as dehydration due to diarrhea. Cystatin C values should also be utilized to evaluate renal function. Management of subjects without clinically likely non-renal causes of renal dysfunction should be discussed with the medical monitor.

11.1.3.6 Elevated Serum Amylase

In the event of asymptomatic increase of serum amylase to > 1.5 × ULN, lipase, fasting triglycerides, and amylase isoenzymes should be drawn. Further management should be discussed with the medical monitor.

11.1.3.7 Interstitial Lung Disease

Dyspnea in subjects in the study should be evaluated with chest X-ray or CT of the chest to determine whether interstitial lung disease is present. Tesevatinib should be discontinued if interstitial lung disease is suspected, and further management discussed with the medical monitor.

11.2 Study Drug Accountability and Subject Treatment Compliance

Drug accountability and subject treatment compliance will be assessed using drug dispensing and return records. The principal investigator is responsible for ensuring adequate accountability of all used and unused study drug. While the principal investigator may delegate components of drug accountability tasks to documented designee(s) (e.g. pharmacist), the ultimate responsibility for drug control and accountability resides with the investigator. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and the maintenance of subject dispensing records and returned study product documentation. Dispensing records will document quantities received from Kadmon and quantities dispensed to subjects, including lot number, date dispensed, subject identification number, subject initials, and the initials of the person dispensing study drug. Reasons for deviation from the expected dispensing regimen also must be recorded.

At study initiation, the study monitor will evaluate and obtain a copy of each site's written standard operating procedure for study drug disposal/destruction in order to ensure that it complies with the requirements of Kadmon.

At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy any remaining unused study drug supplies, including empty containers, according to institutional procedures for destruction, reviewed and approved by Kadmon prior to material destruction. If the site cannot meet the requirements of Kadmon for disposal, arrangements will be made between the site and Kadmon or its representative, for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12 CONCOMITANT MEDICATION AND TREATMENT

If the subject must use a concomitant medication during the study, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded on the eCRF.

Subjects should avoid ingesting grapefruit, pomelo or Seville orange fruits (and juice) with tesevatinib or at any time during the study. Subjects should not take medications that are associated with a risk of QTc(F) interval prolongation and/or torsades de pointes. Additionally, subjects are not permitted to take concomitant medications that moderately or severely inhibit (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) or induce (e.g. phenytoin, carbamazepine, rifampicin, or phenobarbital) the CYP3A4 isozyme. Steroid medications are allowed.

Administration of acid-reducing medications should be avoided during the study as these agents may decrease exposure to tesevatinib. If acid-reducing agents are needed, H-2 antagonists or antacids will be recommended rather than proton pump inhibitors. Administration of acid-reducing agents such as H-2 antagonists or antacids, if required, should take place no less than 2 hours before or after dosing with tesevatinib.

Since tesevatinib is a potent inhibitor of MATE transporter proteins, increased levels of concomitant medications that are secreted by the kidney proximal tubule cells into the renal tubule by MATE transporter proteins may occur. Thus subjects taking cephalexin, cimetidine, dofetilide, fexofenadine, metformin, procainamide, and pyrimethamine should be monitored carefully.

Other prohibited treatments include the following:

- Other investigational drugs;
- Concurrent anti-tumor therapies such as chemotherapy, gene therapy, biologics, radiation therapy, or other immunotherapy;
- Medications known to moderately or severely inhibit the CYP3A4 isozyme or any drugs that are moderate or severe CYP3A4 inducers. A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine) ;

- Drugs associated with torsades de pointes or known to prolong the QTc interval, including anti-arrhythmic medications within 2 weeks prior to Day 1 of treatment on study.

Antiemetics and antidiarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, treatment of symptoms with antiemetic and antidiarrheal medications may be undertaken per standard clinical practice.

12.1 Additional Therapy

A subject should not receive additional therapeutics treatment during the study period without the approval of the sponsor's medical monitor.

12.2 Additional Anti-Cancer Treatment and Radiotherapy

Subjects should not receive additional therapeutic anti-cancer treatment until after progressive disease (PD) has been documented on study and End of Treatment study assessments have been completed. If a subject requires additional anti-cancer treatment, study treatment will be discontinued and the subject will enter the Post-Treatment Period and followed every 8 weeks by phone call. However, subjects with limited peripheral disease progression (oligoprogressive disease) may receive local ablative treatment (radiation therapy or surgery) and then be continued on tesevatinib. Any such patients will be considered to have disease progression at the time of detection of oligoprogressive disease.

12.3 Interaction of Tesevatinib with Other Medications

Microsomal oxidation of tesevatinib involves CYP3A4; the percentage conversion of tesevatinib in human microsomes was low. This suggests a low potential for other drugs to significantly affect the biotransformation of tesevatinib in humans through interaction with CYP3A4-mediated metabolic pathways.

In vitro studies have indicated that tesevatinib has a moderate potential to inhibit the CYP2C8 family of liver enzymes. This inhibition, should it occur clinically, could increase exposure to other drugs that are substrates for this pathway. However, the inhibition of CYP2C8, CYP2C9 and CYP2C9*2 in enzyme assays required tesevatinib levels of 7–9 μM. These levels are well above plasma concentrations achievable in vivo at the doses proposed in this study.

Although not expected to be an issue, inhibitors, inducers, and substrates of CYP2C8, CYP2D6, and CYP1A2 should be avoided in all subjects while receiving study drug. These medications should be used with caution and discussed with the medical monitor prior to use. In addition, subjects must be closely monitored for the desired drug effect and potential AE.

See Appendix D for a list of drugs that are substrates, inhibitors, and inducers of CYP3A4, CYP2C8, CYP2D6, and CYP1A2.

12.3.1 Management of Subjects Requiring Concomitant Medications Associated with QT Interval Prolongation

Tesevatinib has been associated with prolongation of the QT interval. Subjects requiring treatment with drugs known to be associated with torsades de pointes or significant QT interval prolongation may not be enrolled into this study. This includes Class IA antiarrhythmics (e.g. quinidine, procainamide); Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide); phenothiazine anti-psychotics: (e.g. chlorpromazine, mesoridazine, pimozide, thioridazine); quinolone antibiotics: (e.g. gatifloxacin, moxifloxacin, sparfloxacin); macrolide antibiotics (e.g. erythromycin, clarithromycin, and troleandomycin) and other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information.

Appendix E, Concomitant Medications Associated With a Risk of QTc(F) Interval Prolongation and/or Torsades de Pointes, contains a partial list of drugs associated with a risk of QT interval prolongation and/or torsades de pointes.

Drugs associated with QT interval prolongation should be avoided in subjects receiving study drug unless deemed clinically necessary. Should a subject develop a condition for which a medication known to affect QT interval is indicated, consideration should be given to the additive risk of QT interval prolongation versus the potential benefit of treatment with the required medication and/or study drug. Contact the medical monitor prior to the administration of the concomitant medication.

During long-term follow-up, subjects who require short-term (2 to 3 weeks, not to exceed 21 days) treatment with a concomitant medication associated with QT interval prolongation while receiving study drug should have the study drug withheld until the concomitant treatment course is complete. The decision about whether the subject can continue on trial following this interruption will be determined by the medical monitor.

During long-term follow-up, subjects who require chronic treatment with a concomitant medication associated with QT interval prolongation while receiving study drug should be monitored as follows:

- Three ECGs should be obtained prior to start of the concomitant medication. These ECGs should be obtained within a total span of 30 minutes with an interval of approximately 1–2 minutes between recordings;

- If the average QTc(F) interval from these 3 ECGs is > 60 msec above the average Cycle 1 Day 1 (Day 1 predose) value or is ≥ 500 msec, study drug may be discontinued or dose reduced after discussion with the medical monitor;
- If both of the above criteria are not met (i.e., the average QTc[F] interval is no more than 60 msec above Cycle 1 Day 1 and is < 500 msec), ECGs should be obtained daily for the first 3 days of treatment with the concomitant medication;
- Additionally, an ECG should be obtained weekly for 2 weeks, then every 2 weeks for 1 month and monthly thereafter until the concomitant medication is no longer required or study drug is discontinued.

QTc(F) interval prolongation should be managed as noted in Section 11.1.3.3.

13 PHARMACOKINETICS AND PHARMACODYNAMICS

13.1 Plasma and CSF Pharmacokinetics

For subjects with LM (Cohort B), PK samples will be drawn to evaluate tesevatinib pharmacokinetics. A plasma sample for tesevatinib PK analysis will be obtained at predose of tesevatinib on Cycle 1 Day 14 and at predose of tesevatinib on Cycle 3 Day 1. A plasma sample also will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within 4–8 hours after tesevatinib administration of the tesevatinib dose that day (i.e., at approximately the same time as the CSF PK sample is obtained).

For subjects with LM (Cohort B), CSF PK samples will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within approximately 4–8 hours after tesevatinib administration of the tesevatinib dose that day.

For all cohorts, additional samples for the preparation of plasma will be collected for tesevatinib analyses if the QTc(F) interval increases to the level of ≥ 500 msec (sample to be drawn as soon as possible after ECG performed).

13.2 CSF Pharmacodynamics

For subjects with LM (Cohort B), NSCLC cells in the CSF will be evaluated by both standard cytology and by a central rare cell detection methodology at Screening, on Day 14 of Cycle 1, and on Day 1 of Cycle 3. Samples will be evaluated for EGFR mutations (both the EGFR mutation or mutations known to be present in the tumor of a particular subject by prior investigation as well as for the T790M mutation and other EGFR mutations) and for EGFR copy number.

14 EFFICACY

In addition to bone scan at screening, CT scans of the thorax and abdomen will be performed at screening, after Cycle 2, and then every two cycles thereafter until disease progression. Radiological disease assessments by brain MRI will be performed at screening, at C2D1, at C3D1, and then every two cycles until disease progression. Response for peripheral disease and for BM will be evaluated according to RECIST, Version 1.1. Response will be recorded separately for non-CNS disease, for BM, and for LM. All CT and MRI scans will be collected for central review. All clinical decisions during the study will be based on local site radiology assessments, which will also be used for the primary efficacy analysis.

For subjects with BM (Cohort A and Cohort C) efficacy will be evaluated by RECIST 1.1 criteria separately for non-CNS tumor lesions and for BMs at Screening, at Cycle 2 Day 1 (for BM), at Cycle 3, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression.

For subjects with LM (Cohort B), symptoms attributed to leptomeningeal disease will be evaluated at screening, Cycle 1 Day 1, at Cycle 1 Day 14, at Cycle 2 Day 1, at Cycle 3, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression.

The response efficacy endpoints will be evaluated separately for peripheral disease, for BM, and for LM, and a summary response will also be derived (See Table 14-1). For LM, if positive CSF cytology and MRI diagnostic findings were both present at screening, complete response (CR) requires the absence of LM by both modalities. For LM, CR also requires the complete resolution of symptoms and signs attributed to LM. Best overall response, duration of response, and duration of stable disease will be reported, based on the examples in Table 14-1. The median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS time to progression, CNS TTP, and median OS also will be assessed.

Subjects with limited CNS or extra-CNS disease progression (oligoprogressive disease) may receive local ablative therapy (radiation therapy or surgery) and then be continued on tesevatinib. This practice is consistent with data indicating that some patients with NSCLC on TKI therapy who have oligoprogressive disease appear to have significant periods of additional disease control with this approach.[19] Any such patients will be considered to have disease progression for analyses of PFS and for analyses of progression in the relevant (CNS or extra-CNS) compartment at the time of detection of oligoprogressive disease.

Subjects with scans that are on the "borderline" of disease progression (e.g. 21% increase in sum of target lesion diameters or equivocal findings on CSF cytology or MRI) but for whom the investigator determines a clinical benefit may occur in the study. These subjects will be allowed to continue in the study after discussion with the medical monitor. If improvement is documented at the next subsequent staging time point (e.g. 17% increase in sum of target lesion diameters or stable CNS symptoms), the subject will continue on study. If worsening is documented (e.g. 30% increase in sum of target lesion diameters or worsening of CNS symptoms), the subject should be discontinued from the study, and the progression date should be the original date on which "borderline" disease progression was first documented. If stable, then they will be followed until improvement or worsening occurs.

Table 14-1: Summary Response Examples

Peripheral Tumor[1]		Brain Metastases[1]		Leptomeningeal Metastases	Summary Response[3]
Measurable	Non-measurable	Measurable	Non-Measurable		
CR	CR	CR[2]	CR[2]	CR[2]	CR, peripheral, BM and LM
Non-CR, non-PD	Non-CR, non-PD	PR[2]	None	Non-CR, non-PD	PR, BM only
Non-CR, non-PD	Non-CR, non-PD	CR[2]	CR[2]	Non-CR, non-PD	CR, BM only
Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	CR[2]	CR, LM only
Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	None	CR, LM only
Non-CR, non-PD	Non-CR, non-PD	CR[2]	None	CR[2]	CR, BM and LM only
Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	Non-CR, non-PD	SD

BM = bone metastases; CR = complete response; LM = leptomeningeal metastases; PD = progressive disease; PR = progressive response; SD = stable disease

1 Using RECIST 1.1 criteria
2 Diagnosis of BM CR or PR, or LM CR, requires that steroids be at or lower than dose of steroids at Cycle 1 Day 1 (if subject is receiving steroids)
3 All summary response examples assume that no new lesions are present. A new peripheral tumor or brain metastasis, or symptom progression of LM will lead to a summary response of PD in that category.

14.1 Cohort A and Cohort C– Brain Metastases

For subjects with BM (Cohorts A and C) efficacy will be evaluated by RECIST 1.1 criteria separately for non-CNS tumor lesions and for BMs at screening, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression.

14.2 Cohort B – Leptomeningeal Metastases

For subjects with LM, symptoms attributed to leptomeningeal metastases will be evaluated at screening, Cycle 1 Day 1, Cycle 1 Day 14, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression, as well as at the End of Drug Treatment visit. CTCAE v4.03 (www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf) will be utilized for the evaluation of symptoms and signs attributed to leptomeningeal metastases. Symptom improvement is defined as a decrease in 1 grade in at least one CTCAE v4.03 symptom or sign attributed to leptomeningeal metastases without worsening of other neurologic symptoms or signs attributed to leptomeningeal metastases. Symptom progression is defined as an increase of 1 grade in at least one CTCAE v4.03 symptom attributed to leptomeningeal metastases or the appearance of new symptoms or signs of LM. Symptoms or signs attributed to leptomeningeal metastases will be followed as one component of the efficacy evaluation for Cohort B.

For subjects with LM, NSCLC cells in the CSF will be evaluated during the study (screening, Day 14 of Cycle 1, and on Day 1 of Cycle 3) for malignant cells both by standard cytological analysis and by a rare cell detection methodology. CSF obtained at the same time points will be evaluated for protein and glucose levels. Response will be based on standard cytological analysis if cytology was positive at screening. Response categories will be CR (no malignant cells, which must be present on 2 consecutive CSF evaluations to support response of CR), and non-PR, non-PD (continued presence of malignant cells). PD will not be defined by CSF cytology.

For subjects with LM (Cohort B), CSF for isolation of cell-free DNA will be collected at screening, Day 14 of Cycle 1, and Day 1 of Cycle 3. Evaluation for EGFR mutations will be performed. Quantitation of EGFR mutations in cell-free DNA will be utilized for an exploratory efficacy analysis.

LM will also be evaluated by serial MRI of the brain. For patients with positive findings of LM on MRI at screening, response categories will be CR (no evidence of LM on MRI), or non-PR, non-PD (continued presence of evidence of LM on MRI). PD for LM will not be defined by MRI.

15 SAFETY

15.1 Safety Parameters

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03 - www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf) will be used for grading toxicities unless otherwise specified. Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include vital sign measurements, physical examinations, concomitant medications, hematology, serum chemistries, urinalysis, pregnancy testing, ECGs, and ECOG performance status.

15.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs include:

- Suspected adverse drug reactions (abbreviated as either SADR or SAR). This may be serious or not serious;
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity;
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, ECG results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug;
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptoms, or apparently unrelated illnesses.

Findings existing prior to signing informed consent will be recorded as medical history. For the purpose of data collection, all untoward events that occur after informed consent through 30 days after last dose of study treatment are to be recorded on eCRFs by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

An AE does not include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); when the condition that leads to the procedure is an AE;
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, those do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social, and/or convenience admissions);
- Overdose of either tesevatinib or a concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation.

15.3 Evaluating Adverse Events

The investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

15.3.1 Serious Adverse Events

(Notify sponsor or designee within 24 hours of first awareness)

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2A, with Title 21 Part CFR 312.32, and the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies.

SAE: An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death:** This includes any death that occurs while the subject is “on study” as well as any death that occurs within 30 days after last dose of study drug administration.

  Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (e.g. illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- **Life-threatening adverse event:** An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death).
- **Inpatient hospitalization or prolongation of existing hospitalization:**

In the absence of an AE, the investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol;
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center;
- Hospitalization for survey visits or annual physicals.

In addition, a hospitalization planned before the start of the study for a pre-existing condition which has not worsened does not count as an SAE.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/birth defect;
- Important medical event: An event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Some serious events will not be reported as SAEs, including:

- Disease progression;
- Death due to disease progression occurring more than 30 days after the last dose of study drugs;
- Medical or surgical procedures when the condition that leads to the procedure is an AE;
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen;
- Situations for which an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).

15.3.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

(Notify sponsor or designee within 24 hours of first awareness)

A suspected unexpected serious adverse reaction is any adverse drug event, the specificity or severity of which is not consistent with those noted in the current protocol and/or Investigator's Brochure (IB). This refers to any AE that has not been previously observed (e.g. included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product.

15.3.3 Unexpected Adverse Events

An AE is considered "unexpected" if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application. Also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

15.3.4 Non-Serious Adverse Events

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

15.3.5 Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the investigator or the medical monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

15.3.6 Relationship/Causality to Study Drug

The investigator will attempt to assess the relationship of the event to study drug using a 5- point scale (not related, unlikely-related, possibly related, probably related, or definitely related).

15.3.7 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF. The date of onset as well as the duration of the event also should be recorded. In addition, the method used to treat the AE and the outcome of the AE also will be noted. The investigator will assess the relationship of the event to study drug (not related, unlikely-related, possibly related, probably related, or definitely related).

15.3.8 Adverse Event Monitoring and Follow-Up

The investigator will follow all subjects who experience AEs until there is a return to the subject's baseline condition, Grade 1 severity or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

15.3.9 Laboratory and ECG Abnormalities

For the purposes of grading creatinine, the ULN – not the subject's Cycle 1 Day 1 value - will be used to determine grade.

For the purpose of grading sodium, values of 126–130 mmol/L will be considered to be Grade 2 and values of 120–125 mmol/L will be considered Grade 3.

For the purposes of this study, ECG abnormalities will be handled in the same manner as laboratory abnormalities.

Non-Clinically Significant (NCS) Laboratory Abnormalities

All laboratory results must be filed in the subject's medical record and be monitored. The investigator must review laboratory results in a timely manner demonstrated by signature/date and assignment of clinical significance assessment. Non-clinically-significant laboratory abnormalities, i.e., minor deviations from the normal range, are expected and it is likely that no medical intervention will be required. Such results will not be considered to be AEs.

Clinically Significant (CS) Laboratory Abnormalities

Any laboratory abnormality that is considered to be clinically significant by the investigator will be recorded on the AE eCRF. A clinically significant abnormal test result will be considered an AE if:

- It is not associated with an already reported AE, diagnosis or pre-existing condition;
- There is a change in concomitant medication or intervention as needed, in direct response to the laboratory result;
- The investigator exercises his/her discretion to make significance determinations for any subject laboratory result or result that requires intervention.

All such lab abnormalities will be repeated and assessed by the investigator, or licensed (MD), as soon as possible for "seriousness" and if they meet the regulatory definition of "serious", they will be reported as SAEs following regulatory and protocol requirements. Repeat laboratory tests may be run in order to monitor the result.

Serious Laboratory Abnormalities

Any lab abnormality meeting the regulatory definition of "serious" must be recorded on both the AE eCRF/record and the SAE Form. If a subject experiences a serious toxicity or dies, the FDA will be notified within 24 hours, as required.

15.3.10 Pregnancy

If any subject becomes pregnant following the first dose of tesevatinib, the subject will be taken off study and followed regularly until birth or termination of the pregnancy. The pregnancy must be immediately reported to the sponsor. Forms for reporting pregnancies will be provided to the study sites upon request. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report. The outcome of a pregnancy must be reported to the medical monitor as soon as it is known. If the pregnancy ends for any reason before the anticipated date initially reported, the investigator must notify the Kadmon medical monitor as soon as possible.

If the outcome of the pregnancy meets any criterion for classification as a SAE (including stillbirth, neonatal death, spontaneous abortion, or congenital anomaly – including that in an aborted fetus) the investigator must follow the procedures for reporting SAEs. Any neonatal death occurring ≤ 30 days after birth will be reported as a SAE.

15.3.11 Serious Adverse Event Reporting

15.3.11.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the USFDA as well as all other participating investigators of the event.

Under FDA ruling (US CFR, Title 21 CFR Part 312.32) and the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies, the sponsor is required to submit written documentation, in the form of an IND safety report, detailing:

Any event associated with the use of the drug, that is both serious and unexpected, or

Any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor shall also inform all investigators.

15.3.11.2 Time-Frame for Reporting

Any death, pregnancy, or SAE experienced by a subject from the time of informed consent until 30 days after receiving the last dose of study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the investigator becoming aware of the event) by fax to the sponsor (or designee). Fax: 1-646-430-9549.

In the event of an issue with the fax line, forward the SAE form via email to ClinicalSAEReporting@kadmon.com.

The investigator will be able to contact the safety medical monitor at all times:

Sanjay Aggarwal, MD
Vice President Clinical Development, Medical Monitor
Kadmon Corporation
55 Cambridge Parkway
Cambridge, MA 02142
Mobile Phone: 857-253-8642
E-mail: Sanjay.aggarwal@kadmon.com

15.3.11.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE eCRF page. This requirement includes all SAEs that occur after informed consent and through 30 days after last dose of study treatment, and in addition, any SAE that are assessed as possibly related to study treatment by the investigator, even if the SAE occurs more than 30 days after the last dose of study treatment.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (i.e., the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment (not related, unlikely-related, possibly related, probably related, or definitely related). Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Kadmon Drug Safety personnel or designee.

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

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion. There is no requirement that the chosen SAE term be listed in the NCI-CTCAE Version 4.03;

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided;
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgery, e.g. a previously scheduled ventral hernia repair;
    - Procedures for pre-existing conditions that have not worsened after initiation of treatment;
    - Pre-specified study hospitalizations for observation;
    - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g. 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.

15.3.12 Regulatory Reporting

Kadmon Drug Safety (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Kadmon will make a determination as to whether the criteria for expedited reporting have been met.

Kadmon (or designee) will submit SAEs that meet the criteria for expedited reporting to the Regulatory Authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

15.3.13 Follow-up Information on a Serious Adverse Event

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the investigator.

Follow-up data concerning the SAE (e.g. diagnostic test reports, physician's summaries, etc.) also must be submitted to Kadmon, as they become available, by telefax or email transmission, until resolution of the SAE.

15.4 Other Safety Considerations

15.4.1 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the medical monitor. An overdose of tesevatinib without any associated signs or symptoms, unless the subject is hospitalized for observation, will not constitute an AE but will be recorded as a protocol deviation.

15.4.2 Follow-Up of Serious Adverse Events

Any SAE that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until either resolution of the event or determination by the investigator that the event has returned to baseline/resolved, Grade 1 or has become stable. This follow-up guidance also applies to SAEs that occur *more than 30 days after last dose* of study treatment.

16 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, the mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. The summary of time-to-event variables will include Kaplan-Meier methods as appropriate.

Statistical significance will be declared when the two-tailed p-value is found to be less than or equal to 0.05, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings.

Additional statistical details will be provided in a prospective statistical plan.

16.1 General Design

This is a multicenter, open-label Phase 2 study to assess the activity of tesevatinib in subjects with NSCLC and activating EGFR mutations and BM or LM.

16.2 Sample Size Justification

For Cohort A, assuming that 20% of subjects with BM have RECIST 1.1 response (CR or PR), the study has an approximately 80% chance of having at least 3 subjects with RECIST 1.1 response, and an over 90% chance of at least 2 subjects having a response. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments.

For Cohort B, assuming that 20% of subjects with LM have improvement in at least one symptom or sign attributed to leptomeningeal metastases, the study has an approximately 80% chance of having at least 3 subjects with improvement in at least one symptom or sign attributed to leptomeningeal metastases and an over 90% chance of at least 2 subjects having improvement attributed to leptomeningeal metastases. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments.

For Cohort C, assuming that 20% of subjects with BM have RECIST 1.1 response (CR or PR), the study has an approximately 80% chance of having at least 3 subjects with RECIST 1.1 response, and an over 90% chance of at least 2 subjects having a response. All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments.

16.3 Statistical Considerations

16.3.1 Study Populations

Adult subjects with NSCLC who have progressed with BM or LM, or who have brain metastases at initial presentation, will be enrolled.

All subjects who take at least one dose of study drug will be evaluable for safety and efficacy assessments.

Subjects who do not complete the study, for whatever reason, will have all available data (up until the time of termination related to the reason they were terminated) included in the analysis. Completion of the study will be defined as completion of the first cycle of study drug administration, or discontinuation prior to that time for an AE.

The PK population will consist of all subjects who receive at least one dose of tesevatinib, and who have at least one sample for PK for a dosing interval.

16.3.2 Subject Accountability, Demographics, and Cycle 1 Day 1 Characteristics

Subject disposition, demographic information and Cycle 1 Day 1 characteristics will be tabulated by dose cohort and overall for tesevatinib. Any discrepancy between treatment assigned and treatment received will be accounted for in these displays. Data for screen failures, pertaining to why they failed to qualify to enroll will also be collected.

16.3.3 Tesevatinib Exposure

The amount of tesevatinib administered by visit and overall (total dose) will be tabulated and presented by subject in data listings for all cohorts. The distribution of the number of cycles achieved per subject will also be summarized. In addition, delays and all other alterations in tesevatinib administration will be presented.

16.3.4 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2014, Type B2 or later) and the data will be summarized by dose cohort and presented in tables and listings.

16.3.5 Pharmacokinetics

In Cohort B only, plasma samples will be obtained at predose on Day 14 of Cycle 1; and at predose on Day 1 of Cycle 3. A plasma sample will also be obtained on Cycle 1 Day 14, and Day 1 of Cycle 3 within the 4-8 hours after tesevatinib administration.

In all cohorts, additional samples for the preparation of plasma will be collected for tesevatinib analyses if the QTc(F) interval increases by > 60 msec above average Cycle 1 Day 1 (predose on Day 1) or to the level of ≥ 500 msec.

Plasma concentrations of tesevatinib will be summarized by dose, sample collection day, and sample collection time for each drug using descriptive statistics.

For subjects in Cohort B, CSF PK samples will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within approximately 4–8 hours after tesevatinib administration of the tesevatinib dose that day. Tesevatinib concentrations in the plasma and CSF will be summarized at each scheduled collection time point using descriptive statistics, and displayed graphically. These data alone, or pooled with data from other studies, may be analyzed in a population PK analysis using nonlinear mixed effects modeling.

16.3.6 Efficacy/Activity

Descriptive statistics, including 95% confidence intervals for improvement in symptoms attributed to leptomeningeal metastases, clearing of NSCLC cells in the CSF, and clearing of CNS MRI findings will be presented. Exploratory evaluation of efficacy results by EGFR mutation will be performed.

Efficacy/Activity analyses will present results by Cohort and, where appropriate, the three cohorts combined.

In addition, identical statistics for the change and percent change from Cycle 1 Day 1 tumor measurements will be presented. These analyses will be done after each two cycles of therapy, and will include peripheral (non-CNS) tumors as well as brain metastases. Summary statistics will be produced for PFS and OS. The percentage of subjects without disease progression after 3 and 6 months of dosing will also be presented separately by local and central radiograph results.

16.3.7 Safety Data

Safety analyses will be performed on all subjects who received any quantity of study drug. AEs that are not related to treatment and that occur more than 30 days after the administration of the last dose of treatment will not be reported or analyzed.

Safety analyses will present results by Cohort and, where appropriate, the three cohorts combined.

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, physical examinations, pregnancy status, ECG assessments, and pharmacokinetic data.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 18.1 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, according to the most severe grade using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; Version 4.03). The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, related AEs, related SAEs, ≥ Grade 3 AEs, related ≥ Grade 3 AEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by cohort and tesevatinib overall according to SOC and preferred terms. AEs will also be summarized in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE Version 4.03 and summarized by cohort. Laboratory results not corresponding to a coded term will not be graded. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of ≥ Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from Cycle 1 Day 1 to highest grade post-Cycle 1 Day 1 will be displayed. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. ECOG performance status results will be summarized by scheduled time point. Additional statistical details will be provided in a prospective statistical plan.

Digital ECG results and wave intervals measurements will be summarized and reported by subject visit and dose cohort and/or as appropriate. QTc(F) prolongation results will be summarized separately. Covariate analyses will be employed as necessary (e.g. QTc[F] interval vs. plasma drug concentration).

17 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the course of the study, a study monitor (CRA) will make site visits to review protocol compliance, compare eCRFs against individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each investigator will have assured Kadmon of full access to complete source data for study participants and associated necessary support at all times.

In addition to routine monitoring procedures, audits of clinical research activities in accordance with SOPs may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the investigator must immediately inform Kadmon that this request has been made.

Study conduct may be assessed during the course of the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the CRA, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. In the course of the clinical study, access will be available to Kadmon or designee (e.g. CRO) to view the eCRFs after completion of the individual sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

18 ETHICAL ASPECTS

18.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

18.2 Informed Consent

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the International Conference on Harmonization (ICH) guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary. Sample ICFs will be supplied to each site. Kadmon or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Kadmon for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) 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' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. The site will retain the original signed/dated consent form and any associated HIPAA authorization for all consented subject candidates.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. 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 written consent to continue in the study.

18.3 Institutional Review Board

This study is being conducted in compliance with the protocol, the ICH GCP Guidelines, and the applicable regulatory requirements under a United States IND application. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The investigator will send a letter or certificate of IRB approval to Kadmon (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

18.4 Future Use of Subject Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 5 years. This may include pharmacogenomics profiling analyzing CYP enzyme polymorphisms. This will be of particular interest given the use of tesevatinib in a new patient population who may experience toxicity not previously seen in earlier oncology studies, and may help identify those at risk for toxicity at various doses. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 25 2006) and the EMEA Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Kadmon will destroy the samples as described in this FDA guidance. Kadmon will notify the investigator in writing that the samples have been destroyed.

19 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Kadmon representative and the investigator. Protocol modifications will be prepared, reviewed, and approved by Kadmon representatives.

All protocol modifications must be submitted to the IRB 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 when the change involves only logistical or administrative aspects of the trial (e.g. change in monitor, change of telephone number) or to eliminate an immediate hazard to study subjects. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform Kadmon, and the full IRB within 5 business days after the emergency occurs.

20 CONDITIONS FOR TERMINATING THE STUDY

Kadmon has the right to terminate the study at any time. In terminating the study, Kadmon and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

The following data and materials are required by Kadmon before a study can be considered to be complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study, including the follow-up period for all enrolled subjects;
- Case Report Forms/Records. Electronic case report forms (eCRFs) will be used in this study. Records (including correction forms) for all enrolled subjects will be properly completed by appropriate study personnel, and signed and dated by the principal investigator, as required;
- Principal investigator sign-off of all required eCRF forms;
- Completed Drug Accountability Records, Drug Inventory Log, and Inventory of Returned Drug forms or documentation of destruction, as appropriate;
- Return of all unused study drug to Kadmon unless an alternate disposition method is agreed upon at study initiation by Kadmon and investigational site(s);
- Copies of protocol amendments and other documents, and IRB approval/notification, as applicable;
- A summary of the study prepared by the principal investigator (IRB summary closure letter is an acceptable equivalent).

21 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

21.1 Investigator's Files and Retention of Documents

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

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

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, email communication and subject screening and enrollment logs. The investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA is notified. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from Kadmon. If the investigator wants to assign the study records to another party or move them to another location, Kadmon 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 Kadmon 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.

21.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on:

- Medical history;
- Date and time of informed consent with HIPAA authorization either contained in the ICF or presented to the subject candidate as a standalone document;
- Description of the complete consenting process;
- The basic identifying information that linked the subject's medical record with the eCRFs;
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject;
- The medical condition of the subject during their involvement in the study;
- All AEs;
- The subject's exposure to the study medication;
- The subject's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the subject throughout the trial;
- Justification for all entries in the subject's eCRF;
- Radiology images (hard copy and digital), and reports if required;
- Death information and any available autopsy data.

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the investigator will supply Kadmon with any required background data from the study documentation or clinic records. 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.

21.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Kadmon Quality Assurance Unit (or

designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

21.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on electronic case report forms (eCRF) designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made according to 21 CFR Part 11, Electronic Records; Electronic Signatures. There will also be an electronic audit trail. The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to Kadmon in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated by the principal investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

22 MONITORING THE STUDY

All aspects of the study will be carefully monitored by Kadmon or authorized representatives according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations.

It is understood that the responsible Kadmon study monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements. The principal investigator and key trial personnel must be available to assist the monitor during these visits. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

It will be the monitor's responsibility to inspect the eCRFs in comparison to source documents at regular intervals throughout the study according to the monitoring plan, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them and clarifying any data queries. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The completed and corrected eCRFs/CRFs for completed visits will either be collected by the monitor at the end of the study or obtained electronically for data processing. The investigator is responsible for the timely completion of eCRFs by assigned study staff. The eCRFs must be completed within seven (7) days of the subject's visit. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the Investigator's Brochure, and any protocol amendments.

Upon completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Kadmon.

23 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Kadmon and the IRB, subjects should be identified by an identification code and/or initials 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 Kadmon (e.g. subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Kadmon personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drug, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Kadmon.

The principal investigator also agrees that all information received from Kadmon, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information remain the sole and exclusive property of Kadmon during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The principal investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

24 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to Kadmon for review at least 30 days before submission. This allows Kadmon to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that Kadmon coordinates a publication or presentation of study results from all study sites, the participation of investigator or other representatives of study site as a named author shall be determined in accordance with Kadmon policy and generally accepted standards for authorship.

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APPENDIX A: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), VERSION 1.1

Use for Non-CNS Response

Quick Reference

Source: van Persijn van Meerten EL, Gelderblom H, Bloem JL. RECIST revised: Implications for the radiologist. A review article on the modified RECIST guideline (Version 1.1). European Journal of Cancer. 2009; 45:228-247. *Eur Radiol.* 2010:20; 1456–1467.

RESPONSE CRITERIA

Definitions

Evaluable for objective response: Only those subjects who have measurable disease present at screening, have received at least 2 cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 2 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Subjects who have lesions present at screening that are evaluable but do not meet the definitions of measurable disease, have received at least 2 cycles of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as ≥ 20 mm by chest X-ray, as ≥ 10 mm with chest, abdominal, or pelvic CT scan or with MRI of brain, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable if they have increased in size.

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

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

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

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

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

Methods for Evaluation of Measurable Disease

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

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

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

Chest X-ray: Lesions on chest X-ray are not acceptable as measurable lesions in this study.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI in this study is required for evaluation for brain metastases.

FDG-PET-CT: Not acceptable for this study.

Ultrasound: Not acceptable for this study.

Endoscopy, Laparoscopy: Not acceptable for this study.

FDG-PET: Not acceptable for this study.

Response Criteria
Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the Screening sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the Screening sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum

diameters while on study.

Note for subjects with scans that are on the "borderline" of disease progression (e.g. 21% increase in sum of target lesion diameters) but for whom the investigator determines a clinical benefit: These subjects will be allowed to continue in the study after discussion with the medical monitor. If improvement is documented at the next subsequent staging time point (e.g. 17% increase), the subject will continue on study. If worsening is documented (e.g. 30% increase in sum of target lesion diameters), the subject should be discontinued from the study, and the progression date should be the original date on which "borderline" disease progression was first documented.

Target lesions that become "too small to measure".
While on study, all lesions (nodal and non-nodal) recorded at Cycle 1 Day 1 should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at Cycle 1 Day 1 become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of 1 or more non-target lesion(s) and/or

maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of 1 or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Best Overall Response

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

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks. from Screening**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

Note for subjects with scans that are on the "borderline" of disease progression (e.g. 21% increase in sum of target lesion diameters) but for whom the investigator determines a clinical benefit: These subjects will be allowed to continue in the study after discussion with the medical monitor. If improvement is documented at the next subsequent staging time point (e.g. 17% increase), the subject will continue on study. If worsening is documented (e.g. 30% increase in sum of target lesion diameters), the subject should be discontinued from the study, and the progression date should be the original date on which "borderline" disease progression was first documented.

Duration of Response

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

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

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

Progression-Free Survival

PFS will be calculated as a secondary endpoint for all subjects and will represent the time between initiation of therapy to the time of documentation of progression of disease or death.

APPENDIX B: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
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.
3	In bed > 50 % of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100 % bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX C: QTC(F) CALCULATION

The formula is:

$$QT_F = \frac{QT}{RR^{1/3}}$$

1. Manually and carefully measure the QT msec (use the longest)
2. The "RR interval in seconds" = dividing 60/heart rate
3. Power of 1/3 = 0.34
4. Take the RR and elevate it to the power of 0.34
5. Divide the QT by that number

Example:

1. For a QT of 400 msec and a heart rate of 80 bpm
2. RR interval = 60/heart rate = 60/80 = 0.75
3. $0.75^{0.34} = 0.9$
4. 400/0.9 = QTc(F) = 444 msec
5. The QTc(F) for a QT of 400 msec and a heart rate of 80 bpm is 444.

APPENDIX D: CONCOMITANT DRUGS THAT SHOULD BE USED WITH CAUTION*

Use of drugs that are substrates of the CYP3A4/5 family should be with caution in subjects who are receiving tesevatinib if deemed clinically necessary and the subject can be closely monitored for the desired drug effect and potential AEs. The following drugs induce or are a substrate for CYP3A4/5. **This list is not comprehensive, and all concomitant medications should be evaluated for possible interactions with tesevatinib**.

Drug Type	Drug Names
Anti-arrhythmics	**quinidine****
Anti-epileptics	carbamazepine, phenytoin, phenobarbital
Antihistamines	astemizole, chlorpheniramine
Benzodiazepines	alprazolam, diazepam, midazolam, triazolam
Calcium channel blockers	amlodipine, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine
Central nervous system depressants	barbiturates
HMG CoA reductase inhibitors	atorvastatin, cerivastatin, lovastatin, simvastatin
Immune modulators	cyclosporine, tacrolimus
Miscellaneous	amodiaquine, repaglinide, rifampin, torsemide, St John's Wort
Neuro-psychotropics	buspirone, haloperidol, methadone, pimozide
Steroids	estradiol, hydrocortisone, progesterone, testosterone

Reference: http://medicine.iupui.edu/flockhart/table.htm

HMG CoA, hydroxyl-methylglutaryl coenzyme A.

*Should be discussed with medical monitor

**Drugs that must be avoided per Appendix F, Concomitant Medications Associated With a Risk of QTc Interval Prolongation and/or Torsades de Pointes

Use of drugs that are substrates of the CYP2D6 also should be with caution in subjects who are receiving tesevatinib if deemed clinically necessary and the subject can be closely monitored for the desired drug effect and potential AEs.

Substrates of CYP2D6			
Amitriptyline	Doxepin	Methylphenidate	Propranolol
Amoxapine	Doxorubicin	Metoprolol	Protriptyline
Aripiprazole	Duloxetine	Mexiletine	Risperidone
Atomoxetine	Flecainide	Mirtazapine	Sertraline
Betaxolol	Fluoxetine	Moclobemide	Tamoxifen
Captopril	Fluphenazine	Nefazodone	Tamsulosin
Carvedilol	Fluvoxamine	Nortriptyline	Thioridazine
Chloroquine	Haloperidol	Oxycodone	Timolol
Chlorpromazine	Hydrocodone	Paroxetine	Tolterodine
Clomipramine	Imipramine	Perphenazine	Tramadol
Codeine	Labetalol	Pindolol	Trimipramine
Desipramine	Lidocaine	Pipotiazine	Venlafaxine
Dextroamphetamine	Lomustine	Procainamide	Zuclopenthixol
Dextromethorphan	Maprotiline	Promethazine	
Dihydrocodeine	Methamphetamine	Propafenone	

In addition, use of drugs that are CYP1A2 inducers and inhibitors should be with caution in subjects who are receiving tesevatinib if deemed clinically necessary and the subject can be closely monitored for the desired drug effect and potential AEs.

CYP1A2 Inducers	CYP1A2 Inhibitors	
Barbiturates	Artemisinin	Mexiletine
Carbamazepine (e.g. Tegretol)	Atazanavir (Reyataz)	Tacrine (Cognex)
Primidone	Cimetidine (Tagamet)	Thiabendazole
Rifampin (e.g. Rifadin)	Ciprofloxacin (Cipro)	Zileuton (Zyflo
	Enoxacin	
	Ethinyl Estradiol	
	Fluvoxamine	

Concomitant Drugs That Should Be Used with Extreme Caution*

Use of drugs that are inhibitors of the CYP3A4/5 family should be with caution in subjects who are receiving tesevatinib if deemed clinically necessary and the subject can be closely monitored for the desired drug effect and potential AEs. The following drugs are inhibitors of the CYP3A4/5 family. Use of these drugs may alter the pharmacokinetics of the study drug. **This list is not comprehensive, and all concomitant medications should be evaluated for possible interactions with tesevatinib.**

Drug Type	Drug Names
Anti-arrhythmics	**amiodarone****
Antibiotic	norfloxacin, trimethoprim
Antidepressant	fluvoxamine, nefazodone, norfluoxetine
Antiemetic	Aprepitant
Antifungal medications	fluconazole, itraconazole, ketoconazole
Calcium channel blockers	diltiazem, verapamil
Macrolide antibiotics	**clarithromycin*, erythromycin*,** telithromycin
Miscellaneous	cimetidine, gemfibrozil, montelukast, quercetin, grapefruit juice
Oral hypoglycemic agents	Glitazones

*Should be discussed with medical monitor first

**Drugs that must be avoided per Appendix F, Concomitant Medications Associated with a Risk of QTc Interval Prolongation and/or Torsades de Pointes

APPENDIX E: CONCOMITANT MEDICATIONS ASSOCIATED WITH A RISK OF QTC(F) INTERVAL PROLONGATION AND/OR TORSADES DE POINTES

Use of these drugs should be avoided in subjects who are receiving tesevatinib unless deemed clinically necessary. Discuss with medical monitor the appropriate monitoring of subjects while receiving any of these drugs in conjunction with tesevatinib. Subjects should be closely monitored for QTc(F) prolongation and potential AEs. **This list is not comprehensive and all concomitant medications should be evaluated for potential contribution to QTc(F) prolongation. Refer to the following web site for additional listings and information:**

https://crediblemeds.org/index.php?rf=US

Drug Type	Drug Name
Anti-anginal	bepridil
Anti-arrhythmic	amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol
Antibiotic	clarithromycin, erythromycin, azithromycin, sparfloxacin, gatifloxacin, moxifloxacin, troleandomycin
Anti-cancer	arsenic trioxide
Anti-infective/pneumocystis pneumonia	pentamidine
Anti-malarial	chloroquine, halofantrine
Anti-nausea	domperidone, droperidol
Anti-psychotic	haloperidol, mesoridazine, thioridazine
Anti-psychotic/anti-emetic	chlorpromazine
Anti-psychotic/Tourette's tics	pimozide
GI stimulant/heartburn	cisapride
Opiate agonist/pain control/narcotic dependence	levomethadyl, methadone

Reference: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

APPENDIX F: TOPICAL STEROID POTENCY CHART

The following potency chart categorizes brand- name topical steroid medications along with the name of the corresponding generic drug. The medications are listed in order of their potency. Please note that the percentage of ingredient in the medication does not necessarily correlate with the strength of the steroid. The list may not be comprehensive.

Brand Name	Generic Name
Class 1 – Superpotent	
Clobex Lotion/Spray/Shampoo, 0.05%	Clobetasol propionate
Cormax Cream/Solution, 0.05%	Clobetasol propionate
Diprolene Ointment, 0.05%	Augmented betamethasone
Olux E Foam, 0.05%	Clobetasol propionate
Olux Foam, 0.05%	Clobetasol propionate
Temovate Cream/Ointment/Solution, 0.05%	Clobetasol propionate
Ultravate Cream/Ointment, 0.05%	Halobetasol propionate
Vanos Cream, 0.1%	Fluocinonide
Cordran Tape, 0.05%	Flurandrenolide
Class 2 - Potent	
Diprolene Cream AF, 0.05%	Augmented betamethasone
Elocon Ointment, 0.1%	Mometasone furoate
Florone Ointment, 0.05%	Diflorasone diacetate
Halog Ointment/Cream, 0.1%	Halcinonide
Lidex Cream/Gel/Ointment, 0.05%	Fluocinonide
Psorcon E Cream, 0.05%	Diflorasone diacetate
Topicort Cream/Ointment, 0.25%	Desoximetasone
Topicort Gel, 0.05%	Desoximetasone
Class 3 – Upper Mid-Strength	
Cutivate Ointment, 0.005%	Fluticasone propionate
Lidex-E Cream, 0.05%	Fluocinonide
Luxiq Foam, 0.12%	Betamethasone valerate
Topicort LP Cream, 0.05%	Desoximetasone
Class 4 – Mid-Strength	
Cordran Ointment, 0.05%	Flurandrenolide
Elocon Cream/Lotion, 0.1%	Mometasone furoate
Kenalog Cream/Spray, 0.1%	Triamcinolone acetonide

Brand Name	Generic Name
Synalar Ointment, 0.025%	Fluocinolone acetonide
Westcort Ointment, 0.2%	Hydrocortisone Valerate
Class 5 - Lower Mid-Strength	
Capex Shampoo, 0.01%	Fluocinolone acetonide
Cordran Cream/Lotion, 0.05%	Flurandrenolide
Cutivate Cream/Lotion, 0.05%	Fluticasone propionate
Dermatop Cream, 0.1%	Prednicarbate
DesOwen Lotion, 0.05%	Desonide
Locoid Cream/Lotion/Ointment/ Solution, 0.1%	Hydrocortisone butyrate
Pandel Cream, 0.1%	Hydrocortisone probutate
Synalar Cream, 0.025/	Fluocinolone acetonide
Westcort Cream, 0.2%	Hydrocortisone valerate
Class 6 – Mild	
Aclovate Cream/Ointment, 0.05%	Alclometasone dipropionate
Derma-Smoothe/FS Oil, 0.01%	Fluocinolone acetonide
Desonate Gel, 0.05%	Desonide
Synalar Solution, 0.01%	Fluocinolone acetonide
Verdeso Foam, 0.05%	Desonide
Class 7 - Least Potent	
Cetacort Lotion, 0.5%/1%	Hydrocortisone
Cortaid Cream/Spray/Ointment, 1%	Hydrocortisone
Hytone Cream/Lotion, 1%/2.5%	Hydrocortisone
Micort-HC Cream, 2%/2.5%	Hydrocortisone
Nutracort Lotion, 1%/2.5%	Hydrocortisone
Synacort Cream, 1%/2.5%	Hydrocortisone

Abstracted from: National Psoriasis Foundation. Topical treatments for Psoriasis. 2013. http://www.psoriasis.org/document.doc?id=164 (accessed 24 February 2014).

APPENDIX G: EORTC QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (two pages)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX H: EORTC QLQ-BN20 QUESTIONNAIRE (ONE PAGE)

ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4