CLINICAL STUDY PROTOCOL COVER LETTER

A Phase 2, Multicenter Study of Tesevatinib Monotherapy in Patients with Recurrent Glioblastoma

Protocol Number:	KD019-208
IND Number:	129323
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CLINICAL STUDY PROTOCOL

A Phase 2, Multicenter Study of Tesevatinib Monotherapy in Patients with Recurrent Glioblastoma

Protocol Number:	KD019-208
IND Number:	129323
Study Drug:	Tesevatinib
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:** 5 February 2016
Version:	**2.0** 25 March 2016 **3.0** 3 October 2017 **4.0** 03 April 2019

1. PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

All serious adverse events (SAEs)* occurring in patients while on-study or within 30 days of receiving the last dose of 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 11.3 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 patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

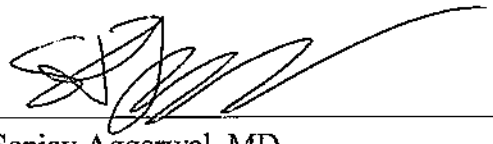
Some serious events will not be reported as SAEs, including:

- 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
- 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 Section 11.3.2 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.



03- APR - 2019

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 patients with a signed and dated copy of their informed consent document, as required by FDA and ICH regulations. I further agree to report to Kadmon any adverse events 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 Monotherapy in Patients with Recurrent Glioblastoma
Clinical phase	Phase 2
Number of study centers	Up to 10 US centers
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), Src, and vascular endothelial growth factor receptor 2 (VEGFR2). Tesevatinib has been evaluated in 6 clinical studies in various solid tumors in more than 275 patients, of whom at least 50 received the recommended dose of 300 mg daily. The safety profile is similar to that of other agents in the class, with predominantly gastrointestinal (GI) and skin adverse events (AEs). QTc prolongation has also been observed, which appears to be dose related. Efficacy has been observed in non-small cell lung cancer (NSCLC) with activating EGFR mutations. For further information see the Investigator Brochure (Version 7.0 dated 23 July 2015).
Study rationale	Gliomas account for 80% of primary malignancies of the central nervous system (CNS). Glioblastomas (World Health Organization (WHO) Grade IV astrocytic tumors) account for 60–70% of gliomas and remain the most aggressive subtype. Glioblastoma occurs mostly in adults (median age of 64 years at diagnosis) with an estimated incidence of 2–3 cases per 100,000 people in Europe and North America. With 1- and 5-year overall survival (OS) rates of 29% and 3%, respectively, the prognosis of glioblastoma remains poor [Central Brain Tumor Registry of the United States 2011] and there is a need to develop more effective therapeutic approaches. Standard treatment for newly diagnosed glioblastoma is surgical debulking followed by radiotherapy and temozolomide (TMZ) with additional maintenance TMZ [Stupp 2005]. Despite the survival benefit associated with such treatment, almost all patients relapse following initial therapy. Patients with recurrent glioblastoma have a median progression-free survival (PFS) of about 4 months and OS of less than 10 months. The optimal management for patients with recurrent glioblastoma remains unclear, as there have been no randomized trials directly comparing active intervention with supportive care. The most important prognostic factors for benefit from re-intervention are pre-treatment performance status and patient age [Kappelle 2001]. Active interventions include repeated surgery, re-irradiation, or systemic therapy in order to improve or preserve neurological function and prolong PFS and OS. Chemotherapy with TMZ demonstrated an increase in survival as second-line therapy in initial trials. However, TMZ is now generally used as a component of first-line treatment and hence there is no established chemotherapy regimen available for recurrent glioblastoma [Stupp 2009; Stupp 2010]. Nitrosourea-based chemotherapy, either as single agents or in combination regimens such as procarbazine, lomustine, and vincristine (PCV), have

	shown some activity in Phase 2 studies of patients who progressed after prior chemotherapy [Schmidt 2006; Fabrini 2009]. Systemic treatment with the anti-VEGF monoclonal antibody bevacizumab has also shown some activity in recurrent glioblastoma [Friedman 2009]. Bevacizumab is currently approved for use in patients with progressive disease following prior therapy in the United States but not in the European Union [Avastin® USPI 2015]. The label specifically mentions that there are no data demonstrating an improvement in disease-related symptoms or increased survival. EGFR gene abnormalities occur commonly in glioblastomas, suggesting that EGFR inhibition could be a useful clinical strategy. Studies indicate that EGFR gene amplification and /or mutation are present in approximately 57% of glioblastomas [Brennan 2013]. EGFR variant III (EGFRvIII), which leads to constitutive EGFR signaling, is seen in approximately 25% of glioblastomas [van den Bent 2009]. Clinical trials of EGFR inhibitors in patients with glioblastomas have produced disappointing results, perhaps because the available agents have poor blood-brain barrier (BBB) penetration. A Phase 2 trial of erlotinib, for instance, led to a 6-month PFS rate of 11% with erlotinib, compared to 24% with physician's choice of temozolomide or carmustine [van den Bent 2009]. In vitro data suggest that some EGFR abnormalities will correlate with clinical sensitivity to erlotinib [Sarkaria 2007]. In addition to targeting EGFR, tesevatinib also has VEGFR2 inhibitory activity, and there may be advantages to the simultaneous inhibition of EGFR and VEGFR2 in glioblastomas. Thus, although the determinants of glioblastoma responsiveness to EGFR inhibitors remain poorly defined, further research on the role of tesevatinib in glioma could be a productive approach to improving glioma treatment. Unlike other agents in its class, tesevatinib effectively penetrates into the brain, with levels in mice and rats with intact BBBs the same or higher than plasma levels [Tonra 2015]. Tesevatinib has levels in the choroid plexus and meninges that are 10 times the plasma levels, suggesting that tesevatinib may penetrate well into cerebrospinal fluid (CSF). There is preliminary evidence of clinical benefit in patients with leptomeningeal metastases in NSCLC [Kadmon data on file]. Thus, there is a good biologic rationale to evaluate tesevatinib in patients with recurrent glioblastoma which has progressed on or after prior therapy. Its role in tumors with and without the EGFR activating mutations, EGFR protein overexpression and gene amplification also needs to be explored.
Study objectives	<u>Primary efficacy objectives</u> • To evaluate the efficacy of tesevatinib as measured by investigator-assessed progression-free survival at 6-months (PFS-6) <u>Secondary efficacy objectives</u> • To evaluate the efficacy of tesevatinib as measured by investigator-assessed PFS-6 in the subgroup of patients with EGFRvIII^{pos} glioblastoma • To evaluate the efficacy of tesevatinib as measured by investigator-assessed PFS-6 in the subgroup of patients with EGFR gene amplified glioblastoma • To evaluate the efficacy of tesevatinib as measured by the overall survival rate at 9 months (OS-9) and OS overall, in all patients and in those with

	EGFRvIII^{pos} and EGFR gene amplified glioblastoma • To evaluate the efficacy of tesevatinib as measured by PFS, objective response rate (ORR) per Response Assessment in Neuro-Oncology (RANO) criteria, and duration of response (DOR) in all patients and in those with EGFRvIII^{pos} and EGFR gene amplified tumors • To evaluate the efficacy of tesevatinib as measured by PFS-6, OS-9, RANO OOR and DOR in: o EGFRvIII^{pos} vs EGFRvIII^{neg} o EGFR amplification^{pos} vs EGFR amplification^{neg} <u>Safety objectives</u> • To evaluate the safety and tolerability of tesevatinib in all patients and in the subgroup of patients with EGFRvIII^{pos} and the subgroup of patients with EGFR amplification^{pos} tumors <u>Exploratory objectives</u> • To evaluate the plasma concentration of tesevatinib in patients with and without systemic steroid treatment • To evaluate the potential association of exploratory tissue and blood biomarkers with response to tesevatinib and with adverse events. These include EGFRvIII mutation and gene amplification and may include circulating tumor DNA • To evaluate the correlation between patients with EGFRvIII^{pos} tumor and those patients with EGFR gene amplification • To evaluate and compare EGFRvIII^{pos} expression and/or other tissue biomarkers potentially associated with response with tesevatinib, in paired primary and recurrent glioblastoma specimens from the same patient, when these are available • To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the M.D. Anderson Symptom Inventory – Brain Tumor questionnaire (MDASI-BT) • To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the M.D. Anderson Symptom Inventory – Brain Tumor questionnaire (MDASI-BT) in the subgroup of patients with EGFRvIII^{neg} and EGFR gene amplification^{neg} tumors as compared to those in patients with EGFRvIII^{pos} and EGFR gene amplification^{pos} tumors
Study design	This is a multicenter, Phase 2 study to assess the activity of tesevatinib in patients with recurrent glioblastoma. **Screening and Study Treatment** The availability of paraffin-embedded tumor sample diagnostic of glioblastoma is mandatory for entry into the study and should be provided with a copy of the original pathology report for central review. Tumor samples will be evaluated for the EGFRvIII mutation and for EGFR gene amplification. Tissue from recurrent surgery is preferred, but tissue from initial surgery is sufficient for study entry. Baseline magnetic resonance

	imaging (MRI) is mandatory within 7 days of study drug administration. After completion of the screening assessments and confirmation of study eligibility, tesevatinib will be orally administered to all patients at a dose of 300 mg once daily. Patients who develop ≥ Grade 3 adverse event 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 glucose in a patient 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 patient with diarrhea) will have study treatment interrupted until the ≥ Grade 3 drug-related toxicities have resolved to ≤ Grade 1 (refer to Section 9.1.3). Once toxicities have resolved to ≤ Grade 1, the patient may resume study treatment at a reduced dose of 250 mg/day. No more than one dose reduction is permitted. Patients who require more than one dose reduction will have study drug discontinued and enter the Follow-up Period. Patients for whom toxicity persists beyond 21 days despite dose interruption may resume study treatment only with permission from the responsible Medical Monitor. If study treatment is withheld, the patient should be instructed not to make up the withheld doses. Study treatment will continue until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death. Assessments for disease response will occur at week 4 and 8 and then every 8 weeks using the RANO criteria (see Appendix 2). Upon treatment discontinuation, patients will be followed every 8 weeks for survival. Tumor samples will be used for exploratory biomarker research including, but not limited to, evaluation of EGFRvIII expression by immunohistochemistry (IHC) or real-time Polymerase Chain Reaction (PCR). An appropriate histopathological definition and cutoff for EGFRvIII^{pos} tumors will be established, and outcome in this subpopulation will be evaluated in addition to the overall study population. To characterize the safety and tolerability profile of tesevatinib, patients will be monitored throughout the study for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation. Patients will undergo safety evaluations, including physical examination (PE), vital sign measurements, hematology, serum chemistry, urinalysis and electrocardiogram (ECG). MRI will be used to evaluate the tumor at baseline (within 7 days of study drug administration). All MRIs taken on study patients will be submitted to the sponsor for possible retrospective analysis (refer to Section 10.1). Subjects who have completed 24 cycles of treatment and who continue to tolerate treatment with KD019 may continue on study with bimonthly visits to clinic for drug dispensing, safety and efficacy assessment.

	End of Treatment Visit An End-of-Treatment visit is to be performed as soon as possible after the patient's last dose of study drug. This may occur at the visit at which disease progression is diagnosed. The patient 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. Patients will undergo PEs; vital sign measurements; hematology, serum chemistry, urinalysis and ECG, 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. If progressive disease has not occurred at the end of the follow-up period MRIs should be repeated every 8 weeks until disease progression per RANO criteria. **Long-Term Follow-Up** Patients are to be contacted by telephone every 8 weeks to assess progression status if not PD when study drug stopped, survival status and any subsequent anti-cancer treatment. If PD was not observed before the 30-day follow-up period, patients will return for follow-up MRI until PD is demonstrated or they start a new anti-cancer treatment. As of Amendment 4, long-term follow-up will no longer be required.
Study population/Number of patients	A total of approximately 40 patients with recurrent glioblastoma will be enrolled at up to 10 US centers.
Diagnosis and main criteria for inclusion	**Inclusion criteria**: Patients will be included if they meet the following criteria: 1) Willingness and ability to provide written informed consent and to comply with the study protocol as judged by the investigator 2) Age ≥ 18 years old 3) Karnofsky performance status (KPS) ≥70% (see Appendix 1). 4) Stable or decreasing dose of corticosteroids within 5 days prior to study enrollment. 5) 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. • 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. • 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 6 months after their last dose of study drug. Effective birth control includes (a) 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. 6) For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 5 above during the treatment period and for at least 6 months after the last dose of study drug. 7) Histologically confirmed glioblastoma. A local pathology report constitutes adequate documentation of histology for study inclusion. Patients with an initial diagnosis of a lower-grade glioma are eligible if a subsequent biopsy was determined to be glioblastoma. 8) First recurrence after concurrent or adjuvant chemoradiotherapy. Imaging confirmation of first tumor progression or regrowth as defined by the RANO criteria (see Appendix 2). A minimum of 12 weeks must have elapsed from the completion of radiotherapy to study entry to minimize the potential for MRI changes related to radiation necrosis that might be misdiagnosed as progression of disease, unless there is a new lesion outside the radiation field or unequivocal evidence of viable tumor on histopathological sampling. 9) Prior treatment with TMZ for low grade glioma or glioblastoma. 10) No more than one prior line of systemic treatment for glioblastoma. Concurrent and adjuvant TMZ-based chemotherapy, including the combination of TMZ with an investigational agent, is considered one line of therapy. 11) Prior therapy with gamma knife or other focal high-dose radiotherapy is allowed, but the patient must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field. 12) Recovery from the toxic effects of prior therapy, with a minimum time of: a) ≥ 28 days elapsed from the administration of any investigational agent b) ≥ 28 days elapsed from the administration of any prior cytotoxic agents, except ≥ 14 days from vincristine, ≥ 21 days from procarbazine, and ≥ 42 days from nitrosureas c) ≥ 14 days elapsed from administration of any non-cytotoxic agent (e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid) 13) Patients who have undergone recent surgery for recurrent or progressive tumor are eligible provided that: a) Surgery must have confirmed the recurrence b) There must be residual disease measurable per RANO criteria e.g. 1 cm x 1cm c) A minimum of 28 days must have elapsed from the day of surgery to first dose of the study drug. For core or needle biopsy, a minimum of 7 days must have elapsed prior to study entry 14) Availability of formalin-fixed paraffin-embedded tumor tissue diagnostic of glioblastoma. **Exclusion criteria:** Patients who meet any of the following criteria will be excluded from study entry: 1) Concurrent therapeutic intervention (including radiation therapy and NovoTTF). 2) Prior exposure to EGFR inhibitors.

	3) Prior exposure to bevacizumab or other VEGF- or VEGF-receptor-targeted agent within 8 weeks of study start. 4) Prior treatment with prolifeprospan 20 with carmustine wafer. 5) Prior intracerebral agent. 6) Evidence of recent hemorrhage on baseline MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving hemorrhagic changes related to surgery, or presence of punctuate hemorrhage in the tumor are eligible. 7) Need for urgent palliative intervention for primary disease (e.g., rapidly increasing intracranial pressure, impending herniation, uncontrolled seizures). 8) Absolute neutrophil count (ANC) < 1.5×10^9/L; platelet count < 100×10^9/L; or hemoglobin (Hb) < 9.0 g/dL within 7 days prior to enrollment. Note: The use of transfusion or other intervention to achieve Hb ≥ 9 g/dL is acceptable. 9) Total bilirubin ≥ 1.5 x ULN (except in patients diagnosed with Gilbert's disease). 10) Aspartate aminotransferase (AST) (SGOT), alanine aminotransferase (ALT) (SGPT), or alkaline phosphatase (ALP) ≥ 2.5 x ULN. 11) Serum creatinine > 1.5 x ULN. 12) Serum potassium or magnesium below the lower limit of normal. 13) International normalized ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (APTT) as follows unless on anticoagulation that is expected to alter coagulation test results: - INR > 1.5 or PT > 1.5 xULN or aPTT > 1.5 xULN 14) Known contraindication to MRI, such as cardiac pacemaker, shrapnel or ocular foreign body. 15) Used any prescription medication during the prior 2 weeks that the investigator judges is likely to interfere with the study or to pose an additional risk to the patient in participating, specifically inhibitors or inducers of cytochrome P450 (CYP)3A4 (refer to Appendix 4). A stable regimen (≥ 4 weeks) of antidepressants of the selective serotonin re-uptake inhibitor (SSRI) class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine). 16) Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval (see Appendix 4). 17) 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. Patients with a history of atrial arrhythmias should be discussed with the Medical Monitor. 18) Uncontrolled diabetes, as evidenced by fasting serum glucose level >200 mg/dL 19) New York Heart Association (NYHA) Grade II or greater congestive cardiac failure. 20) Has marked prolongation of QTc(F) interval at screening or baseline (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate. 21) History of myocardial infarction (within 12 months) or unstable angina (within 6 months) prior to study enrolment. 22) History of stroke or transient ischemic attacks within 6 months prior to study enrolment. 23) Significant vascular disease (e.g., aortic aneurysm requiring surgical

	repair or recent peripheral arterial thrombosis) within 6 months prior to study enrolment. 24) Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation). 25) History of intracranial abscess within 6 months prior to study enrolment. 26) History of another malignancy in the previous 3 years, with a disease-free interval of < 3 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible. 27) Evidence of any active infection requiring hospitalization or IV antibiotics within 2 weeks prior to study enrolment. 28) Known hypersensitivity to any excipients of tesevatinib. 29) Inability to swallow or absorb orally-administered medication.
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 patient-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: Patients will be treated with study drug until disease progression or unacceptable toxicity occurs. Discontinuation: Patients who discontinue tesevatinib treatment will be followed for disease progression (if applicable) and survival.
Concomitant medications	Concomitant treatment and medication information will be collected from the time the patient signs the informed consent form until 30 days after the last dose of study drug or until the patient starts a new treatment, and is to be reported on the appropriate case report form (CRF). 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 CRF including the date, indication, description of the procedure(s), and any clinical finding. Any medication that is considered necessary for the patient'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 CRF. Any changes in documented, permitted concomitant treatment already being taken at the beginning of the clinical study must be recorded in the CRF, noting the type of medication, the duration, and indication. 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.
Prohibited treatments	• Other investigational drugs • Concurrent anti-tumor therapies such as chemotherapy, gene therapy, biologics, tyrosine kinases inhibitors, radiation therapy, or 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 strongly inhibit the CYP3A4 isozyme or any drugs that are strong 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). See Appendix 4. • Steroid medications are allowed • Radiation therapy: need for radiation will be considered to be progressive disease
Safety assessments	The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading toxicities. Safety assessments will include AEs, serious adverse events (SAEs), PEs including full neurologic exam, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), KPS, and ECGs. The AE reporting period for a patient enrolled in the study begins when the patient 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 patients 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 at least 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.
Plasma Concentration Evaluation of Tesevatinib	Plasma samples for tesevatinib concentration analysis will be drawn predose of tesevatinib on Days 15 of Cycle 1; and predose of tesevatinib on Day 1 of every subsequent cycle (up to cycle 6). Data from these samples will contribute to a population PK analysis, and will be used to explore exposure-response relationships.
Pharmacodynamic Evaluation	Samples will be evaluated for the EGFRvIII mutation and for EGFR gene amplification.
Efficacy	Disease assessments will be based on the RANO criteria [Wen 2010] and will comprise radiological assessments, clinical assessments, and corticosteroid use (see Appendix 2). Per the study's schedule of assessments, full disease assessments

	should be performed at week 4 and 8 after the date of first study drug administration and then every 8 weeks. Disease assessments as initially planned according to the schedule of assessments should be maintained regardless of treatment delays. Unscheduled disease assessments may be performed at the discretion of the investigator to allow a decision on further study treatment administration for individual patients. For patients who discontinue treatment for reasons other than progressive disease, disease assessment in the follow-up period should continue every 8 weeks until disease progression. **Radiological Assessment** Radiological assessments will be performed using MRI scans. The acquisition protocol for MRI (provided as a separate document) will provide further details for scan standardization. All efforts should be made to perform MRI scans according to the corresponding specification in order to ensure that quality of MRI will be standardized among all sites. Consistency of subsequent MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions. Patients should be imaged on the same MRI scanner for the duration of the study. A 1.5T or 3T scanner must be used for this study. The use of IV contrast should, as long as clinically possible, be kept consistent. The following sequences of the entire brain must be acquired: • T1 pre-gadolinium • T2/FLAIR • T1 post-gadolinium Target Lesions: Lesions should be measured on the greatest size (bi-dimensional measurement of the longest cross-sectional diameters) observed either on axial, coronal, or sagittal slices, and the most representative observed chosen to be followed for response evaluation (i.e., once selected at baseline, the plane should be maintained across the study, to allow comparison). If there are multiple contrast- enhancing lesions, a minimum of two of the largest lesions, and a maximum of five lesions, should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected. For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. Nontarget Lesions: All other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. A radiological assessment of complete response (CR) or partial response (PR) requires confirmatory imaging at least 4 weeks after the initial assessment of response was observed. **In the event that the radiographic changes are equivocal and it is unclear**

	whether the patient has stable or progressive disease, treatment should be continued and the patient should be closely observed. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which disease progression was first suspected. **Clinical Status** Clinical deterioration is defined as a decline in the Karnofsky performance status from 100% or 90% to ≤ 70%; a decline of ≥ 20% from 80% or less; or a decline from any baseline value to 50% or less, for at least 7 days, unless attributable to comorbid events (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.). Clinical status must be recorded as Improved, Stable, or Worsened. **Corticosteroid Dose** At the time of each disease assessment, the corticosteroid intake will be compared with corticosteroid intake at the time of the last disease assessment. The changes will be recorded as Increased, Unchanged, or Decreased. Increases or decreases in corticosteroid dose should be clinically justified. Note: Increases in corticosteroid dose for reasons other than disease control do not need to be taken into consideration when making this comparison. **Overall Disease Assessment** Based on radiological assessments, clinical status, and corticosteroid use, an overall evaluation of CR, PR, stable disease (SD), or progressive disease (PD) should be made at each disease assessment after baseline according to the RANO criteria (Appendix 2). Progressive disease is defined as any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease or otherwise compared with the smallest recorded sum [nadir] during the study) on stable or increasing doses of corticosteroids • Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses or corticosteroids (compared with baseline or best response after initiation of therapy) • Appearance of any new lesions • Clear progression of nonmeasurable lesions • Definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose • Failure to return for evaluation as a result of death or deteriorating condition Note: Increase in corticosteroid dose alone, in the absence of persistent clinical deterioration related to tumor, will not be used as a determinant of progression. Patients whose corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging do not qualify for disease progression and should continue study treatment. If subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the date of progression should be the first timepoint at which the increase in

	corticosteroids was necessary.
Patient Reported Outcomes and Mini-Mental State Examination	Patient reported outcomes (PROs) of disease- and treatment-related symptom severity and symptom interference will be assessed using the MDASI-BT questionnaire. The MDASI is a validated and reliable self-report measure that was developed to assess symptom severity and interference [Cleeland 2000; Armstrong 2006]. Thirteen items ask patients to rate how severe the symptoms were when "at their worst" in the last 24 hours with regard to pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. The MDASI-BT (see Appendix 3) contains an additional nine items that assess symptoms and concerns specific to primary brain tumor patients (difficulty understanding, difficulty speaking, difficulty concentrating, seizures, weakness, change in appearance, change in vision, change in bowel patterns, irritability), for a total of 28 items. Subjects completing 24 cycles of tesevatinib will no longer be required to complete patient reported outcomes and mini-mental state examinations.
Statistical methods	**Analysis populations** Adult patients with recurrent glioblastoma, meeting all inclusion criteria and no exclusion criteria, with availability of paraffin-embedded tumor samples diagnostic of glioblastoma will be enrolled. Two subgroups of patients are defined as having: EGFRvIII^{pos} and EGFR amplification^{pos} tumors. Primary and secondary efficacy analyses will include all patients who were included in the study. The same analysis methods for the primary and secondary analyses will be applied to both the ITT population and the EGFRvIII^{pos} and EGFR gene amplification^{pos} population. Safety analyses will include all patients who enrolled and received at least one dose of study treatment (the safety population). All patients who take at least one dose of tesevatinib will be evaluable for safety and efficacy assessments. Patients 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. For statistical purposes, completion of the study will be defined as six months after the last patient starts study treatment. The plasma concentration analysis population will consist of all patients who receive at least one dose of tesevatinib, and who have at least one sample analyzed for plasma concentrations.

Sample Size Justification and power calculations:

The power calculation is based on simulations in the Weibull distribution to describe the progression and survival times. The estimation of PFS-6 is done using the Cox model. Based on a one-stage design, with a sample size of 40 patients in the overall population, a PFS-6 of 25% and median PFS of 4.5 months, the trial has 95% power to demonstrate an estimated PFS-6 >15%. Based on a one-sided test on a 5% significance level, the trial has 95% power to show a significant difference above the null hypothesis of 7% and 80% power to show a significant difference above 10%. The study is not powered to detect differences in the secondary endpoints.

Interim Analysis

An interim analysis is included with the possibility to stop for futility. The stopping rule is based on an unacceptable PFS-6 rate of 5% and a desirable PFS-6 rate of 20% or more. The trial will continue after the interim analysis if more than 1 responders are seen in 21 patients giving a 72% probability of stopping if the PFS-6 rate is ≤5%.

Primary efficacy endpoint: PFS-6

PFS is defined as the time between date of first dose and the date of first documented disease progression or death, whichever occurs first. The PFS-6 is defined as a patient being alive and progression free at 6 months (24 weeks). Disease progression will be determined based on investigator assessment with use of radiological assessments, clinical status, and corticosteroid use. Patients without a date of disease progression or death will be analyzed as censored observations on the date of the last disease assessment; if no post-baseline disease assessment is available, PFS will be censored at the date of 1st dose.

The analysis of the primary endpoint and the estimation of PFS-6 is performed with a Cox model. Karnofsky performance status is included as a covariate. Study center is included as a random effect assumed to follow a gamma distribution. Thus, this is a shared Cox gamma frailty model. The model is used to estimate PFS-6 with 2-sided 95% and 90% confidence intervals.

Furthermore, Kaplan-Meier methodology will be used to estimate median PFS with 95% CI and the Kaplan-Meier curve will be constructed to provide a visual description of the PFS over time.

Descriptive statistics overall and for each parameter (radiological assessment, clinical status and corticosteroid dose) in the disease progression assessment are presented for the entire assessment period as well as for 3-, 6-, and 9- month time points.

The analysis of secondary and exploratory endpoints is described in Section 13.4.6 and will be further outlined in the SAP.

Safety and PK:

	AEs/SAEs will be graded using Common Terminology Criteria for Adverse Events Common Terminology Criteria for Adverse Events (CTCAE) V4.03, coded and tabulated using MedDRA (version 18.1 or greater). Laboratory results, ECGs, KPS, PK and vital signs will be tabulated and presented in listings. Concomitant medications will be coded using WHO Drug and tabulated. Expectedness of the AEs will be assessed against the current tesevatinib IB. A statistical analysis plan (SAP) will be written to describe thoroughly the planned analyses.

Table 1: Schedule of Study Assessments

Timepoint (Study Day)	Screen	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7+	EOS Tx [o]	30-Day FU [p] (± 5d)	LTFU	UNS [q]
	-22 to -1	Day 1	Day 15 (± 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												
Tumor sample(s) [a]	X												
Inclusion/exclusion criteria	X												
Physical Examination [b]	X	X	X	X	X	X	X	X	X	X	X		X
Neurological Examination [c]	X				X		X		X				
Vital Signs [d]	X	X	X	X	X	X	X	X	X	X	X		X
Safety Labs [e, f]	X	X	X	X	X	X	X	X	X	X	X		X
Pregnancy Test [g]	X	X		X	X	X	X	X	X	X	X		X
12-Lead ECG [h]	X	X	X	X	X	X	X	X	X	X			X
Disease Assessment [j]	X			X	X		X		X	X			X
• Karnofsky performance status	X			X	X		X		X	X			X
• Corticosteroid use	X			X	X		X		X	X			X
• MRI tumor assessment	X			X	X		X		X	X		X [r]	X
Pt. Reported Outcomes (MDASI-BT) [k]		X		X	X		X		X	X			
Plasma concentration [l]			X	X	X	X	X	X					
Tesevatinib Dosing [m]		X	X	X	X	X	X	X	X				X
Collect/Issue Diary		X		X	X	X	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 [n]	*To be collected from the time of informed consent through 30 days after last dose of study drug.*												
Follow-Up Phone Contact												X [r]	

d = day; ECG = electrocardiogram; EOS = end of study; FU = follow-up; KPS = Karnofsky Performance Status; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; UNS = unscheduled; Tx = treatment

a: Tumor tissue samples (20 slides cut as recently as possible and sections containing adequate tumor) must be available and ready to be sent to the central laboratory or the Sponsor. Samples from the original tumor and any subsequent biopsies will be required. An optional biopsy should be considered. For core or needle biopsy, a minimum of 7 days must have elapsed prior to study entry. See lab manual for definition of adequate tumor sample.

b: At screening, PE to include height and weight. Complete PE including weight is required at all visits except for Day 15 of Cycle 1, when an abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

c: Neurological exam should include full cranial nerve central and peripheral, motor and sensory assessments.

d: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained with patient in sitting position. On Cycle 1, Day 1, and Cycle 1, Day 15 vital signs are to be measured predose and 1 and 4 hours postdose.

e: Safety labs = hematology, coagulation, cystatin-C, clinical chemistry and urinalysis. See Table 2. 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.

f: Coagulation function to be tested at baseline only. INR, PT, APTT.

g: Urine test in women of childbearing potential within 24-hours prior to first dose of study drug. Positive urine results are to be confirmed by serum pregnancy test.

h: Supine 12-Lead ECGs will be performed at screening; predose, and once within the 4 – 8 hours postdose on Days 1 and 15 of Cycle 1; pre-dose on Day 1 of Cycles 2 and beyond; and at End of Study Drug Treatment visit. At each timepoint, repeat ECG three times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs). ECGs will be read by a central laboratory. Following dose reduction and resumption of study drug treatment, ECGs must be repeated weekly for 2 weeks, then on Day 1 of each cycle following restart of study drug.

i: The assessment is intended to be done prior to starting cycle 2, 3, 5, 7+ but should be performed every 8 weeks. Radiological assessment must be performed with a brain MRI scan. The method of radiological assessment should be consistent throughout all visits. Disease assessment during the screening period is to be performed within 7 days before study drug administration and must be used as the baseline radiological assessment. The corticosteroid dose should be kept stable for 5 days prior to the MRI scan. During the study, disease assessments should be performed at week 4 and 8 after the date of first study treatment and then every 8 weeks (at Week 16, 24, etc.), regardless of treatment delays. For patients who discontinue treatment for other reasons than PD, disease assessment in the follow-up period should continue every 8 weeks (according to the original schedule) until disease progression. For patients with PD, disease assessment at the EOS is only required if not performed within the previous 8 weeks.

j: Patients will complete the questionnaire pre-dose on Day 1 of Cycles 1 and 2; every 8 weeks after study drug administration (i.e., coinciding with the schedule of disease assessments); and at the EOS. Patients who discontinue study treatment for reasons other than disease progression will also complete the questionnaire every 8 weeks during follow-up until the time of documented disease progression. Patients must complete the questionnaire prior to any other tests or assessments and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site.

k: Blood samples for tesevatinib plasma concentrations should be drawn prior to study drug administration.

l: Tesevatinib will be administered at the dose of 300 mg once daily. Study drug should be dispensed and accounted for from previous visit.

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 as soon as possible after the patient'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 patients' 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. Assessments for the 30-day follow up may be done by telephone.

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

q: Patients are to be contacted by telephone every 8 weeks to assess progression status if not PD when study drug stopped, survival status and any subsequent anti-cancer treatment. If PD was not observed before the 30-day follow-up period patients will return for follow-up MRI until PD is demonstrated or they start a new anti-cancer treatment. In the case of a patient receiving a new anti-cancer treatment in the absence of PD, the date of the most recent MRI will be used as the date of PD.

Table 2b: Schedule of Study Assessments for Subjects Completing 24 Cycles of Tesevatinib Treatment

Timepoint (Study Day)	Cycle 26 Day 1 (± 3d)	Cycle 28 Day 1 (± 3d)	Cycle 30 Day 1 (± 3d)	Cycle 32 Day 1 (± 3d)	Cycle 34 Day 1 (± 3d)	Cycle 36+ Day 1 (± 3d)	EOS Tx [i]	30-Day FU [j] (± 5d)	UNS [k]
Physical Examination [a]	X	X	X	X	X	X	X	X	X
Neurological Examination [b]	X	X	X	X	X	X			X
Vital Signs [c]	X	X	X	X	X	X	X	X	X
Safety Labs [d]	X	X	X	X	X	X	X	X	X
12-Lead ECG [e]	X	X	X	X	X	X	X		X
Disease Assessment [f]	X	X	X	X	X	X	X		X
Karnofsky performance status	X	X	X	X	X	X	X		X
Corticosteroid use	X	X	X	X	X	X	X		X
MRI tumor assessment	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Tesevatinib Dispensing [g]	X	X	X	X	X	X			X
AE Monitoring[h]	X	X	X	X	X	X	X		X

d = day; ECG = electrocardiogram; EOS = end of study; FU = follow-up; KPS = Karnofsky Performance Status; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; UNS = unscheduled; Tx = treatment

a: Abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

b: Neurological exam should include full cranial nerve central and peripheral, motor and sensory assessments.

c: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained with patient in sitting position.

d: To be drawn and analyzed locally. Safety labs = hematology and clinical chemistry. See Table 2b.

e: Supine 12-Lead ECGs will be performed at each visit.

f: The assessment should be performed every 8 weeks. Radiological assessment must be performed with a brain MRI scan and should be consistent throughout all visits.

g: Study drug should be dispensed and accounted for from previous visit.

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

i: The End-of-Study Drug Treatment visit is to occur as soon as possible after the patient'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.

j: The 30-Day Follow-Up visit should occur 30 days (±5 days) after the patients' 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. Assessments for the 30-day follow up may be done by telephone.

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

Table 3: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis (dipstick)
• WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • mean corpuscular volume (MCV)	• cystatin-c • albumin • amylase (trigger fasting triglycerides if amylase is 1.5 x normal) • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • creatine phosphokinase • phosphorous • potassium • glucose (non-fasting) • sodium • total bilirubin • total protein • magnesium	• 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)
Coagulation*		
• INR • PT • aPTT		

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = International normalized ratio; MCV = mean cell volume; PT = prothrombin time
*Coagulation function only to be tested at baseline visit.

Table 4: Clinical Laboratory Panels for Subjects Completing 24 Cycles of Tesevatinib Treatment

Hematology	Serum Chemistry
• WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • mean corpuscular volume (MCV)	• albumin • amylase (trigger fasting triglycerides if amylase is 1.5 x normal) • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • creatine phosphokinase • phosphorous • potassium • glucose (non-fasting) • sodium • total bilirubin • total protein • magnesium

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = International normalized ratio; MCV = mean cell volume; PT = prothrombin time

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AE(s)	adverse event(s)
ADL	activities of daily living
ADPKD	autosomal dominant polycystic kidney disease
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BBB	blood-brain barrier
BID	twice-a-day
BSA	body surface area
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CYP3A4	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EGFRvIII	epidermal growth factor receptor variant III
eCRF	electronic case report form
EOS	end of study
FU	follow-up
GCP	good clinical practice
GI	gastrointestinal
Hb	hemoglobin
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonization

IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
KPS	Karnofsky performance status
LM	leptomeningeal
LTFU	long-term follow-up
MDASI-BT	M.D. Anderson Symptom Inventory – Brain Tumor questionnaire
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	non-clinically significant
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OS-9	overall survival at 9 months
PCR	polymerase chain reaction
PCV	procarbazine, lomustine, and vincristine
PD	progressive disease
PE	physical exam
PFS	progression-free survival
PFS-6	progression-free survival at 6 months
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
QTc(F)	QT interval, corrected
RANO	Response Assessment in Neuro-Oncology
SADR (or SAR)	suspected adverse drug reactions
SAE(s)	serious adverse event(s)
SD	stable disease

SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SSRI	selective serotonin re-uptake inhibitors
SUSAR	suspected unexpected serious adverse reactions
TMZ	temozolomide
ULN	upper limit of normal
VEGFR2	vascular endothelial growth factor receptor 2
WHO	World Health Organization

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 EGFR, 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 and potentially other solid tumors. 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), which is registered in this indication. 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 activating EGFR mutations. The potential advantage of tesevatinib over erlotinib is that tesevatinib is far more efficient at crossing the blood-brain barrier. It is therefore a good candidate for therapy of brain metastases and primary brain cancers which are driven by EGFR mutations.

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

To date, the tesevatinib clinical program consists of eight completed trials using the tablet formulation (six Phase 1 and two Phase 2 studies). One of the Phase 1 trials (KD019-104) in healthy volunteers compared the tablet formulation to the liquid formulation. Four additional trials of the tablet formulation are included, of which three are ongoing; KD019-101 in autosomal dominant polycystic kidney disease (ADPKD), KD019-204 in metastatic breast cancer, and KD019-206 in patients with NSCLC; and one (KD019-301 in NSCLC) which recently closed due to slow enrollment.

In these studies, over 275 patients with solid tumor malignancies, ADPKD, and healthy volunteers have received tesevatinib. The MTD in patients with solid tumor malignancies was determined to be 300 mg once daily.

Further details of the clinical studies are provided in the Investigator's Brochure.

5.2. Safety Profile of Tesevatinib

Tesevatinib has been evaluated in 6 clinical studies in various solid tumors in more than 275 patients, of whom at least 50 received the recommended dose of 300 mg daily. The safety profile is similar to that of other agents in this class, with predominantly GI and skin AEs. The most frequently reported AEs associated with tesevatinib use are diarrhea, skin rash, fatigue, nausea, cough, dyspnea, dry skin, vomiting, constipation, vomiting, anorexia and QTc prolongation (see

Investigators Brochure for further detail). The AEs of special interest are as follows (refer to Section 9.1.4 for instruction on management of these AEs):

Diarrhea: Diarrhea is an expected AE for agents like tesevatinib that have significant EGFR inhibitor activity. Grade 3 diarrhea was the dose-limiting toxicity. At doses below those that cause dose-limiting toxicity, diarrhea has been effectively managed by starting loperamide upon occurrence of grade 1.

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

In patients with malignancies treated in the clinical program at ≥ 300 mg daily or 350 mg intermittently, the majority of whom had advanced metastatic NSCLC, approximately 20% were found to have QTc prolongation based on machine read ECGs at some time during treatment that met the CTCAE v3 definition of an AE. The majority of these were Grade 2 and 3 with no Grade 4. There were no clinical findings associated with the ECG changes.

No SAEs of syncope, convulsions, sudden death, ventricular tachycardia, fibrillation, flutter, or torsades de pointes have been received for the > 275 patients exposed to tesevatinib.

PK data from the clinical program demonstrated that QTc prolongation increased with increasing tesevatinib plasma concentration which correlated with dose administered.

Patients in this study will be monitored carefully for QTc prolongation, and a central laboratory will review all ECGs.

Skin Rash: Acneiform skin rash is an expected adverse event 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.

Clinical Chemistry: Creatinine elevations have been observed up to Grade 3 in the absence of other indicators of renal failure. 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. This effect appears to be due to inhibition of MATE transporter proteins by tesevatinib. Elevations of creatinine have also been observed in patients with other concurrent causes of renal dysfunction such as dehydration due to diarrhea.

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.

Occasional elevation of amylase and CPK have been observed with tesevatinib treatment. These were asymptomatic and reversible.

Interstitial Lung Disease: Non-fatal interstitial lung disease (ILD) has been reported in association with the use of tesevatinib in one patient with NSCLC out of >275 patients exposed to tesevatinib.

5.3. Rationale

5.3.1. Study Rationale

Gliomas account for 80% of primary malignancies of the CNS. Glioblastomas (WHO Grade IV astrocytic tumors) account for 60–70% of gliomas and remain the most aggressive subtype. Glioblastoma occurs mostly in adults (median age of 64 years at diagnosis) with an estimated incidence of 2–3 cases per 100,000 people in Europe and North America. With 1- and 5-year OS rates of 29% and 3%, respectively, the prognosis of glioblastoma remains poor [Central Brain Tumor Registry of the United States 2011] and there is a need to develop more effective therapeutic approaches.

Standard treatment for newly diagnosed glioblastoma is surgical debulking followed by radiotherapy and TMZ with additional maintenance TMZ [Stupp 2005]. Despite the survival benefit associated with such treatment, almost all patients relapse following initial therapy.

Patients with recurrent glioblastoma have a median PFS of about 4 months and OS of less than 10 months. The optimal management for patients with recurrent glioblastoma remains unclear, as there have been no randomized trials directly comparing active intervention with supportive care. The most important prognostic factors for benefit from re-intervention are pre-treatment performance status and patient age [Kappelle 2001].

Active interventions include repeated surgery, re-irradiation, or systemic therapy in order to improve or preserve neurological function and prolong PFS and OS. Chemotherapy with TMZ demonstrated an increase in survival as second-line therapy in initial trials. However, TMZ is now generally used as a component of first-line treatment and hence there is no established chemotherapy regimen available for recurrent glioblastoma [Stupp 2009; Stupp 2010]. Nitrosourea-based chemotherapy, either as single agents or in combination regimens such as PCV, have shown some activity in Phase 2 studies of patients who progressed after prior chemotherapy [Schmidt 2006; Fabrini 2009]. Systemic treatment with the anti-VEGF monoclonal antibody bevacizumab has also shown some activity in recurrent glioblastoma [Friedman 2009]. Bevacizumab is currently approved for use in patients with progressive disease following prior therapy in the United States but not in the European Union [Avastin® USPI 2015]. The label specifically mentions that there are no data demonstrating an improvement in disease-related symptoms or increased survival.

EGFR gene abnormalities occur commonly in glioblastomas, suggesting that EGFR inhibition could be a useful clinical strategy. Studies indicate that EGFR gene amplification and /or mutation are present in approximately 57% of glioblastomas [Brennan 2013]. EGFR variant III (EGFRvIII), which leads to constitutive EGFR signaling, is seen in approximately 25% of glioblastomas [van den Bent 2009]. Clinical trials of EGFR inhibitors in patients with glioblastomas have produced disappointing results, perhaps because the available agents have poor BBB penetration. A Phase 2 trial of erlotinib, for instance, led to a 6-month PFS rate of 11% with erlotinib, compared to 24% with physician's choice of temozolomide or carmustine [van den Bent 2009]. In vitro data suggest that some EGFR abnormalities will correlate with clinical sensitivity to erlotinib [Sarkaria 2007]. In addition to inhibiting EGFR, tesevatinib also

has VEGFR2 inhibitory activity, and there may be advantages to the simultaneous inhibition of EGFR and VEGFR2 in glioblastomas. Thus, although the determinants of glioblastoma responsiveness to EGFR inhibitors remain poorly defined, further research on the role of tesevatinib in glioma could be a productive approach to improving glioma treatment.

Unlike other agents in its class, tesevatinib effectively penetrates into the brain, with levels in mice and rats with intact BBBs the same or higher than plasma levels [Tonra 2015]. Tesevatinib has levels in the choroid plexus and meninges that are 10 times the plasma levels, suggesting that tesevatinib may penetrate well into CSF. There is preliminary evidence of clinical benefit in patients with leptomeningeal metastases in NSCLC [Kadmon data on file]. Thus, there is a good biologic rationale to evaluate tesevatinib in patients with recurrent glioblastoma which has progressed on or after prior therapy. Its role in tumors with and without and EGFR activating mutations, EGFR protein overexpression and gene amplification also needs to be explored.

Glioblastomas are inherently inaccessible and challenging to assess in terms of repeat biopsy for evaluation of treatment-related biomarkers. Circulating tumor DNA has shown promise as a peripherally accessible source of biomarker information in glioblastoma [Touat 2015, Best 2015].

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 patients with EGFR mutations. In one study, the confirmed PR rate in patients with EGFR mutations was 57% (8/14), and an additional 3 patients with EGFR mutations had unconfirmed PRs.

Tesevatinib 300 mg daily was selected from the regimens tested in the early clinical program based on its benefit-risk profile.

6. STUDY OBJECTIVES

6.1. Primary Objectives

6.1.1. Primary efficacy objective

- To evaluate the efficacy of tesevatinib as measured by investigator-assessed PFS-6

6.1.2. Primary safety objective

- To evaluate the safety and tolerability of tesevatinib in all patients and in the subgroup of patients with EGFRvIII^{pos} and the subgroup of patients with EGFR amplification^{pos} tumors

6.2. Secondary Objectives

- To evaluate the efficacy of tesevatinib as measured by investigator-assessed PFS-6 in the subgroup of patients with EGFRvIII^{pos} glioblastoma
- To evaluate the efficacy of tesevatinib as measured by investigator-assessed PFS-6 in the subgroup of patients with EGFR gene amplified glioblastoma
- To evaluate the efficacy of tesevatinib as measured by the rate OS-9 and OS overall, in all patients and in those with EGFRvIII^{pos} and EGFR gene amplified glioblastoma
- To evaluate the efficacy of tesevatinib as measured by PFS, ORR per RANO criteria, and DOR in all patients and in those with EGFRvIII^{pos} and EGFR gene amplified tumors
- To evaluate the efficacy of tesevatinib as measured by PFS-6, OS-9, RANO OOR and DOR in:
  - EGFRvIII^{pos} vs EGFRvIII^{neg}
  - EGFR amplification^{pos} vs EGFR amplification^{neg}

6.3. Exploratory objectives

- To evaluate the plasma concentrations of tesevatinib in patients with and without systemic steroid treatment
- To evaluate the potential association of exploratory tissue and blood biomarkers with response to tesevatinib and with adverse events. These include EGFRvIII mutation and gene amplification and may include circulating tumor DNA
- To evaluate the correlation between patients with EGFRvIII^{pos} tumor and those patients with EGFR gene amplification
- To evaluate and compare EGFRvIII^{pos} expression and/or other tissue biomarkers potentially associated with response with tesevatinib, in paired primary and recurrent glioblastoma specimens from the same patient, when these are available

- To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the MDASI-BT questionnaire
- To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the MDASI-BT in the subgroup of patients with EGFRvIII^{neg} and EGFR gene amplification^{neg} tumors as compared to those in patients with EGFRvIII^{pos} and EGFR gene amplification^{pos} tumors

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This is a multicenter, Phase 2 study to assess the activity of tesevatinib in patients (n =40) with recurrent glioblastoma. This study will be conducted at up to 10 sites in the United States.

The availability of paraffin-embedded tumor sample diagnostic of glioblastoma is mandatory for entry into the study. Tumor samples will be evaluated for the EGFRvIII mutation and for EGFR gene amplification. Tissue from recurrent surgery is preferred, but tissue from initial surgery is sufficient for study entry. Baseline MRI is mandatory.

After completion of the screening assessments and confirmation of study eligibility by the Medical Monitor upon review of an inclusion package, tesevatinib will be orally administered to all patients at a dose of 300 mg once daily. A cycle will be considered as 28 days. Patients will be evaluated for efficacy according to the RANO criteria.

Patients who develop ≥ Grade 3 adverse event(s) considered by the investigator to be related to study drug (with the exceptions noted in Section 9.1.3) will have study treatment interrupted until the drug-related toxicities have resolved to ≤ Grade 1. Once toxicities have resolved to ≤ Grade 1, the patient may resume study treatment at a reduced dose of 250 mg/day. No more than one dose reduction is permitted. Patients who require more than one dose reduction will have study drug discontinued and enter the Follow-up Period.

Patients for whom toxicity persists beyond 21 days despite dose interruption may resume study treatment only with permission from the responsible Medical Monitor.

If study treatment is withheld, the patient should be instructed not to make up the withheld doses. Section 9.1.3 provides detailed instructions concerning dose interruptions and reductions.

Study treatment will continue until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death. Assessments for disease response will occur at week 4 and week 8 and then every 8 weeks thereafter using the RANO criteria (Appendix 2).

Upon treatment discontinuation, patients will be followed every 8 weeks for survival.

Tumor samples will be used for exploratory biomarker research including, but not limited to, evaluation of EGFRvIII expression by immunohistochemistry (IHC) or real-time Polymerase Chain Reaction (PCR). An appropriate definition and cutoff for EGFRvIII^{pos} tumors will be established, and outcome in this subpopulation will be evaluated in addition to the overall study population.

To characterize the safety and tolerability profile of tesevatinib, patients will be monitored throughout the study for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation. Patients will undergo safety evaluations, including PE, KPS, vital sign measurements, hematology, serum chemistry, urinalysis and ECG.

MRI will be used to evaluate the tumor at baseline. All MRIs taken on study patients will be submitted to the sponsor for possible retrospective analysis.

7.2. Discussion of Study Design

The single arm design assessing PFS-6 in the overall population with the ability to detect a rate of 25% is appropriate as a preliminary test of activity in patients with glioblastoma, based on PFS-6 rates seen in randomized studies with bevacizumab [Weathers 2015; Taal 2014; Galanis 2015]. The sample size of this study is also designed to permit the comparison of results with EGFR amplified and non-amplified tumors, as well as EGFRvIII mutated versus wild-type. The sample size is adequate to characterize the safety profile in patients with glioblastoma.

7.3. 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 patients' interests. 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 patients.
- Patient enrollment is unsatisfactory.
- Drug supply issues.
- Data recording is inaccurate or incomplete.
- Excessive patient self-withdrawal.
- Significant protocol deviations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis).

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 patients.
- Case Report Forms/Records. Electronic case report forms (eCRFs) will be used in this study. Records (including correction forms) for all enrolled patients 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).

8. STUDY POPULATION

8.1. Target Population

This study will be conducted in up to 40 patients with recurrent glioblastoma. Tumor samples will be evaluated for the EGFRvIII mutation and EGFR gene amplification.

8.2. Inclusion Criteria

Patients will be included if they meet the following criteria:

1. Willingness and ability to provide written informed consent and to comply with the study protocol as judged by the investigator.
2. Age ≥ 18 years old.
3. Karnofsky performance status ≥ 70% (see Appendix 1).
4. Stable or decreasing dose of corticosteroids within 5 days prior to study enrollment.
5. 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.
    - 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.
    - 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 6 months after their last dose of study drug. Effective birth control includes (a) 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.
6. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 5 above during the treatment period and for at least 6 months after the last dose of study drug.
7. Histologically confirmed glioblastoma. A local pathology report constitutes adequate documentation of histology for study inclusion. Patients with an initial diagnosis of a lower-grade glioma are eligible if a subsequent biopsy was determined to be glioblastoma.

8. First recurrence after concurrent or adjuvant chemoradiotherapy. Imaging confirmation of first tumor progression or regrowth as defined by the RANO criteria. A minimum of 12 weeks must have elapsed from the completion of radiotherapy to study entry to minimize the potential for MRI changes related to radiation necrosis that might be misdiagnosed as progression of disease, unless there is a new lesion outside the radiation field or unequivocal evidence of viable tumor on histopathological sampling.
9. Prior treatment with TMZ for low grade glioma or glioblastoma.
10. No more than one prior line of systemic treatment for glioblastoma. Concurrent and adjuvant TMZ-based chemotherapy, including the combination of TMZ with an investigational agent, is considered one line of therapy.
11. Prior therapy with gamma knife or other focal high-dose radiotherapy is allowed, but the patient must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field.
12. Recovery from the toxic effects of prior therapy, with a minimum time of:
    a. ≥ 28 days elapsed from the administration of any investigational agent
    b. ≥ 28 days elapsed from the administration of any prior cytotoxic agents, except ≥ 14 days from vincristine, ≥ 21 days from procarbazine, and ≥ 42 days from nitrosureas
    c. ≥ 14 days elapsed from administration of any non-cytotoxic agent (e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid)
13. Patients who have undergone recent surgery for recurrent or progressive tumor are eligible provided that:
    a. Surgery must have confirmed the recurrence
    b. There must be residual disease measurable per RANO criteria e.g. 1 cm x 1 cm
    c. A minimum of 28 days must have elapsed from the day of surgery to first dose of the study drug. For core or needle biopsy, a minimum of 7 days must have elapsed prior to study entry
14. Availability of formalin-fixed paraffin-embedded tumor tissue diagnostic of glioblastoma.

8.3. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Concurrent therapeutic intervention (including radiation therapy and NovoTTF).
2. Prior exposure to EGFR inhibitors.
3. Prior exposure to bevacizumab or other VEGF- or VEGF-receptor-targeted agent within 8 weeks of study start.
4. Prior treatment with prolifeprospan 20 with carmustine wafer.
5. Prior intracerebral agent.

6. Evidence of recent hemorrhage on baseline MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving hemorrhagic changes related to surgery, or presence of punctuate hemorrhage in the tumor are eligible.
7. Need for urgent palliative intervention for primary disease (e.g., rapidly increasing intracranial pressure, impending herniation, uncontrolled seizures).
8. ANC < 1.5 x10^9/L; platelet count < 100 x10^9/L; or Hb < 9.0 g/dL within 7 days prior to enrollment. Note: The use of transfusion or other intervention to achieve Hb ≥ 9 g/dL is acceptable.
9. Total bilirubin ≥ 1.5 x ULN (except in patients diagnosed with Gilbert's disease).
10. AST (SGOT), ALT (SGPT), or ALP ≥ 2.5 x ULN.
11. Serum creatinine > 1.5 x ULN.
12. Serum potassium or magnesium below lower limit of normal.
13. INR, PT, or APTT as follows unless on anticoagulation that is expected to alter coagulation test results:
    - INR > 1.5 or PT > 1.5 xULN or aPTT > 1.5 xULN
14. Known contraindication to MRI, such as cardiac pacemaker, shrapnel or ocular foreign body.
15. Used any prescription medication during the prior 2 weeks that the investigator judges is likely to interfere with the study or to pose an additional risk to the patient in participating, specifically inhibitors or inducers of cytochrome P450 (CYP)3A4 (refer to Appendix 4). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
16. Taking any drugs associated with torsades de pointes or known to moderately or severely prolong the QTc(F) interval (see Appendix 4).
17. 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. Patients with a history of atrial arrhythmias should be discussed with the Medical Monitor.
18. Uncontrolled diabetes, as evidenced by fasting serum glucose level >200 mg/dL.
19. NYHA Grade II or greater congestive cardiac failure.
20. Has marked prolongation of QTc(F) interval at screening or baseline (QTc[F] interval > 470 msec) using the Fridericia method of correction for heart rate.
21. History of myocardial infarction (within 12 months) or unstable angina (within 6 months) prior to study enrolment.
22. History of stroke or transient ischemic attacks within 6 months prior to study enrolment.

23. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to study enrolment.
24. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
25. History of intracranial abscess within 6 months prior to study enrolment.
26. History of another malignancy in the previous 3 years, with a disease-free interval of < 3 years Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible.
27. Evidence of any active infection requiring hospitalization or IV antibiotics within 2 weeks prior to study enrolment.
28. Known hypersensitivity to any excipients of tesevatinib.
29. Inability to swallow or absorb orally-administered medication.

8.4. Removal of Patients from Study

Withdrawal of a patient from the study means that no further study visits or procedures are performed and no further data are collected. Every reasonable effort will be made to keep the patient in the study; however, in the event that a patient 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/adverse events). Refer to Table 1 and

Table 2b: Schedule of Study Assessments for Subjects Completing 24 Cycles of Tesevatinib Treatment

Timepoint (Study Day)	Cycle 26 Day 1 (± 3d)	Cycle 28 Day 1 (± 3d)	Cycle 30 Day 1 (± 3d)	Cycle 32 Day 1 (± 3d)	Cycle 34 Day 1 (± 3d)	Cycle 36+ Day 1 (± 3d)	EOS Tx [i]	30-Day FU [j] (± 5d)	UNS [k]
Physical Examination [a]	X	X	X	X	X	X	X	X	X
Neurological Examination [b]	X	X	X	X	X	X			X
Vital Signs [c]	X	X	X	X	X	X	X	X	X
Safety Labs [d]	X	X	X	X	X	X	X	X	X
12-Lead ECG [e]	X	X	X	X	X	X	X		X
Disease Assessment [f]	X	X	X	X	X	X	X		X
Karnofsky performance status	X	X	X	X	X	X	X		X
Corticosteroid use	X	X	X	X	X	X	X		X
MRI tumor assessment	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Tesevatinib Dispensing [g]	X	X	X	X	X	X			X
AE Monitoringh	X	X	X	X	X	X	X		X

d = day; ECG = electrocardiogram; EOS = end of study; FU = follow-up; KPS = Karnofsky Performance Status; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; UNS = unscheduled; Tx = treatment

l: Abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

m: Neurological exam should include full cranial nerve central and peripheral, motor and sensory assessments.

n: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained with patient in sitting position.

o: To be drawn and analyzed locally. Safety labs = hematology and clinical chemistry. See Table 2b.

p: Supine 12-Lead ECGs will be performed at each visit.

q: The assessment should be performed every 8 weeks. Radiological assessment must be performed with a brain MRI scan and should be consistent throughout all visits.

r: Study drug should be dispensed and accounted for from previous visit.

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

t: The End-of-Study Drug Treatment visit is to occur as soon as possible after the patient'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.

u: The 30-Day Follow-Up visit should occur 30 days (±5 days) after the patients' 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. Assessments for the 30-day follow up may be done by telephone.

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

Table 3.

A termination eCRF must be completed for all enrolled patients.

The patient may be withdrawn from the study for any of the following reasons.

- Voluntary withdrawal by patient
- Patient lost to follow-up
- Termination of the study by sponsor
- Patient death

If a patient dies, Kadmon will actively seek to determine the date and cause of death.

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

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

8.5. Replacement of Patients in Study

Patients discontinued from the trial will not be replaced.

9. STUDY DRUG

9.1. Tesevatinib

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.

Patients will be provided with either a weekly or monthly supply of study drug and instructions for taking the study drug at home. Subjects who have completed 24 cycles of treatment without disease progression or unacceptable toxicity will receive a 2-month supply of tesevatinib at each bimonthly visit. 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:

Kadmon Corporation, LLC
KD019 Tablets 100-mg – 32 tablets/bottle
Lot Number: XXXXX.XXX ____bottles/box
Direction: Take as directed by physician
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
Caution: New Drug-Limited by Federal Law to Investigational Use 21 CFR 312.6(a).
Keep out of reach of children and pets.
Store at USP controlled room temperature of 20°-25°C (68°-77°F). Brief excursions permitted to 15°C-30°C (59°-86°F)
Kadmon Corporation, LLC New York, NY 10016 USA

Kadmon Corporation, LLC
KD019 Tablets 150-mg – 32 tablets/bottle
Lot Number: XXXXX.XXX ____bottles/box
Direction: Take as directed by physician
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
Caution: New Drug-Limited by Federal Law to Investigational Use 21 CFR 312.6(a).
Keep out of reach of children and pets.
Store at USP controlled room temperature of 20°-25°C (68°-77°F). Brief excursions permitted to 15°C-30°C (59°-86°F)
Kadmon Corporation, LLC New York, NY 10016 USA

9.1.1. Randomization and Blinding

This is an open-label, non-randomized study.

9.1.2. 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). Patients 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.

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

Patients will be treated with study drug until disease progression or unacceptable toxicity occurs.

Subjects who have completed 24 cycles of treatment without disease progression or unacceptable toxicity will be eligible to receive tesevatinib until disease progression or unacceptable toxicity occurs.

All patients also will be followed for a period of 30 days following their last dose of tesevatinib.

9.1.3. Dose Modifications and Delays for Toxicity Related to Study Drug

Patients who develop ≥ Grade 3 adverse event(s) considered by the investigator to be related to study drug (with the exceptions noted below) will have study treatment interrupted until all drug-related toxicities have resolved to ≤ Grade 1. Once these toxicities have resolved to ≤ Grade 1, the patient may resume study treatment at a reduced dose of 250 mg/day. No more than one dose reduction is permitted. Patients who require more than one dose reduction will have study drug discontinued and enter the Follow-up Period.

The exceptions are:

- asymptomatic Grade 3 elevations of amylase or lipase,
- Grade 3 elevation of alkaline phosphatase in a patient known to have bone metastases,
- Grade 3 elevation of glucose in a patient receiving systemic corticosteroids,
- Grade 3 creatine phosphokinase [CPK] elevation in the absence of muscle symptoms,
- Grade 3 sodium values ≥126 mmol/L in a patient with diarrhea)

Patients for whom toxicity persists beyond 21 days despite dose interruption may resume study treatment at a reduced dose of 250 mg/day only with permission from the responsible Medical Monitor.

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

Table 5: Dose Adjustments According to CTCAE Toxicity Grade for Related AEs

Occurrence	Grade 1	Grade 2	Grade 3	Grade 4
First appearance	No action with study drug • For diarrhea start loperamide, monitor for dehydration • For rash start topical steroids (see Section 9.1.4.2) • For QTc prolongation no action	No action with study drug • For diarrhea start/increase loperamide, monitor for dehydration • For rash topical steroids ± doxycycline (see Section 9.1.4.2) • For QTc check con-meds and electrolytes, correct as indicated • For confirmed pneumonitis interrupt and consult Medical Monitor	Interrupt treatment until resolved to Grade 0-1. If interruption < 21 days restart at 250 mg/day. If interruption ≥ 21 days, check with Medical Monitor. • In addition, for QTc check con-meds, electrolytes and consult Medical Monitor (see Section 9.1.4.3.1 for restarting and monitoring instructions). • For creatinine in absence of renal dysfunction no interruption.	Discontinue. Consult Medical Monitor if continuation is in patient's best interest. • In addition, for QTc hospitalize patient and perform cardiology evaluation (see Section 9.1.4.3.1) .
Second appearance			Discontinue study drug	Discontinue study drug

9.1.3.1. Requirements for Continuation of Treatment Post Cycle 1

Patients must fulfill the following criteria in order to commence a new cycle of treatment:

- all related ≥ Grade 3 AEs have resolved to ≤ Grade 1
- serum potassium and magnesium above the lower limit of normal
- no arrhythmias, pathologic bradycardia, or associated symptomology
- QTcF ≤ 470 msec and increase from baseline ≤ 60 msec unless Medical Monitor has given permission to continue
- no concurrent medications that prolong QTc (see Appendix 4)
- no evidence of progressive disease
- no additional therapeutic interventions for glioblastoma
- no strong inhibitors or inducers of CYP3A4, CYP2C8, CYP2D6 or CYP1A2 (see Appendix 4)

9.1.3.2. Study Drug Discontinuation

Withdrawal of a patient from study treatment means that no further tesevatinib is administered but the remaining study visits or procedures are performed and follow-up data are collected.

A patient's study drug may be prematurely discontinued for any of the following reasons:

- Progression of disease
- An AE requires permanent discontinuation of study drug
- Voluntary withdrawal by patient
- Protocol deviation
- Patient lost to follow-up
- Patient death
- Termination of study by sponsor

Patients that have study drug discontinued due to toxicity are to be followed until there is either:

- Resolution or stabilization to baseline or Grade 1
- The patient is lost to follow-up
- The event is otherwise explained

9.1.4. Management of Adverse Events of Special Interest

AEs of special interest include the following: diarrhea, skin rash, QTc(F) prolongation, elevated serum creatinine, elevated serum amylase and ILD. Unless otherwise specified, study drug may be held for up to 21 days at the discretion of the investigator.

9.1.4.1. Diarrhea

Diarrhea should be managed with loperamide. On first occurrence of Grade 1 diarrhea initiate loperamide and monitor patient's electrolytes and hydration status. Patients with severe diarrhea who are unresponsive to loperamide or other anti-diarrheals or who become dehydrated require interruption of study drug until resolution to ≤ Grade 1 in severity. If Grade 4 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 interrupted, and appropriate measures should be taken to rehydrate the patient intensively via intravenous fluid administration. In addition, renal function and serum electrolytes, including potassium and magnesium, should be monitored in patients at risk of dehydration.

9.1.4.2. Skin Rash

Skin rash should be managed according to locally accepted clinical recommendations. Study drug may be held up to 21 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:

- Patient 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 5 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 5 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 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 100 mg 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.

9.1.4.3. QT Interval Prolongation

Patients 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 and may require additional monitoring or adjustment if patients develop diarrhea. Medications with potential for QTc(F) prolongation should not be used concurrently or started within 24 hours of tesevatinib administration (see Appendix 4).

9.1.4.3.1. Management of QTc(F) Interval Prolongation

The following guidelines should be used in the management of QTc(F) prolongation. Patients will have ECGs performed at times designated by the protocol (refer to Table 1).

Grade 2 QTc(F) Prolongation:

If the QTc(F) interval increases to an absolute value of ≥ 60 msec above baseline (predose on Day 1) but < 500 msec and the patient 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 the Medical Monitor for discontinuation of any medication found.
- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated.

Grade 3 QTc(F) Prolongation:

If the QTc(F) interval increases to an absolute value of ≥ 500 msec at any evaluation and if the patient 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
- Contact Medical Monitor to discuss appropriate management
- **QTc(F)**: When QTc(F) is within 30 msec of baseline 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.

Grade 4 QTc(F) Prolongation:

If the QTc(F) interval increases to an absolute value of ≥ 500 msec at any evaluation, and if the patient 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:

- The patient should be hospitalized and undergo a thorough cardiology evaluation
- Do not dose with study drug again
- Consult with Medical Monitor
- 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 baseline 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 patient has objective tumor response, consideration will be given to continuing treatment with tesevatinib at a reduced dose after discussion with the Medical Monitor.

9.1.4.4. Elevated Serum Creatinine

Patients 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. Dose interruptions and reductions are not necessary in the absence of renal dysfunction.

9.1.4.5. Elevated Serum Amylase

In the event of asymptomatic increase of serum amylase to > 1.5 × ULN, lipase, fasting triglycerides, and amylase isoenzymes should be monitored. Treatment should only be interrupted if clinical pancreatitis develops, corresponding to Grade 3 CTCAE per Table 5.

9.1.4.6. Interstitial Lung Disease

New or worsening respiratory symptoms suspicious of pneumonitis in patients in the study should be evaluated with high-resolution CT of the chest to determine whether ILD is present. Tesevatinib should be discontinued if interstitial lung disease is suspected, and further management discussed with the Medical Monitor.

9.2. Study Drug Accountability and Patient Treatment Compliance

Drug accountability and patient treatment compliance will be assessed using drug dispensing and return records, and the patient's study diary. 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 patient dispensing records and returned study product documentation. Dispensing records will document quantities received from Kadmon and quantities dispensed to patients, including lot number, date dispensed, patient identification number, patient 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.

9.3. Concomitant Medication and Treatment

If the patient 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.

Patients should avoid ingesting grapefruit, pomelo or Seville orange fruits (and juice) with tesevatinib or at any time during the study. Patients should not take medications that are associated with a risk of QTc interval prolongation and/or torsades de pointes. Additionally, patients are not permitted to take concomitant medications that strongly 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 (see Appendix 4).

Other prohibited treatments include the following:

- Other investigational drugs
- Concurrent anti-tumor therapies such as chemotherapy, gene therapy, biologics, radiation therapy, or other immunotherapy
- Warfarin or other anti-coagulant drugs (Low dose low molecular weight heparin given for deep vein thrombosis (DVT) prophylaxis is allowed)
- 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.

9.3.1. Additional Therapy

A patient should not receive additional therapeutic treatment for glioblastoma during the study period.

9.3.2. Additional Anti-Cancer Treatment and Radiotherapy

Patients should not receive additional therapeutic anti-cancer treatment until after PD has been documented on study and End of Treatment study assessments have been completed. If a patient requires additional anti-cancer treatment, study treatment will be discontinued and the patient will enter the Post-Treatment Period and followed every 8 weeks by phone call.

9.3.3. Interaction of Tesevatinib with Other Medications

Cytochrome P4503A4 is the major metabolic pathway of tesevatinib in humans. This suggests the potential for other drugs to significantly affect the biotransformation of tesevatinib in humans through drug-drug interactions. There is also a moderate potential to inhibit CYP2C8, CYP2D6 and CYP1A2 although this is most likely to occur at higher concentrations than those expected in this study.

Due to these interactions and potential interactions, inhibitors and inducers of CYP3A4, CYP2C8, CYP2D6, and CYP1A2 should be avoided if a substitute is available or otherwise used with caution in all patients while receiving study drug. In addition, patients must be closely monitored for the desired drug effect and potential AE.

Substrates of isoenzymes CYP3A4, CYP2C8, CPY2D6 and CYP1A2 may be used with appropriate clinical monitoring.

See Appendix 4 for a list of drugs that are clinically relevant inhibitors and inducers of CYP3A4, CYP2C8, CYP2D6, and CYP1A2.

9.3.3.1. Management of Patients Requiring Concomitant Medications Associated with QT Interval Prolongation

Tesevatinib has been associated with prolongation of the QT interval. Patients requiring treatment with drugs known to be associated with torsades de pointes or significant QT interval prolongation may not be enrolled into this study (see Appendix 4).

Drugs associated with QT interval prolongation should be avoided in patients receiving study drug unless deemed clinically necessary. Should a patient 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.

As of Amendment 4 this will not be applicable—During long-term follow-up, patients 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 held until the concomitant treatment course is complete. The decision about whether the patient can continue on trial following this interruption will be determined by the Medical Monitor.

During long-term follow-up, patients 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 interval from these 3 ECGs is > 60 msec above the average baseline (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 interval is no more than 60 msec above baseline 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 interval prolongation should be managed as noted in Section 9.1.4.3.

10. EFFICACY ASSESSMENTS

Disease assessments will be based on the RANO criteria [Wen 2010] and will comprise radiological assessments (MRI), clinical assessments (KPS), and corticosteroid use. Based on radiological assessments, clinical status, and corticosteroid use, an overall evaluation of CR, PR, SD, or PD should be made at each disease assessment after baseline according to the RANO criteria (Appendix 2).

Disease assessment during the screening period is to be performed within 7 days before study drug administration and must be used as the baseline radiological assessment. Per the study's schedule of assessments (see Table 1), disease assessment is intended to be done prior to starting cycle 2, 3, 5, 7+. The corticosteroid dose should be kept stable for 5 days prior to the MRI scan. During the study, disease assessments should be performed at week 4 and week 8 after the date of first study treatment and then every 8 weeks (at Week 16, 24, etc.), regardless of treatment delays. For patients who discontinue treatment for other reasons than PD, disease assessment in the follow-up period should continue every 8 weeks (according to the original schedule) until disease progression. For patients with PD, disease assessment at the EOS is only required if not performed within the previous 8 weeks.

Disease assessments as initially planned according to the schedule of assessments should be maintained regardless of treatment delays. Unscheduled disease assessments may be performed at the discretion of the investigator to allow a decision on further study treatment administration for individual patients. For patients who discontinue treatment for reasons other than progressive disease, disease assessment in the follow-up period should continue every 8 weeks (according to the original schedule) until disease progression.

10.1. Radiological Assessment by Brain MRI

The acquisition protocol for MRI (provided as a separate document) will provide further details for scan standardization. All efforts should be made to perform MRI scans according to the corresponding specification in order to ensure that quality of MRI will be standardized among all sites. Consistency of subsequent MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions. Patients should be imaged on the same MRI scanner for the duration of the study. A 1.5T or 3T scanner must be used for this study. The use of IV contrast should, as long as clinically possible, be kept consistent.

The following sequences of the entire brain must be acquired:

- T1 pre-gadolinium
- T2/FLAIR
- T1 post-gadolinium

Target Lesions: Lesions should be measured on the greatest size (bi-dimensional measurement of the longest cross-sectional diameters) observed either on axial, coronal, or sagittal slices, and the most representative observed chosen to be followed for response evaluation (i.e., once selected at baseline, the plane should be maintained across the study, to allow comparison). If there are

multiple contrast- enhancing lesions, a minimum of two of the largest lesions, and a maximum of five lesions, should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected. For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.

Nontarget Lesions: All other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression.

Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible.

A radiological assessment of complete response (CR) or partial response (PR) requires confirmatory imaging at least 4 weeks after the initial assessment of response was observed. **In the event that the radiographic changes are equivocal and it is unclear whether the patient has stable or progressive disease, treatment should be continued and the patient should be closely observed.** If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which disease progression was first suspected.

Sites should save all MRI images as DICOM files or other standard format with unique descriptive file names (e.g. study number, patient initials and number, date and image sequence number) on to anonymized DVD(s) and provide these to the Sponsor upon request.

10.2. Clinical Status by Karnofsky Performance

Clinical deterioration is defined as a decline in the Karnofsky performance status (Appendix 1) from 100% or 90% to ≤ 70%; a decline of ≥ 20% from 80% or less; or a decline from any baseline value to 50% or less, for at least 7 days, unless attributable to comorbid events (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.). Clinical status must be recorded as Improved, Stable, or Worsened.

10.3. Corticosteroid Dose

At the time of each disease assessment, the corticosteroid intake will be compared with corticosteroid intake at the time of the last disease assessment. The changes will be recorded as Increased, Unchanged, or Decreased. Increases or decreases in corticosteroid dose should be clinically justified.

Note: Increases in corticosteroid dose for reasons other than disease control do not need to be taken into consideration when making this comparison.

10.4. Overall Disease Assessment

Based on radiological assessments, clinical status, and corticosteroid use, an overall evaluation of CR, PR, SD, or PD should be made at each disease assessment after baseline according to the RANO criteria (Appendix 2).

11. SAFETY

11.1. Safety Parameters

The NCI-CTCAE; Version 4.03 will be used for grading toxicities unless otherwise specified. Patients 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 Karnofsky performance status.

11.2. Adverse Event Definition

An adverse event (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 patient is hospitalized for observation.

11.3. 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.

11.3.1. 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 adverse event 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 patient 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 patient 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 patient 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)

11.3.2. Suspected Unexpected Serious Adverse Reactions (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.

11.3.3. 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.

11.3.4. Non-Serious Adverse Events

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

11.3.5. 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 patient 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.

11.3.6. Relationships/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).

11.3.7. Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the patient'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).

11.3.8. Adverse Event Monitoring and Follow-up

The investigator will follow all patients who experience adverse events until there is a return to the patient'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.

11.3.9. Laboratory and ECG Abnormalities

For the purposes of grading creatinine, the upper limit of normal – not the patient's baseline 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 patient'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 patient 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 patient experiences a serious toxicity or dies, the FDA will be notified within 24 hours, as required.

11.3.10. Pregnancy

If any patient becomes pregnant following the first dose of tesevatinib, the patient 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.

11.3.11. Serious Adverse Event Reporting

11.3.11.1. Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) as well as all other participating investigators of the event.

Under FDA ruling (US Code of Federal Regulations, 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.

11.3.11.2. Time-Frame for Reporting

Any death, pregnancy, or SAE experienced by a patient 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: 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
Kadmon Corporation
55 Cambridge Parkway
Cambridge, MA 02142
Phone: 857-253-8642
E-mail: sanjay.aggarwal@kadmon.com

11.3.11.3. 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, patient 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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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.

11.3.12. 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.

11.3.13. 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.

11.4. Other Safety Considerations

11.4.1. 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 patient is hospitalized for observation, will not constitute an AE but will be recorded as a protocol deviation.

11.4.2. 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.

11.5. Safety Monitoring

Patients will be closely monitored for adverse events of interest and potential drug-drug interactions through standard safety reporting as well as a regular medical review of safety data outputs from both the clinical and pharmacovigilance databases. Particular attention will be paid to the success of diarrhea and rash management strategies and the use of concomitant medications which have a risk of drug-drug interaction or QTc prolongation. SAEs, including deaths, and withdrawals due to adverse events will also be closely monitored. A central laboratory will be used to monitor for QTc prolongation, and any study drug reintroduction in the case of QTc prolongation will only be performed with the agreement of the Medical Monitor.

A Data Monitoring Committee will not be used for this study.

12. 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 patient takes the first dose of study drug, with subsequent study days numbered sequentially thereafter.

If significant changes from baseline 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).

12.1. Procedures to be Performed

12.1.1. Informed Consent

All patients must take part in the informed consent process. Adequate time must be allowed for the patient 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 patient has signed and dated an IRB/IEC-approved ICF.

12.1.2. Demographics and Medical History

A complete medical history will be taken. Medical history includes clinically significant diseases, surgeries, history of glioblastoma (including date of diagnosis, history of prior low-grade astrocytoma, location of disease, prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to randomization.

Demographic data will include age, sex, and self-reported race/ethnicity.

12.1.3. Complete and Abbreviated 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 pulse, lungs, abdomen (liver/spleen), kidneys, and neurological (symptom directed only). Interval history should be recorded at all study visits.

12.1.4. Detailed Neurological Examination

Neurological exam should include full cranial nerve central and peripheral, motor and sensory assessments.

12.1.5. Vital Sign Measurements

Vital sign measurements will be collected after the patient 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 the appropriate technique (per guidelines of the American Heart Association). Specifically, patients 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 patient's position (if not seated).

12.1.6. Hematology andSerum Chemistries.

Samples for laboratory assessments (hematology andserum chemistries) are to be collected. A Local laboratory will perform hematology andserum chemistry tests and results will be provided to the investigator. Blood and urine samples for hematology, serum chemistry will be prepared using standard procedures. Laboratory panels are defined as listed in

Table 2b: Schedule of Study Assessments for Subjects Completing 24 Cycles of Tesevatinib Treatment

Timepoint (Study Day)	Cycle 26 Day 1 (± 3d)	Cycle 28 Day 1 (± 3d)	Cycle 30 Day 1 (± 3d)	Cycle 32 Day 1 (± 3d)	Cycle 34 Day 1 (± 3d)	Cycle 36+ Day 1 (± 3d)	EOS Tx [i]	30-Day FU [j] (± 5d)	UNS [k]
Physical Examination [a]	X	X	X	X	X	X	X	X	X
Neurological Examination [b]	X	X	X	X	X	X			X
Vital Signs [c]	X	X	X	X	X	X	X	X	X
Safety Labs [d]	X	X	X	X	X	X	X	X	X
12-Lead ECG [e]	X	X	X	X	X	X	X		X
Disease Assessment [f]	X	X	X	X	X	X	X		X
Karnofsky performance status	X	X	X	X	X	X	X		X
Corticosteroid use	X	X	X	X	X	X	X		X
MRI tumor assessment	X	X	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Tesevatinib Dispensing [g]	X	X	X	X	X	X			X
AE Monitoringh	X	X	X	X	X	X	X		X

d = day; ECG = electrocardiogram; EOS = end of study; FU = follow-up; KPS = Karnofsky Performance Status; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; UNS = unscheduled; Tx = treatment

w: Abbreviated PE is acceptable (to be completed in a targeted manner covering related body systems).

x: Neurological exam should include full cranial nerve central and peripheral, motor and sensory assessments.

y: Vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature) to be obtained with patient in sitting position.

z: To be drawn and analyzed locally. Safety labs = hematology and clinical chemistry. See Table 2b.

aa: Supine 12-Lead ECGs will be performed at each visit.

bb: The assessment should be performed every 8 weeks. Radiological assessment must be performed with a brain MRI scan and should be consistent throughout all visits.

cc: Study drug should be dispensed and accounted for from previous visit.

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

ee: The End-of-Study Drug Treatment visit is to occur as soon as possible after the patient'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.

ff: The 30-Day Follow-Up visit should occur 30 days (±5 days) after the patients' 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. Assessments for the 30-day follow up may be done by telephone.

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

Table 3. 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 2 with the exception of Cystatin C.

Subjects who have completed 24 cycles of treatment without disease progression or unacceptable toxicity will have safety laboratory assessments collected at each bi-monthly visit. The local laboratory will perform hematology and serum chemistry tests. Laboratory panels are defined as listed in Table 2b.

Abnormalities in clinical laboratory tests that lead to a change in patient 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 11.3).

12.1.7. Pregnancy Test

Urine pregnancy tests are to be performed for females of childbearing potential. Positive urine tests are to be confirmed by a serum test.

12.1.8. Tumor Samples

The availability of paraffin-embedded tumor sample diagnostic of glioblastoma is mandatory for entry into the study. **Samples from the original tumor and any subsequent biopsies will be required.** Tissue from recurrent surgery is preferred, but tissue from initial surgery is sufficient for study entry.

Twenty (20) slides cut as recently as possible and sections must contain adequate tumor. See the study laboratory manual for definition of adequate tumor sample.

If the archival tissue is neither sufficient nor available, the patient may still be eligible, upon discussion with the Medical Monitor, with the assumption that the patient:

- Can provide sufficient tissue; OR
- Is willing to consent to and undergo a pre-treatment biopsy of the tumor

A detailed description of tissue quality requirements and procedures for collection, handling, preparation and shipping of the samples to the central laboratory will be provided in a separate laboratory manual.

For enrolled patients, part of the available tumor tissue from the tissue submitted will be used to assess EGFRvIII mutation and for EGFR gene amplification biomarkers. Other tissue assessments may include testing of protein expression, activation status, somatic mutations, and other exploratory markers related to tesevatimib and to glioblastoma biology. These assessments will be performed by the Sponsor, at a Sponsor-selected vendor. The remaining tumor tissue block will be returned to the site.

12.1.9. 12-Lead Electrocardiogram (ECG)

Supine 12-Lead ECGs will be performed at screening; predose, and once within 4 – 8 hours postdose on Days 1 and 15 of Cycle 1; pre-dose on Day 1 of Cycles 2 and beyond; and at the End of Study Drug Treatment visit. ECGs will be read by a central laboratory.

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 central ECG laboratory vendor. 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. Although ECGs will be read by a central laboratory, sites should take action if clinically significant abnormalities are detected at time of ECG.

Subjects who have completed 24 cycles of treatment without disease progression or unacceptable toxicity will have ECG assessments performed at each bi-monthly visit. These ECG assessments will be performed locally and read by qualified site personnel.

Prior to enrollment, all patients must demonstrate an average screening QTc(F) value of $\leq$ 470 msec by central digital analysis. Immediate clinical management of patients 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 baseline or to the level of $\geq$ 500 msec requires further monitoring. After discussion with the Medical Monitor (if $\geq$ 500 msec) on appropriate management, the patient may be removed from the trial (see guidelines in Section 9.1.4.3.1).

Abnormalities in the ECG that lead to a change in patient 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 abnormalities meet criteria defining them as serious, they must be reported as SAE (see Section 11.3).

12.1.10. Disease and Response Assessments

Disease assessments will be based on the RANO criteria [Wen 2010] and will comprise radiological assessments (MRI), clinical assessments (KPS), and corticosteroid use. Based on radiological assessments, clinical status, and corticosteroid use, an overall evaluation of CR, PR, SD, or PD should be made at each disease assessment (see Section 10) after baseline according to the RANO criteria (Appendix 2).

Disease assessment during the screening period is to be performed within 7 days before study drug administration and must be used as the baseline radiological assessment. Per the study's schedule of assessments (see Table 1), disease assessment is intended to be done prior to starting cycle 2, 3, 5, 7+. The corticosteroid dose should be kept stable for 5 days prior to the MRI scan. During the study, disease assessments should be performed at week 4 and week 8 after the date of first study treatment and then every 8 weeks thereafter (at Week 16, 24, etc.), regardless of treatment delays. For patients who discontinue treatment for other reasons than PD, disease assessment in the follow-up period should continue every 8 weeks (according to the original schedule) until disease progression. For patients with PD, disease assessment at the EOS is only required if not performed within the previous 8 weeks.

Disease assessments as initially planned according to the schedule of assessments should be maintained regardless of treatment delays. Unscheduled disease assessments may be performed at the discretion of the investigator to allow a decision on further study treatment administration for individual patients. For patients who discontinue treatment for reasons other than progressive disease, disease assessment in the follow-up period should continue every 8 weeks (according to the original schedule) until disease progression.

12.1.11. 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 patient-specific rationale to take it regularly at a different time of day) and can be administered without regard to food intake.

12.1.12. Patient Reported Outcomes (MDASI-BT)

PROs of disease- and treatment-related symptom severity and symptom interference will be assessed using the MDASI-BT questionnaire.

The MDASI is a validated and reliable self-report measure that was developed to assess symptom severity and interference [Cleeland 2000; Armstrong 2006].

Thirteen items ask patients to rate how severe the symptoms were when "at their worst" in the last 24 hours with regard to pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. The MDASI-BT (see Appendix 3) contains an additional nine items that assess symptoms and concerns specific to primary brain tumor patients (difficulty understanding, difficulty speaking, difficulty concentrating, seizures, weakness, change in appearance, change in vision, change in bowel patterns, irritability), for a total of 28 items.

All patients will complete the self-administered questionnaire pre-dose on Day 1 of Cycles 1 and 2; every 8 weeks after enrollment (i.e., coinciding with the schedule of disease assessments); and

at the End of Study Drug Treatment visit (EOS). Additionally, patients who discontinue study treatment for reasons other than disease progression will complete the questionnaire every 8 weeks during follow-up until the time of documented disease progression. The questionnaire will take patients ~5–10 minutes to complete. Patients must complete the questionnaire prior to any other tests or assessments and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site.

Subjects who have completed 24 cycles of treatment without disease progression or unacceptable toxicity will not be required to complete the MDASI-BT questionnaire at subsequent bi-monthly visits.

12.1.13. Tesevatinib Plasma Concentrations

Blood samples will be drawn to evaluate tesevatinib plasma concentrations. Plasma samples for tesevatinib concentration analysis will be drawn predose of tesevatinib on Days 15 of Cycle 1; and predose of tesevatinib on Day 1 of every subsequent cycle (up to cycle 6). Data from these samples will contribute to a population PK analysis, and will be used to explore exposure-response relationships.

12.1.14. Pharmacodynamics

The tumor tissues submitted should be a formalin-fixed, paraffin-embedded tumor specimen that enables the definitive diagnosis of glioblastoma and determination of EGFR status, to permit stratification for the purposes of the efficacy analyses.

A tissue block (preferred) or 20 serial, freshly cut, unstained slides accompanied by an associated pathology report is required for participation in this study. Tissue quality and adequate viable tumor cell content are specified in the accompanying lab manual.

Cytological samples are not acceptable.

For enrolled patients, part of the available tumor tissue from the tissue submitted will be used to assess exploratory biomarkers. Tissue assessments may include testing of protein expression, activation status, somatic mutations, and/or gene amplification of EGFR, and other exploratory markers related to tesevatinib and to glioblastoma biology. These assessments will be performed by the Sponsor, at a central laboratory, or by a Sponsor-selected vendor. The remaining tumor tissue block will be returned to the site.

12.1.15. Prior and Concomitant Medications

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

12.1.16. Adverse Event Assessments

Information regarding the occurrence of AEs and SAEs will be collected from the time the patient signs the informed consent form throughout their participation in the study, including a period of 30 days after the patient'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 patient's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor.

12.1.17. Study Diary

Patients 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.

12.2. Schedule of Visits

12.2.1. Screening Visit

At the screening visit (Day -22 to -1), information will be collected and patients will have clinical evaluations as follows:

- Informed consent
- Medical history
- Demographics
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Neurological examination
- Tumor sample; original tumor and any subsequent biopsies required
- Inclusion/exclusion criteria
- Complete physical examination, including height and weight
- Hematology, cystatin-C, serum chemistry, coagulation, and urinalysis
- Urine pregnancy test, if applicable. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Positive results are to be confirmed with serum 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)
- Disease assessment (MRI, clinical status, and corticosteroid use) - within 7 days before study drug administration
- Baseline AE assessment
- Baseline concomitant medications

12.2.2. Cycle 1; Day 1

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

- Vital sign measurements (predose and 1 and 4 hours postdose) (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination, including weight
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis) (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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
- Completion of PRO – MDASI-BT
- Concomitant medications
- AE assessment
- Issue study drug diary
- Dispense study drug

12.2.3. Cycle 1; Day 15

At the Cycle 1, Day 15 visit (± 3 days), the following evaluations will be performed:

- Vital sign measurements (predose and 1 and 4 hours postdose) (sitting blood pressure, heart rate, respiratory rate, temperature)
- Limited physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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
- Plasma sample predose for tesevatinib concentration

- Concomitant medications
- AE assessment

12.2.4. Cycle 2; Day 1

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Completion of PRO – MDASI-BT
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)
- Tesevatinib administration
- Plasma sample predose for tesevatinib concentration
- Concomitant medications
- AE assessment
- Issue study drug diary
- Dispense study drug

12.2.5. Cycle 3; Day 1

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)

- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Neurological examination
- Plasma sample predose for tesevatinib concentration
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)
- Tesevatinib administration
- PRO – MDASI-BT
- Concomitant medications
- AE assessment
- Collect/Issue study drug diary
- Dispense study drug

12.2.6. Cycle 4; Day 1

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Plasma sample predose for tesevatinib concentration
- Tesevatinib administration
- Concomitant medications
- AE assessment

- Collect/Issue study drug diary
- Dispense study drug

12.2.7. Cycle 5; Day 1

At the Cycle 5, Day 1 visit (± 3 days), the following procedures and evaluations will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Neurological examination
- Plasma sample predose for tesevatinib concentration
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)
- Tesevatinib administration
- PRO – MDASI-BT
- Concomitant medications
- AE assessment
- Collect/Issue study drug diary
- Dispense study drug

12.2.8. Cycle 6; Day 1

At the Cycle 6, Day 1 visit (± 3 days), the following procedures and evaluations will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination

- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Plasma sample predose for tesevatinib concentration
- Tesevatinib administration
- Concomitant medications
- AE assessment
- Collect/Issue study drug diary
- Dispense study drug

12.2.9. Cycle 7-24; Day 1

At the Cycle 7+, Day 1 visit (± 3 days), the following procedures and evaluations will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Neurological examination
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)
- Tesevatinib administration
- PRO – MDASI-BT
- Concomitant medications
- AE assessment

- Collect/Issue study drug diary
- Dispense study drug

12.2.10. Cycle 26+; Day 1

At the Cycle 26+, Day 1 visit (± 3 days), the following procedures and evaluations will be performed:

- **Limited physical examination**
- **Neurological examination**
- **Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)**
- **Clinical laboratory tests (hematology and serum chemistry panel**
- **12-Lead ECG**
- **Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)**
- **Karnofsky performance status**
- **Concomitant medications**
- **Tesevatinib dispensing**
- **AE assessment**

12.2.11. 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 evaluation will be performed:

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

12.2.12. End-of-Study Drug Treatment Visit (EOS)

As soon as possible after the last dose of study drug, patients are to return to the study site to complete all end-of-study drug treatment assessments as described below. This may occur at the visit at which disease progression is diagnosed.

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)

- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (to be performed predose, and 4 - 8 hours postdose 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])
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment) if not done within the previous 8 weeks. If PD was not observed prior to the EOS visit, disease assessments should be performed until PD.
- PRO – MDASI-BT
- Concomitant medications
- AE assessment
- Collect study drug diary
- Collect study drug

12.2.13. 30-Day Follow-up

The 30-Day Follow-Up should occur 30 days (± 5 days) after the patients' 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.

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination
- Clinical laboratory tests (hematology, cystatin-C, serum chemistry panel and urinalysis)
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Concomitant medications
- If PD was not observed prior to the 30-day follow-up visit, disease assessments should be performed until PD.
- AE assessment

12.2.14. Follow-up Phone Contact

Beginning 8 weeks after the 30-Day Follow-Up Visit, patients are to be contacted by telephone every 8 weeks to assess survival status and any subsequent anti-cancer treatment. If PD was not observed before the 30-day follow-up period patients will need to return for follow-up MRI until PD is demonstrated or they start a new anti-cancer treatment. In the case of a patient receiving a new anti-cancer treatment in the absence of PD, the date of the most recent MRI will be used as the date of PD.

12.2.15. Unscheduled Visits: To Occur as Needed

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, temperature)
- Complete physical examination, including weight
- Hematology, cystatin-C, serum chemistry and urinalysis
- Urine pregnancy test, if applicable. Positive results are to be confirmed with serum testing.
- Supine 12-Lead ECG (repeat three times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs].
- Disease assessment (MRI, clinical status, corticosteroid use and overall disease assessment)
- Tesevatinib administration (if appropriate)
- AE assessment
- Concomitant medications
- Perform drug accountability, review patient diary, and collect old and dispense new study drug (if appropriate)

13. STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available SAS statistical software or the most recently released and available version of R, unless otherwise noted.

Additional statistical details will be provided in a prospective statistical analysis plan (SAP).

13.1. General Design

This is an open-label phase 2, multicenter study of tesevatinib monotherapy in patients with recurrent glioblastoma.

13.2. Sample Size Justification

This phase 2 trial is designed primarily to allow a preliminary assessment of the efficacy and safety of tesevatinib in the overall population of 40 patients with recurrent glioblastoma as well as to permit exploratory comparisons between predefined subgroups (by EGFRvIII mutation status and by EGFR gene amplification status). The target PFS-6 rate in the overall study population is 25%. PFS-6 rates seen in randomized studies with bevacizumab [Weathers 2015; Taal 2014; Galanis 2015] are of the order of 15-18%. Bevacizumab is registered in this indication.

With a sample size of 40 patients in the overall population, PFS-6 = 25% and median PFS-6 = 4.5 months, the trial has 95% power of having an estimated PFS-6 >15%. Addressing uncertainty by the lower 90% confidence limit of the estimated PFS-6 – corresponding to a one-sided test on 5% significance level, the trial has 95% power to show a significant difference above 7% and 80% power to show a significant difference above 10%.

The power calculation is based on simulations in the Weibull distribution to describe the progression and survival times. The median PFS and the PFS-6 and the corresponding shape and scale parameters from the Weibull distribution are shown in Table 6 below.

Table 6: Median PFS and PFS-6 Distributions

	Median PFS (months)	6 month PFS	Weibull shape parameter	Weibull scale parameter
Overall population	4.5	25%	5.24	2.41

For the trial outcome, two subpopulations (A and B) are defined in Table 7.

Table 7: Assumptions for Distribution of EGFR Subpopulations

Subpopulation	Description	Assumed proportion of subjects
A	Patients with an assumed beneficial mutation (EGFR gene amplified glioblastoma)	57%
B	Patients with an assumed beneficial mutation (EGFRvIII^{pos} glioblastoma)	27%

The trial is not stratified to include a specific proportion of patients with the EGFR gene mutations and is not powered to show significant differences for the secondary endpoints that estimate differences in PFS-6 for the two subgroups compared to patients without the EGFR gene mutations.

13.3. Interim Analysis

An interim analysis is included with the possibility to stop for futility. The stopping rule is based on an unacceptable PFS-6 rate of 5% and a desirable PFS-6 rate of 20% or more. The trial will continue after the interim analysis if more than 1 responder is seen in 21 patients giving a 72% probability of stopping if the PFS-6 rate is ≤5%.

13.4. Statistical Considerations

For categorical variables, the number and percent of each category within a parameter will be calculated for observed data only. 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.

13.4.1. Study Populations

Adult patients with recurrent glioblastoma with availability of paraffin-embedded tumor samples diagnostic of glioblastoma will be enrolled.

Two subgroups of patients are defined as having: EGFRvIII^{pos} and EGFR amplification^{pos} tumors.

Primary and secondary efficacy analyses will include all patients who were included in the study. The same analysis methods for the primary and secondary analyses will be applied to both the ITT population and the EGFRvIII^{pos} and EGFR gene amplification^{pos} population.

Safety analyses will include all patients who enrolled and received at least one dose of study treatment (the safety population).

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

Patients 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.

For statistical purposes completion of the study will be defined as six months after the last patient starts study treatment.

The plasma concentration analysis population will consist of all patients who receive at least one dose of tesevatinib, and who have at least one sample analyzed for plasma concentrations.

13.4.2. Patient Accountability, Demographics, and Baseline Characteristics

Patient disposition, demographic information and baseline characteristics will be tabulated for the overall population as well as by subgroups. Minimal data for screen failures, pertaining to why they failed to qualify to enroll will also be collected and listed.

13.4.3. Tesevatinib Exposure

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

13.4.4. Concomitant Medications

Concomitant medications will be coded using the current WHO Drug Dictionary and the data will be summarized and presented in tables and listings.

13.4.5. Plasma Concentrations

Plasma samples for tesevatinib concentration analysis will be drawn predose of tesevatinib on Day 15 of Cycle 1; and predose of tesevatinib on Day 1 of every subsequent cycle (up to cycle 6). Due to the sparse number of time points data are summarized using descriptive statistics by time points, systemic steroid treatment and subgroup.

These data, pooled with data from other studies, may be analyzed in a population PK analysis using nonlinear mixed effects modeling.

13.4.6. Efficacy/Activity

13.4.6.1. Primary efficacy endpoint

Progression-Free Survival at 6 months (PFS-6).

PFS is defined as the time between date of first dose and the date of first documented disease progression or death, whichever occurs first. The PFS-6 is defined as a patient being alive and progression free at 6 months (24 weeks). Disease progression will be determined based on investigator assessment with use of radiological assessments, clinical status, and corticosteroid

use. The specific criteria for disease progression is defined in Appendix 2. Patients without a date of disease progression or death will be analyzed as censored observations on the date of the last disease assessment; if no post-baseline disease assessment is available, PFS will be censored at the date of 1st dose.

The analysis of the primary endpoint and the estimation of PFS-6 is performed with a Cox model. Karnofsky performance status is included as a covariate. Study center is included as a random effect assumed to follow a gamma distribution. Thus, this is a shared Cox gamma frailty model. The model is used to estimate PFS-6 with 2-sided 95% and 90% confidence intervals.

Furthermore, Kaplan-Meier methodology will be used to estimate median PFS with 95% CI and the Kaplan-Meier curve will be constructed to provide a visual description of the PFS over time.

Descriptive statistics overall and for each parameter (radiological assessment, clinical status and corticosteroid dose) in the disease progression assessment are presented for the entire assessment period as well as for 3, 6 and 9-month time points.

13.4.6.2. Secondary efficacy endpoints

The following subgroup PFS-6 endpoints:

- Investigator-assessed PFS-6 in the subgroup of patients with EGFRvIII^{pos} glioblastoma
- Investigator-assessed PFS-6 in the subgroup of patients with EGFR gene amplified glioblastoma

are evaluated using the same methodology as for the primary endpoint. The analysis is performed by including a subgroup factor as fixed effect in the model used to analyze the primary endpoint. PFS-6 with 95% confidence intervals are estimated for each subgroup as well as for the residual population.

Comparison of the efficacy between the subgroups and the residual group is performed by estimating the hazard ratio (HR) with 2-sided 95% and 80% confidence intervals and the p-value for the null hypothesis: HR=1.

Furthermore, Kaplan-Meier methodology will be used to estimate median PFS with 95% CI using Greenwood's formula and the Kaplan-Meier curves will be constructed to provide a visual description of the PFS for the subgroups over time.

Descriptive statistics overall and for each parameter in the disease progression assessment are presented for the entire assessment period as well as for 3, 6 and 9-month time points by subgroup.

The secondary endpoint:

- OS rate at 9 months (OS-9) and OS overall, in all patients and in those with EGFRvIII^{pos} and EGFR gene amplified glioblastoma

where OS is defined as the time between date of first dose of study drug and the date of death due to any cause. OS-9 is defined as the percentage of patients who are alive at 9 months.

Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive; if no post-baseline data are available, OS will be censored at the date of first study drug. The analysis methods will be the same as for the PFS.

The secondary endpoints:

- ORR per RANO criteria, and DOR in all patients and in those with EGFRvIII^{pos} and EGFR gene amplified tumors

where ORR is defined as a CR or PR. Patients without a post-baseline disease assessment will be considered as non-responders. The analysis population for ORR will be all enrolled patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. CIs for the difference in ORRs between the subgroups will be determined using the normal approximation to the binomial distribution. In addition, ORR is analyzed with a generalized logistic regression analysis. Subgroup is included as fixed effect, KPS as a covariate and study center as random effect. The adjusted odds ratio for being a responder is estimated and the two-sided 95% confidence interval presented.

DOR is defined as the time from the initial response to disease progression or death among patients who have experienced a CR or PR during study. Patients who have not progressed or died at the time of analysis will be censored at the last disease assessment date. DOR will be estimated using Kaplan- Meier methodology. Comparisons between subgroups through use of the unstratified log-rank test will be made for descriptive purposes only.

- To evaluate the efficacy of tesevatinib as measured by PFS-6, OS-9, RANO ORR and DOR in the subgroups:
    - EGFRvIII^{pos} vs EGFRvIII^{neg}
    - EGFR amplification^{pos} vs EGFR amplification^{neg}

The statistics for these subgroup comparisons are described at each of the endpoints.

In addition, statistics for the change and percent change from baseline tumor measurements will be presented. These analyses will be done after each two cycles of therapy. Summary statistics will be produced for PFS and OS. The percentage of patients without disease progression after 3 and 6 months of dosing will also be presented separately by local (investigator) and potentially by central radiography results. Sites will provide copies of all MRI image sets for central retention in case central radiology review is required.

13.4.6.3. Sensitivity analysis for primary and secondary PFS and OS endpoint analysis

As a sensitivity analysis for the primary and secondary PFS and OS analysis the estimation of PFS-X, medium PFS, OS-X and median OS is performed with parametric survival analysis models, the models are compared to the Cox model based on the AIC-value. For each model the PFS-X, medium PFS, OS-X and median OS confidence intervals are estimated.

13.4.6.4. Exploratory endpoints

The analysis of the exploratory endpoints will be further detailed in the SAP.

- To evaluate the potential association of exploratory tissue and blood biomarkers with response to tesevatinib (PFS-6) and with adverse events. These include EGFRvIII mutation and gene amplification and may include circulating tumor DNA expression of these and other factors
- To evaluate the correlation between patients with EGFRvIII^{pos} tumor and those patients with EGFR gene amplification with respect to survival and safety
- To evaluate and compare EGFRvIII^{pos} expression and/or other tissue biomarkers potentially associated with response with tesevatinib, in paired primary and recurrent glioblastoma specimens from the same patient, when these are available
- To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the MDASI-BT questionnaire

The MDASI-BT score is analyzed using a repeated measurement analysis with the MDASI-BT score as dependent variable, baseline score as covariate and cycle as fixed effect. Patient and center as included as random effects.

The data are summarized as scores and as change from baseline, as well as the categorical variables severe, moderate and mild cognitive impairment.

- To evaluate patient-reported outcomes of disease and treatment-related symptom severity and interference as measured by the MDASI-BT questionnaire in the subgroup of patients with EGFRvIII^{neg} and EGFR gene amplification^{neg} tumors as compared to those in patients with EGFRvIII^{pos} and EGFR gene amplification^{pos} tumors

Comparisons will be performed by using the mixed model and including subgroup and a subgroup-cycle interaction.

Data will be modelled with the MDASI-BT score as dependent variable and with a categorical response (binary or three categories).

13.4.6.5. Safety Data

Safety analyses will be performed on all patients 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 overall results and results by subgroups.

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, physical examinations, ECG assessments, and plasma levels.

Treatment-emergent AEs will be summarized using MedDRA® (Version 18.1 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a preferred term will be included, according to the most severe grade using the 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 subgroup and tesevatinib overall according to SOC and preferred terms. All AEs will be 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. 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 baseline to highest grade post-baseline 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. Karnofsky 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 patient visit and dose cohort and/or as appropriate. QTc prolongation results will be summarized separately. Covariate analyses will be employed as necessary.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 patient 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.

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 patient 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 patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. 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.

Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study.

The monitor will visit the sites 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 patient 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 should be completed within seven (7) days of the patient'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.

14.2. 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.

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 protocol, the principles of GCP and any applicable regulatory requirements. A regulatory authority or IRB may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority or IRB 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 patient data will be treated confidentially. 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 patient 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.

Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. ETHICAL ASPECTS

15.1. 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. 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 Patients", and Part 56, "Institutional Review Boards". 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 patient informed consent form (ICF) prior to implementation.

Voluntary written informed consent must be obtained from every patient prior to participation in this clinical study. The rights, safety, and well-being of participating patients 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).

15.2. Good Clinical Practice

The principal investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 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 patient to this part that the applicant or 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 patient has completed the protocol-defined activities.

15.3. 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 patient before the patient 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 Patients (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 patient (or the patient'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 patient is unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient 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 patient or to the patient'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 patient candidates.

The eCRF for this study contains a section for documenting informed patient consent, and this must be completed appropriately. Signed ICFs must remain in each patient'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 patients (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.

15.4. 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 patient enrollment and whenever subsequent modifications to the protocol are made.

15.5. Future Use of Patient 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 patient 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 patient 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.

16. PROTOCOL AMENDMENTS

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 patients, 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 patients. 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.

17. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1. 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) patient 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.

Patient clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include patient 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 patient 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 patient 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 patient, appropriate copies should be made for storing outside of the study site.

17.2. Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each patient 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 patient candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the patient'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 patient
- The medical condition of the patient during their involvement in the study
- All AEs
- The patient's exposure to the study medication
- The patient's exposure to any concomitant therapy
- All relevant observations and data on the condition of the patient throughout the trial
- Justification for all entries in the patient's eCRF
- Radiology images (hard copy and digital), and reports if required
- Death information and any available autopsy data

A patient log of all potentially eligible patients considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain patients' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented patients 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 patient confidentiality is protected.

17.3. 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 patient who receives any amount of study drug. This includes submission of retrievable data on patients 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 patient stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

17.4. Confidentiality of Trial Documents and Patient Records

The investigator must ensure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Kadmon

and the IRB, patients should be identified by an identification code and/or initials and not by their names. The investigator should keep a patient enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to Kadmon (e.g. patients' 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, patient 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.

18. PUBLICATION POLICY

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.

This study will be posted to clinicaltrials.gov to permit publication in appropriate peer reviewed journals.

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APPENDIX 1. KARNOFSKY PERFORMANCE STATUS CRITERIA

Score (%)	Criteria
100	Normal, no complaints, no signs of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment
10	Moribund, rapidly progressive fatal disease processes
0	Death

APPENDIX 2. RANO CRITERIA

Response	Criteria
Complete response (CR)	Requires **all** of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions • Patients must be off corticosteroids (or on physiological replacement doses only) • Clinical status is stable or improved
Partial response (PR)	Requires **all** of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks • No progression of nonmeasurable T1enhancing disease • No new lesions • Stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease
Stable disease (SD)	Requires **all** of the following: • Patient does not qualify for complete response, partial response, or progression • Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression (PD)	Defined by **any** of the following: • ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (of no decrease) or best response, on a stable or increasing dose of corticosteroids • Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of steroids compared with baseline scan or best response after initiation of therapy, not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, seizures, postoperative changes, or other treatment effects) • Presence of any new lesions • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or decreases in corticosteroid dose • Failure to return for evaluation due to death or deteriorating condition • Clear progression of nonmeasurable disease

FLAIR = fluid-attenuated inversion recovery, RANO = Response Assessment in Neuro-Oncology (adapted from Wen 2010)

APPENDIX 3. MD ANDERSON SYMPTOM INVENTORY-BRAIN TUMOR MODULE

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐

PDMS # : ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life

Symptoms frequently interfere with how well we function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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APPENDIX 4. CONCOMITANT DRUGS THAT SHOULD BE AVOIDED, SUBSTITUTED OR USED WITH CAUTION

Drugs with QTc risk should be avoided per Section 9.3.3.1 of the protocol. Drugs that inhibit or induce the CYP isoenzymes 3A4, 2C8, 2D6, 1A2 should be substituted when possible or used with caution in view of their potential to alter tesevatinib exposure. Drugs that are secreted by the kidney proximal tubule cells into the renal tubule by MATE transporter proteins should be used with caution. **This list is not comprehensive, and all concomitant medications should be evaluated for possible interactions with tesevatinib**. See the Indiana University P450 drug interaction table for complete information (http://medicine.iupui.edu/clinpharm/ddis/main-table/).

Drug Type	Drugs with QTc Risk: AVOID	Drugs with CYP or MATE Interaction Risk: CAUTION
Anti-anginal	bepridil	
Anti-arrhythmics	amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol	amiodarone, quinidine, dofetilide, procainamide
Antibiotics/anti-fungals	clarithromycin, erythromycin, azithromycin, sparfloxacin, gatifloxacin, moxifloxacin, troleandomycin, pentamidine	fluoroquinolones, clarithromycin, erythromycin, rifampin, rifabutin, terbinafine, itraconazole, ketoconazole, cephalexin, pyrimethamine
Anti-depressant		fluvoxamine, bupropion, fluoxetine, paroxetine, duloxetine, clomipramine, doxepin, nefazodone
Anti-epileptics		carbamazepine, phenytoin, phenobarbital
Anti-malarial	chloroquine, halofantrine, quinidine	quinidine,
Anti-nausea/emetics	domperidone, droperidol	
Anti-platelet		ticlopadine,
Anti-psychotic	haloperidol, mesoridazine, thioridazine, chlorpromazine, pimozide	aripiprazole, haloperidol,
Anti-viral		efavirenz, indinavir, nelfinavir, ritonavir, nevirapine
Asthma and allergy		chlorpheniramine, diphenhydramine, montelukast, fexofenadine
Calcium channel blockers		verapamil, diltiazem
CNS depressants		barbiturates
GI stimulant/heartburn/GERD	cisapride	cimetidine
Glucose lowering agents		Pioglitazone, troglitazone, metformin
Immune modulators		cyclosporine, tacrolimus
Lipid lowering		gemfibrazole,
Miscellaneous		St John’s Wort, grapefruit juice, Seville oranges,
Opiates/dependence	levomethadyl, methadone	Suboxone, methadone

APPENDIX 5. 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

Brand Name	Generic Name
Elocon Cream/Lotion, 0.1%	Mometasone furoate
Kenalog Cream/Spray, 0.1%	Triamcinolone acetonide
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).