STATISTICAL ANALYSIS PLAN

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

Protocol Number: KD019-206

Statistical Analysis Plan Version:	Date of Statistical Analysis Plan:
Version 1	5 October 2018

SIGNATURE PAGE

05-OCT-2018 Zhongming Yang

Date

Prepared by: Dr. Zhongming Yang
Director, Clinical Development,
Kadmon Corporation, LLC

05-OCT-2018

Date

Reviewed by: Dr. Sanjay Aggarwal
Vice President, Clinical Development,
Kadmon Corporation, LLC

DOCUMENT HISTORY

Version	Author	Description
1.0	Zhongming Yang	New Document

Table of Contents

Table of Tables

LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	Adverse event
BM	Brain metastases
CNS	Central nervous system
CR	Complete response
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
HLT	High level terms
LM	Leptomeningeal metastases
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
QTcF	QT interval corrected by Fredericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTP	Time to progression
VS	Vital signs

1 Study Summary

1.1 Study Objectives

1.1.1 Cohort A

Primary objectives:

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

Secondary objectives:

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

Exploratory Objective

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

1.1.2 Cohort B

Primary objectives:

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

Secondary objectives:

- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by decreases in NSCLC cells in the cerebrospinal fluid (CSF) using standard cytology.
- To evaluate the activity of tesevatinib in subjects with NSCLC, EGFR activating mutations and LM as measured by improvement in CNS magnetic resonance imaging (MRI) findings.
- To evaluate the pharmacokinetics (PK) of tesevatinib in CSF versus plasma.
- To evaluate changes in QOL in subjects receiving tesevatinib for LM.

- To determine the median PFS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP.
- To determine the median OS.

Exploratory Objective

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

1.1.3 Cohort C

Primary objectives:

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

Secondary objectives:

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

Exploratory Objective

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

1.2 Study Design

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

1.2.1 Sample Size Justification

For Cohort A, assuming that 20% of subjects with BM have response (complete response [CR] or partial response [PR]), N=20 has an approximately 80% chance of

having at least 3 subjects with response, and an over 90% chance of at least 2 subjects having a response.

For Cohort B, assuming that 20% of subjects with LM have improvement in at least one symptom or sign attributed to LM, N=20 has an approximately 80% chance of having at least 3 subjects with improvement in at least one symptom or sign attributed to leptomeningeal metastases and an over 90% chance of at least 2 subjects having improvement attributed to LM.

For Cohort C, assuming that 20% of subjects with BM have response (CR or PR), N=20 has an approximately 80% chance of having at least 3 subjects with response, and an over 90% chance of at least 2 subjects having a response.

1.2.2 Study Population / Number of Subjects

Up to 20 subjects with NSCLC who have progressed with BM will be enrolled in Cohort A. Up to 20 subjects who have initial presentation or progressed with LM will be enrolled in Cohort B. Up to 20 subjects with NSCLC and BM and no prior systemic therapy will be enrolled in Cohort C. Cohort A, Cohort B, and Cohort C will be open for enrollment simultaneously; when one cohort has completed enrollment the other cohorts will remain open for enrollment until enrollment in those cohorts are also complete.

1.2.3 Dosage and Admiration

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.

1.2.4 Duration of treatment/ Discontinuation

Subjects will be treated with study drug until disease progression or unacceptable toxicity occurs. However, subjects with limited peripheral disease progression (oligoprogressive disease) may receive local ablative (radiation therapy or surgery) while study drug is withheld for up to 28 days, and then be continued on tesevatinib.

Subjects who discontinue tesevatinib treatment will be followed for survival.

1.2.5 Analysis Populations

All subjects who take at least one dose of study drug will be included in efficacy and safety analysis. Non-evaluable response will be classified as non-responder.

1.3 Efficacy Assessments

1.3.1 Efficacy Endpoints

1.3.1.1 Primary endpoints

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

For Cohort B: symptoms and signs attributed to leptomeningeal disease will be evaluated at screening, Cycle 1 Day 1, at Cycle 1 Day 14, at Cycle 2 Day 1, at Cycle 3, and then every 2 cycles (approximately 8 weeks) thereafter until disease progression National Cancer Institute CTCAE (NCI CTCAE; Version 5). Symptom improvement is defined as a decrease in 1 grade in at least one CTCAE v4.03 symptom or sign attributed to LM without worsening of other symptoms or signs that are attributed to LM. Symptom progression is defined as an increase of 1 grade in at least one CTCAE v4.03 symptom or the appearance of new symptoms or signs of LM.

1.3.1.2 Secondary endpoints

- The PFS, the OS, rate of CNS non-progression at 3 and 6 months, non-CNS TTP, and CNS TTP
- QOL will be evaluated via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ-BN20 questionnaires administered at Screening, on Day 1 of Cycle 3, and on Day 1 of odd-numbered cycles thereafter.
- For Cohort B, decreases in NSCLC cells in the CSF using standard cytology
- For Cohort B, improvement in CNS MRI findings

1.3.1.3 Exploratory Endpoints

- For Cohort B, decreases in NSCLC cells in the CSF using rare cell capture techniques
- For Cohort B, decreases in CSF cell-free DNA
- For Cohort B, To utilize CSF cell-free DNA to detect activating EGFR mutations

1.3.2 Safety Assessments

The NCI CTCAE; Version 5 will be used for grading toxicities. Safety assessments will include adverse events (AEs), serious adverse events (SAEs), physical examinations, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), Eastern Cooperative Oncology Group (ECOG) scores, and electrocardiograms (ECGs).

The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through 30 days after the last dose of

study drug or until start of new treatment. All AEs that occur in enrolled subjects during the AE reporting period specified in the protocol must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the investigator assesses as possibly related to tesevatinib should be included.

Vital sign measurements, including sitting blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study.

1.3.3 Pharmacokinetic Endpoints

For subjects in Cohort B

- Plasma and CSF PK samples will be obtained on Cycle 1 Day 14 and on Cycle 3 Day 1, within approximately 4–8 hours after tesevatinib administration
- Plasma PK sample will be obtained at predose on Day 14 of Cycle 1 and at predose on Day 1 of Cycle 3

Tesevatinib concentrations in the plasma and CSF will be summarized at each scheduled collection time point using descriptive statistics, and displayed graphically

1.3.4 Pharmacodynamic Endpoints

Some pharmacodynamics endpoints have been included as exploratory endpoints.

2 Statistical Methods

No formal hypothesis testing will be conducted. Descriptive statistics including 95% confidence intervals for response rate, time-to-event and continuous measurements will be summarized by cohorts.

Tesevatinib concentrations in the plasma and CSF will be summarized at each scheduled collection time point using descriptive statistics, and displayed graphically.

AEs, SAEs, Grade 3&4 AEs, related AEs, related SAEs, related Grade 3&4 AEs, death, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by cohort and overall according to high level terms (HLT) and preferred terms (PT). Adverse events will also be summarized in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. The ECOG performance status results will be summarized by scheduled time point.

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

The table of list of tables, listings, and figures is displayed in Table 1.

Table 1 Content of efficacy tables

T/F/L	Number	Title	Order	Population	Summary Statistics
T	1.1.1	Response rate by cohort	Primary efficacy	All treated subjects	ORR, CR, PR, exact CI
T	1.1.2	Response rate by visit and cohort	Primary efficacy	All treated subjects	ORR, CR, PR, exact CI
L	1.1.1	Tumor size / symptoms and signs by visit and cohort	Primary efficacy	All treated subjects	
T	1.2.1	Progression-free survival (PFS) by cohort	Secondary efficacy	All treated subjects	descriptive statistics
T	1.2.2	Overall survival (OS) by cohort	Secondary efficacy	All treated subjects	descriptive statistics
T	1.2.3	non-CNS time to progression by cohort	Secondary efficacy	All treated subjects	descriptive statistics
T	1.2.4	CNS time to progression by cohort	Secondary efficacy	All treated subjects	descriptive statistics
F	1.2.1	Progression-free survival (PFS) by cohort	Secondary efficacy	All treated subjects	KM curve
F	1.2.2	Overall survival (OS) by cohort	Secondary efficacy	All treated subjects	KM curve
F	1.2.3	non-CNS time to progression by cohort	Secondary efficacy	All treated subjects	KM curve
F	1.2.4	CNS time to progression by cohort	Secondary efficacy	All treated subjects	KM curve
T	1.3.1	QOL by visit and cohort	Secondary efficacy	All treated subjects	Descriptive Statistics
L	1.4.1	NSCLC cells in the CSF using standard cytology by visits	Secondary efficacy	All treated cohort B subjects	Descriptive Statistics
T	1.4.2	CNS MRI findings by visits and change from baseline	Secondary efficacy	All treated cohort B subjects	Descriptive Statistics
L	1.4.2	CNS MRI findings by visits	Secondary efficacy	All treated cohort B subjects	source date
L	1.5.1	NSCLC cells in the CSF using rare cell capture techniques by visits	Exploratory Endpoints	All treated cohort B subjects	source date
L	1.5.2	CSF cell-free DNA by visits	Exploratory Endpoints	All treated cohort B subjects	source date
L	1.5.3	EGFR mutations by visits	Exploratory Endpoints	All treated cohort B subjects	source date
T	1.6.1	Plasma concentration by visit	PK	All treated cohort B subjects	Descriptive Statistics
L	1.6.1	Plasma concentration by subject and visit	PK	All treated cohort B subjects	source date
F	1.6.1	Plasma concentration by subject and visit	PK	All treated cohort B subjects	source date
T	1.6.2	CSF concentration by visit	PK	All treated cohort B subjects	Descriptive Statistics
L	1.6.2	CSF concentration by subject and visit	PK	All treated cohort B subjects	Descriptive Statistics

F	1.6.2	CSF concentration by subject and visit	PK	All treated cohort B subjects	source date

Table 2 Content of safety tables

T/F/L	Part	Number	Title	Population
T	Disposition	1.1.1	Patient disposition by cohort	All enrolled patients
L	Disposition	1.1.1	Patient disposition	All enrolled patients
L	Disposition	1.2.1	Protocol deviations	All enrolled patients
T	Demo	2.1.1	Demographics and baseline characteristics by cohort	All treated patients
L	Demo	2.1.1	Demographics and baseline characteristics	All treated patients
L	Demo	2.2.1	Medical history	All treated patients
L	Demo	2.3.1	Disease history	All treated patients
L	CM	3.1.1	Prior and concomitant medications	All treated patients
T	Exposure	4.1.1	Treatment exposure and compliance by cohort	All treated patients
L	Exposure	4.1.1	Treatment exposure and compliance	All treated patients
L	Exposure	4.2.1	Dose modifications	All treated patients
T	AE	6.1.1	Overall summary of TEAEs by cohort	All treated patients
T	AE	6.1.2	TEAEs by SOC/PT and cohort	All treated patients
T	AE	6.1.3	Treatment related AEs by SOC/PT and cohort	All treated patients
T	AE	6.1.4	Serious TEAEs by SOC/ PT and cohort	All treated patients
T	AE	6.1.5	Serious Treatment Related AEs by SOC/PT and cohort	All treated patients
T	AE	6.1.6	Grade 3 and 4 TEAEs by SOC/PT and cohort	All treated patients
T	AE	6.1.7	Treatment Related Grade 3 and 4 AEs by SOC/PT and cohort	All treated patients
T	AE	6.1.8	TEAEs by HLT and cohort	All treated patients
T	AE	6.1.9	Treatment related AEs by HLT and cohort	All treated patients
T	AE	6.1.10	Grade 3 and 4 TEAEs by HLT and cohort	All treated patients
T	AE	6.1.11	Treatment Related Grade 3 and 4 AEs by HLT and cohort	All treated patients
L	AE	6.1.1	AEs	All treated patients

L	AE	6.1.2	AE Leading to Treatment Discontinuation	All treated patients
L	AE	6.1.4	Death	All treated patients
T	Lab	7.1.1	Lab values and their change from baseline by cohort	All treated patients
T	Lab	7.1.3	Shifts in toxicity grading from baseline to highest grade post-baseline of laboratory abnormalities by cohort	All treated patients
L	Lab	7.1.1	Lab values with CTCAE grade >= 3	All treated patients
T	VS	8.1.1	Vital signs and their change from baseline by cohort	All treated patients
L	VS	8.1.1	Vital signs	All treated patients
L	VS	8.2.1	Physical examinations	All treated patients
T	ECG	9.1.1	ECG parameters and their change from baseline by cohort	All treated patients
T	ECG	9.2.1	QTcF abnormalities by cohort	All treated patients
L	ECG	9.1.1	ECG values	All treated patients

Abbreviations: AE = adverse event; CNS = central nervous system; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HLT = high level terms; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TEAEs = treatment-emergent adverse events; VS = vital signs