CLINICAL RESEARCH PROTOCOL

DRUG:	MGCD265
STUDY NUMBER(S):	265-109
PROTOCOL(S) TITLE:	Phase 2, Parallel-Arm Study of MGCD265 in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with Activating Genetic Alterations in Mesenchymal-Epithelial Transition Factor
IND NUMBER:	78394
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DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	01 May 2015	NA
Protocol Amendment, Version 2.0	17 May 2016	• Added EUDRACT Number to protocol title page. • Updated protocol version and date. • Background information: o Updated clinical safety data from MGCD265 clinical trials to be consistent with most recent version of Investigator's Brochure. o Added Phase 1 safety and PK data using the SDD (spray-dried dispersion) tablet formulation of MGCD265 and compared to results using MGCD265 non-aqueous capsule formulation results. o Removal to trastuzumab as an example of a tyrosine kinase inhibitor. • Study population/patient eligibility: o Clarified prior receipt of at least one treatment to include a platinum-based chemotherapy regimen. o Reinforced and clarified text concerning collection and use of blood as well as tumor tissue to identify eligible tumor gene alterations. o Reinforced need for Sponsor approval of tumor genotyping laboratories. o Reinforced that patients entering the study based on Sponsor-approved local laboratory tumor genotyping using tumor tissue or blood must have a sample collected before dosing on study to submit for retrospective tumor genotyping by the central laboratory. Results of the central laboratory test are not required prior to start of treatment on study. o Clarified that the exclusion criterion concerning prior positive *EGFR* mutation or *ALK* gene rearrangement requires known testing of patients with adenocarcinoma; testing for patients with non-adenocarcinoma is not required however, existing positive test is exclusionary. o Provided detailed list of tumor gene alterations qualifying for study entry (Section 7.1.1). o Updated list of central laboratories approved by Sponsor to perform tumor genotyping.

		• Study objective: Changed wording of primary objective from determination of the efficacy of MGCD265 to determination of tumor response to MGCD265 based on feedback from an ethics committee. • Region or country specific requirements added at request of Health Authorities or Ethics Committees: o Poland - screening pregnancy test must be completed within 7 days of Cycle 1, Day 1; Day 1 (pre-dose) for all subsequent cycles and at the 28-day follow up visit. o United Kingdom – screening pregnancy test must be completed within 7 days of Cycle 1, Day 1. o United Kingdom - pregnancy added as a criterion for discontinuation from study treatment. o European Union – contraception using condoms with spermicide is not an acceptable method for this study. • Assessments: o ctDNA – clarified that a sample should be collected at pre-screening for all patients, and additional samples may be requested if needed by the central laboratory. o PK – added unscheduled samples to be taken at least one week after any MGCD265 dose modification or change in study drug formation to strengthen population PK analysis. o PD – updated sample tubes from heparin to K2EDTA and, 5-mL to 10 mL vacutainers. o CT Scans – added CT of pelvis as required for routine disease evaluation (e.g., CT of chest, abdomen and pelvis at each assessment) to ensure sufficient evaluation to support central radiology review. o Bone Scans – clarified that one-half the frequency of other disease evaluations is equivalent to every 12 weeks. o PET Scans – added guidance on limited role for use of PET scans in disease evaluations. o Triplicate ECGs – clarified two sets to be taken Cycle 1 Day 1 are to be within 30 minutes prior to dosing (e.g., at 15 minute intervals). o Single ECG – clarified this is done at end of treatment. o Lesion Flair Assessment – added a modification to RECIST 1.1 to allow suspension of conclusion of a

		disease assessment until the outcome of an apparent tumor flair becomes clear. • Study Treatments: o Added details on formulation and packaging of both soft-gel capsule and SDD tablet formulations for MGCD265. o Added details on storage and stability of SDD tablet formulation. o Added starting dose and dose modification details concerning SDD tablet formation. o Amended the section regarding missed and vomited doses. Missed doses may be allowed to be made up (not doubled up); but vomited doses should not be made up. o Added allowance to switch patients initially treated with soft-gel capsules to SDD tablets, at the discretion of the investigator. o Added expectation that ongoing food-effect evaluation may result in liberalizing fasting guidelines around dosing of MGCD265. Any change in guidance will be communicated. • Concomitant Medications: Reduced redundant text concerning use of anti-diarrheal medications. • Safety Reporting: Added definition of Hy's Law and guidance on patient management in such an event. • Study Analysis: o Changed mITT to include all patients that receive at least one dose of study treatment, eliminating caveats concerning specific eligibility criteria. The option to replace patients and allowance for 10% non-evaluable rate based on these caveats were eliminated, adjusting the expectation for total enrollment from 320 to 290 patients, and corresponding adjustments per treatment arm. This was modified throughout the protocol. o Further described the control of Type I error by use of the Bayesian designed applied to each study treatment arm separately. o Clarified evaluation of enrollment stopping rules with regard to inclusion of data under specified circumstances (e.g., exclusion from the denominator of patients just beginning treatment on study). Updated rules align with the IDMC Charter. o Added the possibility that the IDMC may elect to include only patients receiving the SDD formation in evaluating the enrollment stopping rules to

		mitigate potential confounding effects from formulation change. • Addressed clerical errors and made minor clarifications of language.
Protocol Amendment, Version 3.0	23 Mar 2017	• Updated protocol version and date. • Study Summary: o After discussion and acceptance by the Food and Drug Administration (FDA), the target population has been updated to include patients that have received either a platinum-based chemotherapy or licensed immunotherapy based on changing standard of care for first line therapy. o Added clarification that disease assessments must be based on a calendar schedule not cycle schedule. o Change cohorts from 1-4 to A-D for consistency with other study documents. • Schedule of Assessments: o Informed Consent - clarified that both pre-screening and full clinical screening consent must be obtained prior to entering full clinical screening. o Disease Evaluations – clarified the window for on-study assessments are to start 6 weeks after dosing date (Cycle 1, Day 1). Clarified that disease assessments should be done on a calendar schedule from first dosing. Additional details provided on when brain and bone assessments need to be continued on-study (based on identification by investigator OR by the central radiology reviewer). o Adverse Events - additional details provided about reporting SAEs only to the safety vendor during the screening period. The 28 day follow up as well as further survival follow up can be done via remote contact. o Long Term Follow up – clarified that long term follow- up is required every 2 months from the end of treatment visit. • Schedule for PK, Triplicate ECG, and PD Assessments: o Revised the table and footnotes to provide clarification and modifications on the timing of assessments for ECGs, PK and PD collections. • Introduction and Rationale: o Provided rationale to why immunotherapy has now been added to the eligibility requirement for prior therapy.

		• Clinical Data: o Updated clinical data for single-agent studies with MGCD265 based on the revised Investigators Brochure. • Study Design: o Added clarification that disease assessments must be based on a calendar schedule not cycle schedule. o Changed cohorts from 1-4 to A-D for consistency with other study documents. • Inclusion Criteria: o Inclusion criteria #2 updated to include licensed immunotherapy as acceptable prior treatment. o Exclusion criteria #3 updated to include washout period for immunotherapy. o Exclusion criteria #8 updated to allow for a 2 week washout from stereotactic radiosurgery (gamma knife). • Study Treatment: o Formulation and Packaging – information regarding bottle size and tablet count have been removed from the protocol and will be detailed in the Pharmacy Manual. • Reporting of SAEs and AEs: o Reporting period - clarified that SAEs are reported from the time of main study informed consent. • References: o New reference added. • Addressed clerical errors and made minor clarifications of language.

STUDY SUMMARY

Title:	Phase 2, Parallel-Arm Study of MGCD265 in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with Activating Genetic Alterations in Mesenchymal-Epithelial Transition Factor (*MET*).
Rationale:	MET plays a central role in epithelial tissue remodeling and morphogenesis and is one of the most frequently dysregulated receptor tyrosine kinases (RTKs) in several human cancers. Oncology indications in which *MET* is reported to be genetically altered by mutation or gene amplification include lung, renal, colorectal, glioblastoma, gastric, and head and neck cancers. *MET* mutations and/or gene amplification have recently been reported as part of the Cancer Genome Atlas program in approximately 7% of lung adenocarcinoma patients. Furthermore, the expression of both MET and Hepatocyte Growth Factor (HGF), its sole, high-affinity ligand, was demonstrated to correlate with poor prognosis or metastatic progression in a number of major human cancers, including NSCLC. Inappropriate activation of MET is involved in multiple tumor oncogenic processes such as cell growth, angiogenesis, invasive growth, and especially in the metastatic process. MGCD265 is a small molecule inhibitor of MET and Axl. In vitro studies have demonstrated that MGCD265 is a potent inhibitor of tumor cell proliferation in cells where MET is overexpressed or activated, but not in cells that lacked MET expression/activation. These results are consistent with in vivo studies demonstrating activity of MGCD265 in human tumor xenograft-bearing mouse models including marked tumor regression in models exhibiting *MET* mutations and/or gene amplification. Additionally, Axl dysregulation may contribute to tumor progression or further cooperate in drug resistance, and simultaneous inhibition of both of these targets may cooperate to overcome therapeutic resistance to selected anticancer agents.
Target Population:	Patients with locally advanced or metastatic NSCLC with activating genetic alterations of *MET* (mutations or gene amplifications), who have received at least one platinum-based chemotherapy or licensed immunotherapy regimen for advanced/metastatic NSCLC.
Number in Primary Trial:	Total enrollment up to approximately 290 patients

Primary Objective:	• To determine the tumor response to MGCD265 in the selected patient population.
Secondary Objectives:	• To evaluate the safety and tolerability of MGCD265 in the selected population. • To evaluate secondary efficacy endpoints with MGCD265 treatment in the selected population. • To assess correlation between selected tumor gene alterations using different analytical techniques in tumor tissue and circulating tumor deoxyribonucleic acid (ctDNA). • To assess change in genetic alteration status in ctDNA with MGCD265 treatment over time in the selected population. • To assess the population pharmacokinetics/pharmacodynamics (PK/PD) of MGCD265 in the selected population.
Primary Endpoint	• Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Endpoints	• Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.
	• Secondary efficacy endpoints:
	  o Duration of Response (DR);
	  o Progression-Free Survival (PFS);
	  o 1-Year Survival Rate; and
	  o Overall Survival (OS).
	• Gene alterations in tumor tissue and ctDNA at prescreening/baseline.
	• Change in ctDNA through time.
	• Blood plasma MGCD265 concentration.
	• Blood plasma concentration of selected soluble biomarkers.

Study Design: Study 265-109 is an open-label, parallel arm, Phase 2 trial evaluating the efficacy of MGCD265 in patients with locally advanced, unresectable or metastatic NSCLC exhibiting activating genetic alterations of *MET*.

To be eligible for enrollment, patients must have documented evidence of a genetic alteration activating *MET* as determined by a Sponsor-approved central or local laboratory.

The primary objective of the study is to determine the tumor response to MGCD265 as measured by ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, genetic alterations in tumor tissue and ctDNA at pre-screening/baseline, change in ctDNA through time, and population PK/PD. The Schedule of Assessments to be performed in the study is presented in Table 1, Table 2, and Table 3.

MGCD265 will be administered as an oral therapeutic twice daily (BID) in 21-day cycles. Guidelines for study drug administration and dose reduction in the event of toxicity are provided in the protocol. Study treatment will continue until disease progression, unacceptable adverse events, patient refusal or death.

Disease response and progression as documented by the investigator in the Case Report Form (CRF) will be the basis for patient management, study expansion decision making and secondary and supportive statistical analyses. Central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval, as well as the duration of response and PFS. The importance of timely and complete disease assessments in this study is critical for the efficacy endpoints. The need to truncate treatment cycles to manage toxicity may result in inconvenient scheduling of disease assessments. Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias into the assessment of efficacy based on toxicity.

This Phase 2, parallel-arm study will be conducted in four groups of patients having genetic tumor alterations activating *MET*:

A. *MET* activating mutations in tumor tissue,

B. *MET* gene amplifications in tumor tissue,

C. *MET* activating mutations in ctDNA, and

D. *MET* gene amplifications in ctDNA.

The Phase 2 study will use a Bayesian Predictive Probability Design (Lee-2008), applied separately and using the same assumptions in each treatment arm (see Statistical Considerations). Emerging efficacy data will be evaluated continuously beginning after 10 patients in each treatment arm have completed their first on-study disease assessment and are considered part of the Modified Intent-to-Treat (mITT) population (defined under Statistical Considerations). Stopping rules for futility are described under Statistical Considerations. Assuming the stopping rules are not triggered, the total sample size to be evaluated in each treatment arm of the Phase 2 study is 45 patients. The primary analysis will be conducted in the mITT population.

There is potential for one or more arms of the Phase 2 study to yield results indicating that MGCD265 should be considered to provide an important advancement in treatment in this setting of unmet medical need. If emerging data indicate that an accelerated approval market application may be undertaken for MGCD265 for one or more of the selected patient populations, an analysis of the combined populations may be undertaken, or additional patients may be enrolled into the study, to increase the precision of the 95% confidence interval around the ORR endpoint and/or to increase the size of the safety database in the target patient population. As many as 55 additional patients included in the mITT population may be enrolled in up to two treatment arms to ensure collection of sufficient data to support an accelerated approval market application.

Considering the sample size planned for the four treatment arms in the Phase 2 study (45 patients each) and the possible addition of patients to prepare for market application in this setting (55 patients in each of two treatment arms), the ultimate sample size for this study could include as many as 290 patients. Enrollment through the stages of this study will proceed without planned interruption while data are accruing. Decisions will be made expeditiously by the Internal Data Monitoring Committee to prevent excessive over-enrollment and include only outcomes among the specified number of patients according to the stopping rules.

Statistical Considerations

This Phase 2, parallel-arm study will use a Bayesian Predictive Probability Design (Lee-2008) that minimizes the number of patients enrolled to test the hypothesis. The design will be applied separately and using the same assumptions in each of four treatment arms.

ORR in accordance with RECIST 1.1 is the primary endpoint. With currently available treatments, ORR is assumed to be 20% (p_0); thus this rate is considered uninteresting. The target ORR using MGCD265 in this study is 40% (p_1). The trial will monitor the number of observed responses continuously after evaluating the first on-study disease assessments of the first 10 patients in each treatment arm in the mITT population. In creating the statistical design, the Type 1 error (α) is constrained to < 0.05 and Power ($1-\beta$) is constrained to ≥ 0.90.

Using the parameters identified, the ultimate sample size for each treatment arm is as many as 45 patients in the mITT population. The stopping rules (rejection regions), expressed as number of responses per patients treated, are 0/10, 1/14, 2/18, 3/22, 4/26, 5/29, 6/32, 7/35, 8/37, 9/39, 10/41, 11/43, 12/44, and 13/45. Thus, if more than 13 responses are observed among the first 45 patients enrolled who meet the criteria for the mITT population, the drug will be declared efficacious. If the true ORR is 20% (null hypothesis), the probability of early termination during the study is 0.92, and the expected sample size prior to termination is 28 patients; the Type 1 error equal to 0.0499 and Power equal to 0.9065. If the true ORR is 40% and N=45, the exact 95% confidence interval (Clopper-Pearson) around the point estimate for ORR will be (25.7; 55.7).

If the outcome is promising and the option is taken to enroll an additional number of patients up to 100 in the mITT population in a specific treatment arm to increase the size of the safety database and narrow the confidence interval around the ORR point estimate, the 95% confidence interval around a true ORR of 40% will be (30.3; 50.3). Data collected in patients enrolled beyond the planned Phase 2 sample size will be used in secondary and supportive analyses.

For the purpose of making decisions for continued enrollment and for conduct of the final analysis for the Phase 2, the mITT population is defined as all patients who receive at least one dose of MGCD265.

Table 1: Pre-screening Assessments

To establish potential eligibility for future enrollment into Study 265-109, pre-screening for tumor genotype may be performed in advance of anticipated clinical screening for study entry, e.g., during treatment with chemotherapy required prior to study entry.

	Guidance
Informed Consent for Tumor Genotyping Pre-screening	Informed consent must be obtained prior to sending tumor tissue or blood for Sponsor-approved local or central laboratory genotyping. The informed consent form and process may be performed in accordance with documented institutional practice or using the study-specific, IRB-approved pre-screening ICF. An IRB/EC approved process for obtaining consent from patients who are remotely located may be used.
Tumor Tissue Genotyping for *MET* Gene Alteration	Testing Samples from the most recent biopsy or excision are preferred; however if no recently obtained materials are available, samples from any time during patient's prior disease course are accepted. If study enrollment is based on Sponsor-approved local laboratory results, a tumor tissue sample for confirmatory testing by the central laboratory is expected to be available.
Circulating Tumor DNA Genotyping for *MET* Gene Alteration	Samples consisting of two 10 mL tubes of whole blood are collected in Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures.
Evaluation of overall health status for future clinical trial participation	Study eligibility requires adequate performance status and organ function. Patients undertaking pre-screening for tumor /genotype with the goal of considering Study 265-109 should have health status consistent with meeting eligibility criteria in the future when they may become a candidate for the study.

Table 2: Schedule of Assessments – During Study

The Schedule of Assessments provides an overview of the protocol visits and procedures. Refer to Section 7 for detailed information on each assessment. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating adverse events.

Assessments	Screen/ Baseline	Cycle 1		Cycle 2		≥ Cycle 3	End of Treatment[14]	
	Within 28 days	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Study Participation Informed Consent[1]	Before study specific assessments							
Tumor Tissue for Genotyping[2]	X							
Medical History, Disease History, Prior Therapy	X							
ECOG Performance Status	X							
Physical Exam[3]	X						X	
Abbreviated Physical Exam[3]		X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	
Pregnancy Test[5]	X	As clinically indicated						
Hematology[6,7]	X	X	X	X	X	X	X	
Coagulation[6,7]	X	As clinically indicated						
Serum Chemistry[6,7]	X	X	X	X	X	X	X	
PK Sampling[8]		X	X	X	X			
PD Sampling[9]		X	X	X	X			
ctDNA[10]	X			At assessment for confirmation of disease response (PR or CR)			X	
12-Lead ECG[11]	X	X	X	X			X	
Disease Evaluation[12]	X	Q 6 weeks until Week 49 (~1 year) and then Q 12 weeks						
Study Treatment Dispensing and/or Reconciliation		X		X		X		
Adverse Events[13] and Concomitant Medications	SAEs only	Throughout						
Long Term Follow-Up[15]								X

Footnotes located on the following page.

1. Study Participation Informed Consent (ICF): May be performed prior to 28 days before first dose of study treatment. Patients entering full clinical screening must have both the pre-screening ICF as well as the clinical screening ICF signed.
2 Tumor Tissue for Genotyping: Collection of tumor tissue may occur well prior to the study screening period (See Table 1). The informed consent process may be performed in accordance with documented institutional practice or using the study-specific, IRB-approved pre-screening ICF. Tumor tissue samples preferred for testing are the most recent tumor sample available; however, testing may be performed on samples taken any time during the disease course. Testing may be performed on primary, recurrent, or metastatic lesions. If study enrollment is based on Sponsor-approved local laboratory results, a tumor tissue sample for retrospective confirmation by the central laboratory is expected to be available and to be collected prior to dosing.
3 Physical Examinations: A complete physical examination required at Screening and End of Treatment only. Height will be recorded at screening only. All other evaluations will be symptom-directed, abbreviated evaluations.
4 Vital Signs: Weight, temperature, blood pressure, respiratory rate, and pulse rate to be assessed prior to dosing as indicated.
5 Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected. For patients enrolled in the United Kingdom, a pregnancy test must be completed within 7 days of Cycle 1 Day 1 (as part of screening or a repeat test). For patients enrolled in Poland, a pregnancy test must be completed within 7 days of Cycle 1 Day 1 (as part of screening or a repeat test), Day 1 (pre-dose) for all subsequent cycles and at the 28-day follow up visit.
6 Indicated Cycle 1, Day 1 Assessments: Repeat assessment on Cycle 1, Day 1 not required if screening assessment performed within 7 days before the first dose.
7 Safety Laboratory Assessments: Hematology, coagulation, and chemistry evaluations will be performed by local laboratories.
8 PK Sampling: Samples to be taken following vital signs and electrocardiograms (ECGs). See Table 3 for details of timing related to ECGs. In the event of significant toxicities or withdrawal due to toxicity, an additional unscheduled PK blood sample should be drawn as soon as possible. In the event of a dose modification or formulation change, an additional unscheduled PK sample should be drawn at least one week after the modification or change. Each PK blood sample will consist of a 4 milliliter (mL) whole blood draw collected in one 6-mL K2EDTA tube.
9 PD Sampling: Samples to be taken as detailed in Table 3. Each PD sample will consist of whole blood draw collected in one 10-mL K2EDTA tube.
10 ctDNA: Collection of ctDNA for eligibility purposes may occur well prior to the study screening period (See Table 1). The informed consent process may be performed in accordance with documented institutional practice or using the study-specific, IRB-approved pre-screening ICF. If study enrollment is based on prospective testing by the central laboratory, an additional sample may be requested prior to dosing to ensure enough material is available for all protocol defined analyses. If study enrollment is based on Sponsor-approved local laboratory results, a ctDNA sample for retrospective confirmation by the central laboratory is expected to be available and to be collected prior to dosing. On-study samples to be taken at the time of disease assessment to confirm response (PR or CR) and at End of Treatment visit. Samples consisting of two 10mL tubes of whole blood collected in Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures.
11 ECGs: Assessments will include an evaluation of rhythm, heart rate, and PR, QRS, QT, and QTc intervals. Single ECG to be performed at screening and at the end of treatment visit. Triplicate ECGs at Cycles 1 and 2 as described in Table 3.
12 Disease Evaluations: To be performed at screening (28-day window allowed) and every 6 weeks from dosing date [Cycle 1, Day 1] (-7/+10 days window allowed for first on-study assessment, ± 10 days window for all other assessments) until Week 49 (~1 year) and then every 12 weeks. All on-study disease assessments should be based on a calendar schedule beginning from the first day of dosing. In general, assessments at screening/baseline as well as on-study are to include Computed Tomography (CT) scan with contrast or Magnetic Resonance Imaging (MRI) of the chest abdomen and pelvis. In addition, at screening/baseline, a MRI with and without gadolinium or CT with contrast of the brain, a whole-body bone scan and evaluation of any superficial lesions will be performed. Subsequent disease assessments should also include whole body bone scans and/or MRI of the brain if metastatic disease is identified at screening/baseline by either the **investigator OR the central radiology reviewer.** Bone scans may be performed at one-half the frequency of other radiology evaluations (every 12 weeks) and should be performed during assessment for confirmation of disease response. All scans will be sent to the central radiology reviewer. More detailed guidance on exceptional circumstances is provided in the protocol (Section 7.3).

13 Adverse Events: SAEs are to be reported from the time of informed consent for study participation (i.e., excluding prescreening informed consent) until resolution of all SAEs observed on study (SAEs occurring during the screening period are only reported to the safety vendor). Adverse events will be reported from the first day of study treatment until at least 28 days after last dose of study drug, and until resolution or stabilization of acute AEs and/or ongoing SAEs. Post-treatment 28-day follow-up and beyond may be performed by remote contact (e.g., telephone call).

14 End of Treatment: Assessments that have been completed in the previous 3 weeks do not need to be repeated (6 or 12 weeks for tumor assessments in accordance with schedule).

15 Long Term Follow-up: Survival status and subsequent therapies will be collected by telephone contact every 2 months (±14 days) from end of treatment visit until death or lost to follow-up.

Table 3: Schedule of PK, Triplicate ECG, and PD Assessments

	Cycle 1, Days 1 and 15 (± 2 days Day 15 only)				**Cycle 2, Days 1 or 15 (± 2 days)**	
Collection Time and Allowable Window	**Pre-dose**		**2 hour (1-3 hour)**	**6 hour (4-8 hour)**	**Pre-dose (-0.5-0 hour)**	**6 hour (4-8 hour)**
Triplicate ECG	X (-1 - 0 hour)	X (-0.5-0 hour)	X	X	X	X
PK Sample	X (-0.5-0 hour)		X	X	X	X
	Cycle 1, Days 1 and 15 (± 2 days Day 15 only)				**Cycle 2, Days 1 and 15 (± 2 days)**	
Collection Time and Allowable Window	Pre-dose (-0.5-0 hour)				Pre-dose (-0.5-0 hour)	
PD Sample	X				X	

- On Cycle 1, Day 1 Pre-dose, two sets of triplicate ECGs should be done to firmly establish the baseline for the patient.
  - Example: ~1.0 hr (Triplicate ECGs); ~30 mins (Triplicate ECGs); ~15 mins (Vitals/PK)
- Vital signs should be assessed prior to blood sampling.
- ECGs should be taken in triplicate, each reading approximately 2 minutes apart.
- In Cycle 2, Pre-dose and 6 hour samples may be collected on either Day 1 or Day 15. Flexibility has been provided so if samples are missed on Day 1, they can be done on Day 15 (pre-dose and/or 6 hour). Steady-state exposure is expected, so samples should be representative regardless of when they are collected.
- If the MGCD265 dose is taken before arrival in the clinic, special care is needed to collect the exact dosing time from the patient.
- In the event of significant toxicities or withdrawal due to toxicity, an additional unscheduled PK blood sample should be drawn as soon as possible. In the event of a dose modification or formulation change, an additional unscheduled PK sample should be drawn at least one week after the modification or change.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-12}	Area Under the Plasma Concentration Versus Time Curve From Time Zero to 12 Hours
BID	Twice daily
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTA	Clinical Trial Application
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Cell DNA
DNA	Deoxyribonucleic Acid
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EIU	Exposure In-Utero
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescent In Situ Hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDPE	High-Density Polyethylene
HGF	Hepatocyte Growth Factor
IB	Investigator's Brochure

LIST OF ABBREVIATIONS

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Internal Data Monitoring Committee
IND	Investigational New Drug
INR	International Normalized Ration
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-Epithelial Transition Factor
mg	Milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next-Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Objective Progression of Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic
RTK	Receptor Tyrosine Kinase

LIST OF ABBREVIATIONS

RTPCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDD	Spray-Dried Dispersion
SOC	System Organ Class
$t_{1/2}$	Plasma Half-Life
TCGA	The Cancer Genome Atlas Research
T_{max}	Time to Maximum Observed Concentration
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Disease and Therapeutic Strategy

1.1.1 Non-Small Cell Lung Cancer

Lung cancer remains the leading cause of cancer-related death in the United States (US). Approximately 221,200 new cases of lung cancer are expected to be diagnosed in the US in 2015, and approximately 158,040 deaths will be attributed to lung cancer (Cancer Facts and Figures-2015). Non-small cell lung cancer (NSCLC) accounts for approximately 83% of lung cancer cases (Cancer Facts and Figures-2015), of which approximately half are classified as adenocarcinoma of the lung; squamous cell carcinoma accounts for approximately one-third of NSCLC cases and large cell carcinoma is less frequently diagnosed.

In 1995, the use of cisplatin-based chemotherapy was reported to lead to modest improvement in survival in patients with advanced NSCLC as compared to best supportive care, with a 27% reduction in death as reported in a meta-analysis of 11 trials (NSCLC Collaborative Group-1995). Subsequently, other chemotherapeutic agents have been reported to be active in NSCLC, leading to a comparison of 4 platinum-based doublets in the first-line treatment setting, all of which demonstrated similar activity (Schiller-2002). The importance of histology in the selection of first-line treatment for NSCLC was later described in the development of bevacizumab and pemetrexed. In a Phase 3 clinical trial, treatment with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), demonstrated an improvement in survival when added to doublet chemotherapy, specifically in patients with non-squamous NSCLC (Sandler-2006). Similarly, treatment with pemetrexed, an antifolate chemotherapeutic agent, results in an improvement in survival when used as part of a chemotherapy doublet in patients with non-squamous NSCLC, but with a probable decrease in survival among patients with squamous cell NSCLC (Scagliotti-2008). Based on the results of these and other trials, platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, remain a standard of care for most patients with advanced NSCLC in the first-line treatment setting. More recently, a trial of pembrolizumab, a humanized monoclonal antibody directed against PD-1, demonstrated an advantage of pembrolizumab over standard chemotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumor PD-L1 expression. Improvement was reported across multiple efficacy endpoints including survival along with a favorable safety profile (Reck-2016), leading to the approval of pembrolizumab in the first-line treatment setting in this patient population in the US.

Non-clinical and clinical studies have led to increased understanding of the molecular mechanisms underlying the pathogenesis of NSCLC. Abnormalities of genes involving signaling pathways have been described primarily in adenocarcinoma, and have included mutations in *EGFR*, *HER2*, *ROS*, *RON*, *MET*, *KRAS*, and *BRAF*, as well as translocations

such as *EML4-ALK*. In tumors harboring gene mutations in these pathways, the activation of the involved pathway is critical for the survival and maintenance of the malignancy. Such observations have been made in concert with the development and market authorization of several drugs targeting these pathways, including gefitinib (Mok-2009), erlotinib (Shepherd-2005; Rosell-2012), and afatinib (Sequist-2013) inhibiting the EGFR (Epidermal Growth Factor Receptor) pathway; as well as crizotinib (Shaw-2013) and ceritinib (Shaw-2014) inhibiting the ALK pathway. Clinical trials with these targeted agents have demonstrated that patient selection on the basis of tumor genetics can result in high disease response rates in all lines of treatment and have revolutionized the treatment of NSCLC, with targeted agents rapidly becoming standard of care among those patients with sensitizing tumor mutations (NCCN-2016). These observations have led to the paradigm whereby adenocarcinoma of the lung often occurs in the setting aberrant signaling pathways, and the identification and targeting of these pathways lead to significant improvements in outcomes for these patients.

Ongoing studies indicate that aberrations in the MET pathway may be similarly important in identifying patients with NSCLC, particularly those with adenocarcinoma, for targeted therapy. The MET pathway may be dysregulated through many mechanisms in NSCLC, including focal gene amplification, mutations leading to aberrant splicing such that the amino acid sequence correlating to exon 14 is deleted from the protein, or other activating mutations. As a consequence of these abnormalities, the MET pathway is overactive and acts as a tumor driver. Agents targeted to exploit the dependency on the MET pathway may be associated with significant activity, and with the potential for a better safety profile as compared to current treatment options.

1.1.2 Tyrosine Kinase Inhibitors

Receptor tyrosine kinases (RTKs) provide ideal targets for cancer therapeutics. The rationale for use of kinase inhibitors to treat cancer is supported by a well-established paradigm in oncology that robust clinical efficacy can be achieved with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification. Examples of tyrosine kinase inhibitors that have become standards of care in cancer diseases include imatinib in gastrointestinal stromal tumors with mutant *c-KIT* or chronic myelogenous leukemia with *BCR-ABL* gene translocations, erlotinib in NSCLC with mutant EGFR, sunitinib targeting the VHL (von Hippel-Lindau)-dependent VEGF pathway in renal cell carcinoma, and vemurafenib in $BRAF^{V600E}$ mutation-positive melanoma.

1.1.3 Dysregulation of Receptor Tyrosine Kinases in Cancer

RTKs are families of kinases involved in the transmission of signals that regulate cell growth, survival, and migration. Dysregulation of RTKs through genetic alteration or ectopic or uncontrolled expression is implicated in cell proliferation and tumor progression.

MET is one of the most frequently mutated or otherwise abnormally activated RTKs in several human cancers (Christensen-2005). Malignancies in which *MET* has been reported to be genetically altered by mutation or gene amplification include lung, renal, colorectal, glioblastoma, gastric, and head and neck cancers (Christensen-2005). *MET* mutations and high level gene amplification were also recently identified as significant cancer gene alterations in lung adenocarcinoma studies performed as part of the Cancer Genome Atlas consortium project (TCGA-2014a). In the Cancer Genome Atlas lung adenocarcinoma genomics analysis, MET dysregulation resulted from exon 14 skipping, which results in increased protein stability, overexpression, and activation. Approximately 6.5% of lung adenocarcinoma sample demonstrated *MET* exon 14 splice site mutations with exon 14 skipping or high level amplification of the *MET* gene. Furthermore, the expression of both *MET* and *HGF*, its sole, high-affinity ligand, were demonstrated to correlate with poor prognosis or metastatic progression in a number of major human cancers including NSCLC (Christensen-2005). Inappropriate activation of MET is involved in multiple tumor oncogenic processes such as cell growth, angiogenesis, invasive growth, and especially in the metastatic process. MET has also been implicated as a key factor in resistance to both targeted agents and chemotherapeutics. A key example is illustrated by the amplification of *MET* or the overexpression of MET or HGF in patients whose disease failed to respond or acquired resistance to EGFR inhibitors, including erlotinib, gefitinib and cetuximab (Engelman-2007; Yano-2011). The simultaneous inhibition of MET and EGFR in nonclinical lung cancer models with acquired resistance to erlotinib through dysregulation of MET, circumvented resistance and led to tumor regression (Engelman-2007; Yano-2011).

Overexpression or ectopic expression of the Axl RTK and its ligand Gas6 has been reported in a wide array of human cancers including lung, colon, head and neck, breast, ovarian, hepatocellular, and glioblastoma (Li-2009; Rankin-2010). The ectopic expression of high levels of Axl in fibroblasts or epithelial cells resulted in a tumorigenic phenotype implicating it as a transforming oncogene (O'Bryan-1991; Li-2009; Rankin-2010). Axl has been demonstrated to regulate tumor cell proliferation and survival and has also been implicated in tumor angiogenesis (Li-2009; Rankin-2010). Axl expression was correlated with clinical stage and lymph node status in NSCLC. Furthermore, a fusion of *AXL* with *MBIP* was recently reported in NSCLC. Through this fusion, MBIP provided Axl with dimerization motifs enabling Axl kinase to be constitutively activated and become a primary oncogenic driver (Seo-2012). Moreover, recent data have implicated Axl in the resistance to EGFR inhibitors such as erlotinib in NSCLC and cetuximab in HNSCC (Zhang-2012; Byers-2013).

Collectively, the dysregulation of MET and Axl through genetic alterations and ectopic expression in multiple cancers and during cancer drug resistance provides an important opportunity to utilize MGCD265 in the therapeutic intervention in these cancers.

1.1.4 Tumor Gene Sequencing Using Blood Plasma

Whereas analytical techniques evaluating tumor genes in tumor tissue have become accepted for identification of patients for clinical trials of targeted therapies, increasing evidence supports the genetic analysis of circulating DNA in the blood plasma of patients with cancer as an effective and quantitative method for evaluating tumor genetic mutation profiles. Tumor cells release a significant amount of DNA into circulation during cancer progression; cell-free circulating tumor DNA (ctDNA) can comprise greater than 90% of total circulating plasma DNA (Bettegowda-2014, Diehl-2008). Correlative analyses have demonstrated a high degree of concordance for detection of selected genetic mutations (e.g., EGFR, KRAS or multi-gene panels with annotated known cancer mutations) between tumor tissue and ctDNA with specificity for plasma vs. tissue concordance of 99% for mutations with allelic fractions > 0.10% (Bettegowda-2014, Newman-2014). The clinical utility of a ctDNA-based assay to identify a patient population that benefits from treatment with a specific therapeutic agent was demonstrated using a plasma DNA-based companion diagnostic to detect EGFR mutations in the tumors of patients with NSCLC treated with gefitinib (Douillard-2014); the result was European regulatory approval for gefitinib in the indication.

Availability of tumor tissue for tumor gene sequencing and other potentially interesting diagnostic testing is inherently limited in the NSCLC disease setting and becoming more problematic with the increasing number of targeted therapies under study and the required testing with multiple co-diagnostic tests. The capability to evaluate tumor mutation status with non-invasive techniques has the potential to benefit a significant segment of the patient population. In addition, specimens available for tumor tissue-based analysis are frequently archival diagnostic biopsy tissue that are not necessarily reflective of tumor genetic status in more advanced and treated disease. A benefit of analysis of ctDNA is that the sample represents a patient's current tumor genetic profile. In addition, it allows ongoing monitoring to identify new mutations that may occur and indicate resistance to treatment.

In the current study, a ctDNA-based targeted next-generation sequencing (NGS) platform will be used to identify patients having selected *MET* mutations and/or *MET* gene amplification. The ctDNA-based NGS platform was evaluated in more than 150 paired tumor and plasma samples, collected across multiple clinical institutions. The evaluation used 10 well-established genetic markers and demonstrated 97% diagnostic accuracy, 98% specificity and more than 85% sensitivity for the comparison of tumor genes in tissue and plasma samples (data on file at central laboratory). In addition, the analytical technique passed quality control analysis for 99.8% of the more than 500 samples tested. Based on this evidence of robust performance and concordance with tissue-based analyses, the method will be used to identify patients for two independent study treatment arms in the current study, patients having *MET* mutations or *MET* gene amplification.

1.2 MGCD265

MGCD265 is an orally administered multi-targeted RTK inhibitor that primarily targets the Axl and MET receptors. Additional RTK targets potentially include the MERTK, DDR2, and PDGFRα and β receptors.

1.2.1 Drug Substance

Generic Name:	MGCD265 (free base)
Chemical Name:	N-(3-fluoro-4-(2-(5-((2-methoxyethylamino)methyl)pyridine-2-yl)thieno[3,2-b]pyridine-7-yloxy)phenylcarbamothioyl)-2-(4-fluorophenyl)acetamide
Chemical Formula:	$C_{31}H_{27}F_2N_5O_3S_2$
Molecular Weight:	619.71 g/mol

1.2.2 Non-Clinical Data

MGCD265 has demonstrated potent, concentration-dependent inhibition of the kinase activity of MET, Axl family, PDGFR family, DDR2, in biochemical assays and inhibited phosphorylation in cell-based assays. MGCD265 also inhibited MET-dependent cell viability and migration and endothelial tube formation and angiogenesis in cell-based experiments. In a variety of human tumor xenograft models, MGCD265 has demonstrated anti-tumor efficacy including robust tumor regression in models exhibiting genetic alterations of the MET RTK including *MET* mutations and gene amplification.

Based on cytochrome P450 inhibition, induction and metabolism experiments, MGCD265 is expected to have a low potential for drug-drug interactions.

MGCD265 was evaluated in a toxicology program using oral administration to Sprague-Dawley rats and Beagle dogs. In the 28-day rat study, target organ toxicity was observed in bone marrow, liver, kidney and reproductive organs; additional findings were noted in thymus, adrenal gland, exocrine glands, and spleen. In the 28-day dog study, increased emesis and non-formed feces correlated with decreased food consumption and body weight gain; no target organs were identified during histopathology review.

1.2.3 Clinical Data

MGCD265 has been evaluated using various oral formulations and regimens in Phase 1 and 1/2 clinical trials in over 370 patients with advanced malignancies. The safety profile of single agent administration and combinations of MGCD265 and docetaxel or

erlotinib has been evaluated. Details on clinical trial experience are presented in the MGCD265 Investigator's Brochure (IB).

When MGCD265 was administered as a single agent, the most common related treatment-emergent adverse events (TEAEs) were diarrhea (62%), nausea (39%), fatigue (31%), vomiting (26%), aspartate aminotransferase increased (25%), and alanine aminotransferase increased (20%). Grade 3 related TEAEs reported in more than one patient included diarrhea (8%), fatigue (5%), aspartate aminotransferase increased, alanine aminotransferase increased, lipase increased, nausea, and vomiting (2% each), and abdominal pain, anemia, blood alkaline phosphatase increased, blood phosphorus decreased, dehydration, hypertension, and hypokalemia (1% each); Grade 4 related TEAEs included lipase increased (1%) and amylase increased and lymphocyte count decreased (< 1%).

The MGCD265 formulation and regimen to be used at the initiation of the current study is non-aqueous suspension capsules (MGCD265 free base suspended in Miglyol® in soft gelatin capsules and referred to as soft gel capsules), administered twice daily (BID) in a continuous regimen (delivered in 21-day cycles). In the Phase 1 study, MGCD265 systemic exposure increased with increasing dose from 600 to 1050 mg BID, with a less than dose proportional manner between 1050 and 1200 mg BID. The maximum tolerated dose with the soft gel capsules was established at 1050 mg BID. Following single dose administration of 1050 mg BID soft gel capsules, MGCD265 was absorbed, with maximum concentration (C_{max}) occurring at a median time of 8 hours (4-12 hours range) after dosing. The mean elimination half-life was 36.7 ± 13.6 hours (mean ± SD). At steady state, the geometric mean $C_{max,ss}$, $C_{ave,ss}$ and $AUC_{0-12,ss}$ values were 510 ng/mL, 464 ng/mL, and 5572 ng•h/mL, respectively. Drug accumulation was observed after multiple dose administration, whereby C_{max} and AUC_{0-12} were 3.9-fold and 5.2-fold higher, respectively, than single dose administration of 1050 mg soft gel capsules. Mean peak to trough ratio at steady state was 1.18.

A solid, oral MGCD265 drug product consisting of a spray-dried dispersion (SDD) tablet formulation was developed in order to reduce the number of unit doses (pill burden) and eliminate the Miglyol® excipient used in the soft gel capsule formulation. The SDD tablet formulation was introduced into this study with Protocol Version 2.0. The SDD tablet formulation was evaluated in the Phase 1 trial at doses of 500, 750 and 1000 mg BID; 750 mg BID was established as the maximally tolerated dose. Following single dose administration of 750 mg SDD tablets, MGCD265 was absorbed, with C_{max} occurring at a median time of 6 hours (2-24 hours range) after dosing. The mean elimination half-life was 30.9 ± 13.9 hours (mean ± SD) hours. At steady state, geometric mean $C_{max,ss}$, $C_{ave,ss}$ and $AUC_{0-12,ss}$ values were 432 ng/mL, 396 ng/mL, and 4751 ng•h/mL, respectively. Drug accumulation with this regimen was observed and was associated with a C_{max} and AUC_{0-12} values 4.0-fold and 4.5-fold higher than single dose administration, respectively, and mean peak to through ratio at steady state was 1.12. The relative bioavailability comparing 750 mg BID SDD to 1050 mg BID capsules based on steady state dose normalized parameters was around 1.2. The increase in

exposure from 500 mg BID to 750 mg BID at steady state was less than dose proportional with the 750 mg BID dose level yielding approximately 17% higher steady state exposure (geometric mean $C_{ave,ss}$ and $AUC_{0-12,ss}$) than the 500 mg BID dose level.

The rates of absorption and elimination of multiple dose administration of 750 mg BID SDD were comparable to 1050 mg BID soft gel capsules, while the extent of absorption at steady state was approximately 1.2 times greater with 1050 mg BID soft gel capsules as compared to 750 mg BID SDD tablet.

Table 4: Pharmacokinetic Parameters of MGCD265 Soft Gel Capsules and SDD after Single and Multiple BID Administration under Fasting Conditions

MGCD265 Dose Status	**Fasted**			
Formulation	**Soft Gel Capsules**		**Spray Dried Dispersion**	
MGCD265 Dose	**1050 mg, BID**		**750 mg, BID**	
	Single	Steady	Single	Steady
	Dose	State	Dose	State
N	28	26	4	4
Parameter	**Geometric Mean (CV% Geometric Mean)**			
AUC_{0-12} (ng•h/mL)	1214 (63.6)	5572 (44.9)	1149 (76.2)	4751 (60.1)
AUC_{0-24} (ng•h/mL)	2513 (70.9)	11110 (41.7)	2251 (83.7)	9257 (62.1)
$C_{ave,ss}$ (ng/mL)	-	464 (44.9)	-	396 (60.1)
C_{max} (ng/mL)	149 (65.8)	510 (44.8)	124 (85.1)	432 (57.2)
T_{max}[a] (h)	8 (4, 12)	4 (2, 12)	6 (2, 24)	2 (2, 4)
$t_{½}$[b] (h)	36.7 ± 13.6	-	30.9 ± 13.9	-

a. Median (Min, Max);
b. Mean ± SD
Data Source: 265-101 Final Pharmacokinetic Data (02 May 2016)
N = total number of patients
Single dose = PK blood samples were collected up to 48 hours after the first dose in Cycle

To date, the safety profile of the SDD formulation shows a trend for reduced frequency and severity of adverse events. Based on this outcome from the SDD tablet dose escalation, the 750 mg BID dose was established as the recommended Phase 2 dose for the MGCD265 SDD tablet formulation.

Detailed background information concerning MGCD265 can be found in the MGCD265 Investigator's Brochure.

1.3 Study Rationale

MET plays a central role in epithelial tissue remodeling and morphogenesis and is one of the most frequently dysregulated RTKs in several human cancers. Oncology indications in which *MET* was reported to be genetically altered by mutation or gene amplification include lung, renal, colorectal, glioblastoma, gastric, and head and neck cancers. *MET* mutations and/or gene amplification have recently been reported as part of the Cancer Genome Atlas program in approximately 7% of lung adenocarcinoma patients. Furthermore, the expression of both MET and HGF, its sole, high-affinity ligand, was demonstrated to correlate with poor prognosis or metastatic progression in a number of major human cancers including NSCLC. Inappropriate activation of MET is involved in multiple tumor oncogenic processes such as cell growth, angiogenesis, invasive growth, and especially in the metastatic process.

MGCD265 is a small molecule inhibitor of MET and Axl. In vitro studies have demonstrated that MGCD265 is a potent inhibitor of tumor cell proliferation in cells where MET is overexpressed or activated, but not in cells that lacked MET expression/activation. These results are consistent with in vivo studies demonstrating activity of MGCD265 in human tumor xenograft-bearing mouse models, including marked tumor regression in models exhibiting *MET* mutations and/or gene amplification. Additionally, anti-tumor activity has been observed in patients treated with MGCD265 in the Phase 1 study.

The current study is designed to evaluate the tumor response to MGCD265 in patients with NSCLC with activating genetic alterations of *MET* consisting of either *MET* activating mutations or *MET* amplification. The primary endpoint of the study is Objective Response Rate (ORR).

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- To determine the tumor response to MGCD265 in the selected patient population.

2.1.2 Secondary Objective

- To evaluate the safety and tolerability of MGCD265 in the selected population.
- To evaluate secondary efficacy endpoints with MGCD265 treatment in the selected population.
- To assess correlation between selected tumor gene alterations using different analytical techniques in tumor tissue and ctDNA.
- To assess change in genetic alteration status in ctDNA with MGCD265 treatment over time in the selected population.
- To assess the population PK/PD of MGCD265 in the selected population.

2.2 Endpoints

2.2.1 Primary Endpoints

- ORR as defined by RECIST 1.1.

2.2.2 Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.
- Secondary efficacy endpoints:
    - DR;
    - PFS;
    - 1-Year Survival Rate; and
    - OS.
- Gene alterations in tumor tissue and ctDNA at prescreening/baseline.
- Change in ctDNA through time.
- Blood plasma MGCD265 concentration.
- Blood plasma concentration of selected soluble biomarkers.

3 STUDY DESIGN

Study 265-109 is an open-label, parallel arm, Phase 2 trial evaluating the tumor response to MGCD265 in patients with locally advanced, unresectable or metastatic NSCLC exhibiting activating genetic alterations of *MET*.

To be eligible for enrollment, patients must have documented evidence of a genetic alteration activating *MET*, based on molecular testing performed by a Sponsor-approved central or local laboratory.

The primary objective of the study is to determine the tumor response with MGCD265 as measured by ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, tumor genetic alterations in tumor tissue and ctDNA at prescreening/baseline, change in ctDNA through time, and population PK/PD. Schedule of Assessments to be performed in the study is presented in Table 1, Table 2, and Table 3.

MGCD265 will be administered as an oral therapeutic twice daily (BID) in 21-day cycles. Guidelines for study drug administration and dose reduction in the event of toxicity are provided in Section 5.2. Study treatment will continue until disease progression, unacceptable adverse events, patient refusal or death.

Disease response and progression as documented by the investigator in the CRF will be the basis for patient management, study expansion decision making, and secondary and supportive statistical analyses. Central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval as well as the duration of response and PFS. The importance of timely and complete disease assessments in this study is critical for the efficacy endpoints. The need to truncate treatment cycles to manage toxicity may result in inconvenient scheduling of disease assessments. Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias into the assessment of efficacy based on toxicity.

This Phase 2 parallel-arm study will be conducted in four groups of patients having genetic tumor alterations activating *MET*:

A. *MET* activating mutations in tumor tissue,

B. *MET* gene amplifications in tumor tissue,

C. *MET* activating mutations in ctDNA, and

D. *MET* gene amplifications in ctDNA

Full and timely enrollment of patients into Treatment Arms A and B are central to this study meeting its objectives. In addition, for patients enrolled based on a

Sponsor-approved local test, retrospective analysis by the central tissue testing laboratory is key.

Treatment Arms C and D, based on documentation of target gene alteration using the ctDNA test, are intended to include patients for whom central laboratory tumor tissue testing fails for technical reasons, or the search for suitable tumor tissue or test results prove that none exist (to be documented in the patient records).

Individual patients with gene alterations are likely to qualify for entry into two or more treatment arms. The correlation between target gene mutations in tumor tissue and ctDNA is expected to be high. In addition, patients may have both target gene mutation and amplification. The priority for assignment to treatment arm will be in the order A to D listed above.

The Phase 2 study will use a Bayesian Predictive Probability Design (Lee-2008), applied separately and using the same assumptions in each treatment arm (see Section 9.1). Emerging tumor response data will be evaluated continuously beginning after 10 patients in each treatment arm have completed their first on-study disease assessment and are considered part of the mITT population. Stopping rules for futility are described in Section 9.1. Assuming the stopping rules are not triggered, the total sample size to be evaluated in each treatment arm of the Phase 2 study is 45 patients. The primary analysis will be conducted in the mITT (defined in Section 9.3.1).

There is potential for one or more arms of the Phase 2 study to yield results indicating that MGCD265 should be considered to provide an important advancement in treatment in this setting of unmet medical need. If emerging data indicate that an accelerated approval market application may be undertaken for MGCD265 for one or more of the selected patient populations, an analysis of the combined populations may be undertaken, or additional patients may be enrolled into the study, to increase the precision of the 95% confidence interval around the ORR endpoint and/or to increase the size of the safety database in the target patient population. As many as 55 additional patients in the mITT population may be enrolled in up to two treatment arms to ensure collection of sufficient data to support an accelerated approval market application. Whether additional enrollment will include patients with *MET* mutation and/or *MET* gene amplification will depend on the emerging efficacy data in the populations as the study progresses.

Considering the sample size planned for the four treatment arms in the Phase 2 study (45 patients each) and the possible addition of patients to prepare for market application in this setting (55 patients in each of two treatment arms), the ultimate sample size for this study could include as many as 290 patients. Enrollment through the stages of this study will proceed without planned interruption while data are accruing. Decisions will be made expeditiously by the Internal Data Monitoring Committee to prevent excessive over-enrollment and include only outcomes among the specified number of patients according to the stopping rules.

4 SUBJECT SELECTION AND ENROLLMENT

Patient eligibility must be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study. No exceptions to the patient eligibility requirements will be granted by the Sponsor.

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histologically confirmed NSCLC with metastatic or unresectable, locally advanced disease.

2. Receipt of at least one prior platinum-containing chemotherapy or licensed immunotherapy regimen in the advanced disease setting.

3. Molecular analysis of patient-derived samples using a Sponsor- approved method and laboratory that demonstrates a genetic alteration activating *MET* in tumor tissue and/or ctDNA. If eligibility is established using a Sponsor-approved local laboratory, a tumor tissue specimen and/or blood sample is expected to be available for retrospective sequencing in the central laboratory selected by the Sponsor.

4. Measurable disease, as per RECIST version 1.1.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 (Appendix 1).

6. Adequate bone marrow and organ function demonstrated by:

   a. Absolute neutrophil count $\geq 1{,}000/mm^3$ ($\geq 1.0 \times 10^9/L$)

   b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ Upper Limit of Normal (ULN), or $\leq 5.0 \times$ ULN for patients with documented liver metastases. Alkaline phosphatase levels $\leq 2.5 \times$ ULN. In the presence of extensive bone metastases, there is no upper limit for alkaline phosphatase.

   c. Total bilirubin $\leq 1.5 \times$ ULN or $\leq 3.0 \times$ ULN for patients with Gilbert Syndrome or documented liver metastases.

7. $\geq$ 18 years of age.

8. Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment.

9. Completed informed consent process, including signing IRB/EC-approved informed consent form.

10. Willing to comply with clinical trial instructions and requirements.

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Prior treatment with a small molecule or antibody inhibitor of MET or HGF.

2. Prior positive test for *EGFR* mutation or *ALK* gene rearrangement

    - Testing and documentation is required for patients with adenocarcinoma histology;

    - Testing is not required for patients with non-adenocarcinoma histology; however if documentation of a positive test is available, the patient will not be eligible.

3. Most recent prior systemic therapy (e.g. chemotherapy or immunotherapy) or investigational agent discontinued ≤ 2 weeks before first dose date.

4. Absence of recovery from the adverse effects of prior therapy at the time of enrollment to ≤ Grade 2 (excluding alopecia).

5. History of stroke or transient ischemic attack within the previous 6 months.

6. Any of the following cardiac abnormalities:

    a. Unstable angina pectoris,

    b. Congestive heart failure ≥ NYHA Class 3, or

    c. QTc > 480 msec.

7. Known or suspected presence of another malignancy that could be mistaken for metastatic NSCLC during disease assessments.

8. Symptomatic or uncontrolled brain metastases requiring current treatment (less than 4 weeks from last cranial radiation, 2 weeks from stereotactic radiosurgery [gamma knife], or 2 weeks from last steroids). Known conditions associated with significant risk of intracranial bleeding including but not limited to vascular malformations and pituitary adenoma.

9. Inability to swallow oral medications or pre-existing gastrointestinal disorders that might interfere with proper absorption of oral drugs.

10. Known hypersensitivity to any of the components of the MGCD265 Drug Product.

11. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within the screening period prior start of study drug.

12. Breast-feeding or planning to breast feed during the study or within 6 months after study treatment.

13. Any serious illness, uncontrolled inter-current illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.

4.3 Life Style Guidelines

Patients who are biologically capable of having children and sexually active must agree to use an acceptable method of contraception for the duration of the treatment period and for at least 6 months after the last dose of study treatment. The investigator will counsel the patient on selection of contraception method and instruct the patient in its consistent and correct use. Examples of acceptable forms of contraception may include:

1. Oral, inserted, injected or implanted hormonal methods of contraception, provided it has been used for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide
   (Exception: in the European Union, this option does not meet criteria for highly effective contraception and therefore is not an acceptable form of contraception for this study; please refer to the following guidance:

   http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.)

4. Male sterilization with confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

The investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Note: Women are considered post-menopausal and/or not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least

6 months ago. In case of any ambiguity, the reproductive status of the woman should be confirmed by hormone level assessment.

4.4 Enrollment into Study

Genotyping of the tumor sufficient for establishing study eligibility may have been performed historically or more recently for the purpose of considering enrollment in this study. In all cases, informed consent for tumor genotyping (using tumor tissue or ctDNA) must be documented prior to submission of samples for testing. The informed consent for tumor testing may be performed in accordance with established institutional practice, or using the study-specific, IRB-approved pre-screening informed consent associated with this study.

If the Sponsor-provided central laboratory is used to perform tumor genotyping to establish eligibility for the study, a 14-day turn-around time should be expected from the time of receipt of adequate samples at the central lab to test results returned to the study site. Questions concerning adequacy of samples will cause delay beyond this timeframe.

Following completion of the full, study-specific informed consent process and review of all screening procedures, patient eligibility will be confirmed by appropriately qualified staff at the investigational site. Patients will be enrolled by entry into a patient registration log provided by the Sponsor and maintained by the study site and completion of the patient registration procedure detailed in the Study Manual. Each patient will be assigned a sequential number by the study site. The patient number must be used on all documentation and correspondence with the Sponsor, Contract Research Organization (CRO) and laboratory vendors.

5 STUDY TREATMENT

5.1 Study Drug Management

5.1.1 Formulation and Packaging

MGCD265 study drug will be supplied by the Sponsor. At the beginning of the study, the presentation was soft gel capsules containing the free-base form of MGCD265 and inert excipients: Miglyol®, Labrafil®, fractionated coconut oil, Capsule Gel 60, Gelatin 195 Acid Bone and glycerin. Dosage strength is 150 mg (white opaque capsule), calculated as free-base corrected for purity.

Soft gel capsules are supplied in 40 count, high-density polyethylene (HDPE) bottles with child resistant closures. Bottles will be labeled in compliance with the legal requirements per country. Labels will be printed in the languages required in the countries in which the study is conducted.

MGCD265 Spray-Dried Dispersion [SDD] tablet formulation is being introduced with a protocol amendment (Version 2.0). Dosage strength will be 100 mg and 250 mg. Inert excipients in the SDD tablet include hydroxypropylmethyl cellulose (HPMC), Avicel® (or equivalent), Kollidon® (or equivalent), sodium bicarbonate, sodium chloride, Syloid® (or equivalent), and magnesium stearate, as necessary.

SDD tablets will be supplied in HDPE, white opaque bottles. A tamper-proof heat induction seal and a child-resistant closure are used. Tablet bottles will be received by the pharmacy in foil pouches that are to be kept intact until the bottles are dispensed to the patient. Bottles will be labeled in compliance with the legal requirements per country. Labels will be printed in the languages required in the countries in which the study is conducted.

Refer to the Pharmacy Study Manual for details on available study drug presentations, unit dose strengths, bottle sizes, and number of units per bottle supplied.

5.1.2 Drug Storage and Accountability

MGCD265 study drug should be stored as directed on the package labeling. The storage area should be secure with limited access and monitored for temperature using a calibrated thermostat. Shelf-life evaluation of the intact bottles is ongoing. Available stability data for the soft-gel capsules support ≥ 24-months shelf-life when stored at room temperature (suggested temperature range 15-30°C, 59-86°F).

SDD tablets, while stored in the study site pharmacy, should be kept in the unopened foil pouches under refrigerated conditions (suggested temperature range 2-8°C, 36-46°F). Once dispensed to patients, bottles should be stored at room temperature (suggested temperature range 15-30°C, 59-86°F). Available stability data for the SDD tablets support > 12 months shelf-life for pharmacy storage at refrigerated conditions and > 4 months shelf-life when stored at room temperature after dispensation to the patient.

All study treatment supplies will be accounted for in the drug accountability inventory forms supplied by the Sponsor or using forms according to local site procedures that include all required information. The drug accountability inventory forms must identify the study drug, including batch or lot numbers and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

5.1.3 Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Study site personnel should dispense to patients the appropriate number of study drug units of each strength to support a 21-day cycle. An additional number equivalent to

two dosing days may be dispensed at the discretion of the study site to provide for holidays or inclement weather. Study drug should be dispensed in the Sponsor provided HDPE bottles with child resistant closures. Patients should be made aware of the storage temperature requirements.

5.1.4 Compliance

Study site personnel should provide each patient with dosing information and review it with the patient during clinic visits. Patients will be asked to record their daily dosing on Sponsor provided diary cards and report any missed doses or lost study drug at the next clinic visit. Patients will also be told to bring study drug bottle(s) (empty or not) with them to the clinic visit for a compliance check and unit count. Study site personnel will record compliance information in the source document and on the CRF and retain the bottle(s) until a monitor has completed reconciliation. See the Study Manual for additional details regarding compliance and reconciliation.

5.1.5 Destruction

At the end of the study, all unused drug supplies must be destroyed in accordance with local Standard Operating Procedure provided to the Sponsor for the Trial Master File, or returned to the Sponsor or its appointed agent, as directed by the Sponsor.

5.2 Administration

MGCD265 study drug will be administered orally twice daily (BID) in 21-day cycles. The starting dose of MGCD265 using the soft gelatin capsules was 1050 mg BID. The starting dose using the SDD tablets will be 750 mg BID. At the time of protocol amendment (Version 2.0) approval at each institution, newly enrolled patients will begin dosing at 750 mg BID with the SDD tablet formulation. Ongoing patients who initiated treatment with soft-gel capsules will be allowed to switch to the SDD tablet formulation at their next treatment cycle. The dose level of the SDD tablet will need to be discussed on a case-by-case basis with the Sponsor prior to the patient receiving the SDD tablet formulation.

MGCD265 doses should be taken approximately every 12 hours at approximately the same times each day, on an empty stomach (1 hour fast before each dose and no food for a minimum of 1 hour after each dose). Each dose should be taken with approximately 200 mL of water.

A food effect evaluation is currently being conducted in the MGCD265 Phase 1 study. If the outcome of that evaluation indicates that patients may take MGCD265 SDD tablets with food, this change will be communicated to participating institutions.

If the patient vomits after taking the study drug, s/he should not make up the missed dose or increase the next dose.

5.2.1 Dose Modification

Study treatment-related adverse events that are intolerable or severe will be managed by treatment interruption and/or dose reduction depending on the circumstance. In response to observed toxicity, daily doses should be reduced by steps of at least 15-20% within the constraints of the available capsule or tablet dose strengths. Necessary dose reductions will typically be made in sequential steps but, under some circumstances, dose reduction by two steps (i.e., 30-40%) may be advisable and may be considered in consultation between the investigator and Sponsor (See Table 5 and Table 6). Dose reductions below the current guidelines may be allowed after consultation between the investigator and Sponsor. Patients requiring greater than 3 weeks to recover from drug-related toxicity should be considered for discontinuation from study treatment.

Table 5: Dose Adjustment Guidelines Soft Gel Formulation

Soft Gel - Capsule Formulation		
Dose Level	**265 Daily Dose (BID Dose)**	**Number of capsules (150 mg capsule strength)**
0 (Starting Dose)	2100 mg (1050 mg BID)	14 total (7 BID)
-1	1800 mg (900 mg BID)	12 total (6 BID)
-2	1500 mg (750 mg BID)	10 total (5 BID)

Table 6: Dose Adjustment Guidelines Spray Dried Dispersion Formulation

Spray Dried Dispersion – Tablet Formulation		
Dose Level	**265 Daily Dose (BID Dose)**	**Number of tablets (100 mg and 250 mg tablet strength)**
0 (Starting Dose)	1500 mg (750 mg BID)	6 total (3 BID) [3-250 mg BID]
-1	1200 mg (600 mg BID)	6 total (3 BID) [2-250 mg BID; 1-100 mg BID]
-2	1000 mg (500 mg BID)	4 total (2 BID) [2-250 mg BID]

Dosage interruptions to assess or treat intercurrent illnesses are allowed as needed in the judgment of the investigator.

5.2.2 Adverse Event Management Guidelines

Management of toxicities ≥ Grade 3 and considered to be treatment-related should include treatment interruption until resolution of toxicity to ≤ Grade 1 or to baseline

value. If the toxicity may be adequately managed by routine supportive care (such as anti-emetics, anti-diarrheals, or electrolyte supplementation), treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose as described in Table 7. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for more than 3 weeks, permanent discontinuation from study treatment should be considered.

Table 7: Dose Modifications – Treatment-Related Toxicities

Toxicity	Treatment Delay	Dose Modification
< Grade 3	May be implemented based on Investigator and patient discretion	
Grade 3 or 4, manageable with routine supportive care	Hold until ≤ Grade 1 or return to baseline	Not required
Grade 3 or 4, not manageable with routine supportive care	Hold until ≤ Grade 1 or return to baseline	Resume at a dose level one or more levels below that inducing the toxicity

5.2.2.1 Management of Diarrhea

Prevention and treatment of diarrhea should be aggressive to limit patient morbidity and to prevent potentially premature study drug discontinuation. Example treatment regimens are recommended here and in Section 5.4.1, Concomitant Medications.

Prophylactic anti-diarrheal treatment may be implemented at the discretion of the investigator. A regimen recommended for primary prophylaxis for diarrhea is loperamide 2-4 mg beginning with the first dose of MGCD265, followed by 2 mg every 6–8 hours. Loperamide use may be titrated as needed.

To date, diarrhea has been effectively managed after onset in most subjects by symptomatic treatment with Imodium® (loperamide) and, when indicated, with the addition of Lomotil® (diphenoxylate and atropine). Patients treated with MGCD265 should be given instructions to be aware of the potential of developing diarrhea while taking MGCD265 and to start treatment with loperamide immediately upon the first sign of diarrhea. If there is no improvement in severity of symptoms within 24 hours, additional anti-diarrheal medication in the form of Lomotil® should be added. If this does not effectively control symptoms, patients should be instructed to contact their physician and their dose held until resolution of symptoms followed by a dose reduction as indicated per protocol. Patients with severe or prolonged diarrhea should be observed and treated for dehydration.

5.2.2.2 Management of Increased Transaminases

Increased transaminases should be evaluated to determine whether confounding factors exist, such as metastatic lesions or biliary obstruction. For cases where treatment-related

increases are likely, dose modifications may be made with investigator discretion in consideration of clinical factors. Suggested recommendations are shown in Table 8.

Table 8: Treatment Modification for Increased Hepatic Transaminase

Toxicity	Treatment Delay	Dose Modification
Grade 1 (> ULN to 3.0 × ULN)	May be implemented based on Investigator and patient discretion	
Grade 2 (> 3.0 to 5.0 × ULN)	Not required	Decrease by 1 dose level
Grade 3/4 (> 5.0 × ULN)	Hold until ≤ Grade 1 or return to baseline	Decrease by at least 2 dose levels for a first dose reduction; decrease by at least 1 dose level if dose is already reduced.

5.2.2.3 Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increases in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN), that is not attributable to liver metastases or biliary obstruction, investigational study treatment should be permanently discontinued.

5.3 Medication Error

Medication errors may involve patient exposure to a wrong study drug, at a wrong dosing frequency, or at a wrong dose level (e.g., a dose that is not planned in the study). Medication errors occurring during the conduct of this study will be documented as AEs (regardless of whether clinical signs or symptoms are observed) and if serious consequences are observed, will be reported on Serious Adverse Event (SAE) forms. In all cases of medication error, the sponsor should be notified immediately.

5.4 Concomitant Therapies

5.4.1 Concomitant Medication(s)

Concomitant medications must be locally-approved and used at doses and regimens that are considered standard of care.

Treatment for co-morbidities, disease signs and symptoms and treatment emergent adverse events should be provided as necessary in the judgment of the investigator. Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria or treatment plan. Supportive medication (e.g., antiemetics, analgesics, anti-diarrheals, etc.) is permitted.

Prophylactic anti-diarrheal medication may be administered at the discretion of the investigator as described in Section 5.2.2.1.

Antibiotics and analgesics should be used as needed. Patients with neutropenic fever or infection should be treated promptly. Therapeutic colony-stimulating factors should be used in accordance with American Society for Clinical Oncology guidelines. Packed red blood cell and platelet transfusions may be administered as clinically indicated.

5.4.2 Concomitant Surgery or Radiation Therapy

The use of surgery or radiation to manage cancer lesions during study treatment can jeopardize assessment of the primary objective of the study, evaluation of disease status; thus where clinically justified and possible, such treatment should be undertaken prior to study enrollment.

Although bleeding events have been reported with MGCD265 treatment, there have been no reported bleeding complications following surgical procedures performed in subjects treated with MGCD265. Significant inhibition of the VEGF receptor (VEGFR) pathway is not expected with MGCD265. For patients requiring surgery while on-study, MGCD265 dosing should be held for 3-7 days prior to any applicable procedure when possible, and treatment should be re-initiated once adequate closure or healing of the surgical site is established.

Any foreseeable need for palliative radiotherapy should be addressed before study entry, if possible and clinically appropriate (e.g., bone lesions at risk for spontaneous micro-fractures or painful lesions). However, these treatments may be used on-study where it is medically necessary. For patients requiring radiation while on-study, MGCD265 should be interrupted during the period that the patient is receiving radiation treatment.

5.4.3 Other Anticancer or Experimental Therapy

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period, including chemotherapy, biological response modifiers, hormone therapies or immunotherapy. No other investigational drug may be used during treatment on this protocol. Concurrent participation in another therapeutic clinical trial is not allowed.

6 STUDY ASSESSMENTS

6.1 Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed. Patients who completed the informed consent process but did not enroll on the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.

6.2 Study Period

For details on procedures during the study period, see Schedule of Assessments as shown in Table 2.

6.3 End of Treatment Assessment

All patients will be followed for adverse events and serious adverse events for at least 28 days following the last dose of MGCD265. See the Schedule of Assessments (Table 2) for evaluations to be performed at the End of Treatment visit.

6.4 Long-Term Follow-up and End of Study Assessment

Patients will be followed for survival at two month intervals as outlined in the Schedule of Assessments (Table 2). Treatments received following participation in the study will be collected in the CRF.

6.5 Patient Discontinuation/Withdrawal

Patients may discontinue from study treatment or from the study at any time at their own request, or they may be discontinued at any time at the discretion of the investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Criteria that may be used to discontinue patients from receipt of study medication will include, but will not be limited to:

- Objective disease progression according to RECIST 1.1 as determined by the investigator (patients who may derive clinical benefit may continue on treatment at the discretion of the investigator);
- Global deterioration of health status requiring discontinuation;
- Adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Refusal for further treatment;
- Study termination by Sponsor;
- Pregnancy;
- Death.

Reasons for discontinuation from study follow-up may include:

- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. At least 2 attempts should be made to contact the patient, and each attempt should be recorded in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient returns for a final visit, and if applicable, follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study treatment and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such refusal for further follow-up.

7 PROCEDURES

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that there may be circumstances outside of the control of the investigator that may make it unfeasible to perform a protocol-specified assessment. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed, the investigator will document in the source document and CRF the reason and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1 Molecular Testing for *MET* Mutations and Amplifications

To be eligible for enrollment, patients must have documented evidence of a genetic tumor alteration activating *MET*.

7.1.1 Genetic Tumor Alterations Required for Study Entry

Presence of an eligible *MET* gene alteration is defined as follows:

1. *MET* Mutations (based on human genome **GRCh37**/hg19 assembly and MET reference sequence NM_000245):

    - *MET* mutations that result in the alternative splicing or selective deletion of MET exon 14 as determined by gene sequencing or ribonucleic acid (RNA)-based reverse transcription polymerase chain reaction (qRT-PCR) analysis indicating:

        - point mutations involving c2888 or c3028 splice sites (or equivalent according to analytical reference standard), or

        - insertion or deletion mutations involving or proximal to c2888 or c3028 splice sites (or equivalent according to analytical reference standard), and/or

        - selective deletion of MET exon 14

    - *MET* activating mutations including but not limited to, P991S, Y1003F, Y1003N, Y1003*, V1070E, V1070R, V1092L, H1094L, H1094Y, H1094R, H1106D, M1131T, T1173I, V1188L, L1195V, V1220I, D1228H, Y1230C, Y1230H, Y1230D, Y1235D, Y1235H, M1250T.

        - Please note that these mutations have an alternative nomenclature based on GRCh37/hg19 assembly and MET reference sequence NM_001127500 as follows: P1009S, Y1021F, Y1021N, Y1021*, V1088E, V1088R, V1110L, H1112L, H1112Y, H1112R, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, D1246H, Y1248C, Y1248H, Y1248D, Y1253D, Y1253H, M1268T.

2. *MET* Gene Amplification in tumor tissue defined by any of the following:

    - Loose or tight clusters of *MET* too numerous to count as determined by *MET* 2-color fluorescent in situ hybridization (FISH)

    - *MET*/CEP7 ratio of > 5.0 in > 10% of evaluated cells as determined by *MET* 2-color FISH

    - Greater than or equal to 10 copies of *MET* per nucleus as determined by *MET* 2-color FISH

    - Greater than 8 copies in an appropriate molecular assay (DNA sequencing-based platform).

For ctDNA based analysis, a positive result for *MET* mutation or gene amplification by the Sponsor-provided central laboratory (Guardant) is required.

The method used to establish eligibility and the result will be documented in the patient's site source documents and the CRF.

7.2 Molecular Testing Methods

Potential study candidates will undergo molecular testing of tumor tissue or blood in order to first establish eligibility of molecular alterations; those patients with qualifying mutations will then undergo clinical screening, and eligible patients [based on both qualifying mutation(s) and clinical screening] will then be assigned into a patient treatment arm upon confirmation of study eligibility.

Testing of tumor tissue is prioritized over ctDNA for the purpose of determining eligibility for this study. Tumor tissue samples preferred for testing are the most recent tumor sample available; however, testing may be performed on samples taken any time during the disease course. Testing may be performed on primary, recurrent, or metastatic lesions. Biopsies having significant risk should not be performed for the purpose of determining patient eligibility, including but not limited to biopsies of the lung/mediastinum or endoscopic procedures extending beyond the esophagus, stomach, or bowel. However, in the event that a patient desires to consider study participation and no tumor specimen is available, procedures having less risk may be considered.

Tumor tissue or ctDNA may be tested using the Sponsor-provided central laboratory or a Sponsor-approved local laboratory to establish eligibility, with follow-up tissue or ctDNA sample(s) retrospectively analyzed in the Sponsor-provided central laboratory.

Qualifying results by ctDNA testing may be the basis for study eligibility if the search to locate tumor tissue that is suitable for testing shows that none exists.

The analytical techniques employed by the Sponsor-provided central laboratories and criteria for acceptable genetic tumor alterations for this study are described in the Study Laboratory Manual. Included are:

1. Gene panels for the next generation sequencing tests for tumor tissue and ctDNA samples,

2. List of *MET* mutations known to be activating,

3. Description and use of RT-PCR for detection of *MET* exon 14 deletion mutations, and

4. Definitions for quantitative thresholds for positive test results.

If study eligibility is to be based on tumor tissue or ctDNA testing at the Sponsor-provided central laboratory, a 14-day turn-around time should be expected from the time of receipt of adequate samples at the central lab to test results returned to the study site. Questions concerning adequacy of samples will result in delays beyond this timeframe. It is possible that testing could be more rapid, e.g., 8-10 days, but the patient and site should be prepared to wait for confirmation of eligibility for the full duration.

The laboratories employed by the Sponsor to perform initial or retrospective confirmatory evaluation of tumor gene alterations are certified by Clinical Laboratory Improvement Amendments (CLIA). Guidance on sample preparation and submission can be found in the Study Laboratory Manual.

The following laboratories are considered Sponsor-approved local laboratories for this study and prospective confirmation of eligibility from our central laboratory is not required prior to enrollment. Additional Sponsor-approved local laboratories may be added during the study. Tissue and ctDNA samples for retrospective analysis are requested for all patients that are enrolled based on a Sponsor-approved local laboratory test:

- FoundationOne®, a commercially available next generation gene sequencing test for tumor tissue performed by Foundation Medicine, Inc.
- Caris Molecular Intelligence ®, a commercially available next generation gene sequencing test for tumor tissue performed by Caris Life Sciences.
- Guardant360®, a commercially available next generation gene sequencing test for ctDNA performed by Guardant Health.

On a case-by-case basis, information in addition to what is typically reported for commercial tests may be needed from Foundation Medicine, Caris Life Sciences and Guardant to make a final determination of eligibility (e.g., quantitative results for gene amplification).

Positive results from a site-specific local laboratory that may meet the criteria for molecular profiling eligibility will need to be confirmed by the Sponsor-provided central laboratory prior to full clinical screening.

7.3 Efficacy

All patients enrolled in the study are to be evaluated for disease activity as outlined in the Schedule of Assessments (Table 2). Disease assessments are to be performed as scheduled according to the calendar days regardless of treatment delays. On-study assessments will be performed at 6 week intervals until approximately 1-year and then every 12 weeks. The allowable windows for assessments are 4 weeks prior to first study treatment for screening/baseline assessments and ±10 days for on-study disease assessments. CT scans should be performed with contrast agents unless contraindicated for medical reasons. If intravenous contrast is medically contraindicated, the imaging modality to be used (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and MRI should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not

adequate for evaluation of lung parenchyma but should also be performed to evaluate all other aspects of the chest. MRI of the abdomen and pelvis should substitute for CT with contrast unless the method does not adequately depict the individual's disease, in which case CT without contrast is preferred.

For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions.

Screening/baseline tumor assessments should include CT or MRI of the chest and abdomen, pelvis, whole body bone scan, MRI of the brain and evaluation of any superficial lesions. For those sites that routinely use PET scans for assessment of bone lesions in lieu of skeletal scintigraphy, PET scans may be used on-study, with the same modality planned throughout the study for any given patient. CT or MRI of the chest, abdomen, and pelvis will be conducted at every subsequent assessment. Disease assessments subsequent to baseline assessment should also include whole body bone scans and/or MRI of the brain if metastatic disease is identified at screening/baseline by either the investigator OR the central radiology reviewer. Bone scans may be performed at one-half the frequency (every 12 weeks) of other disease assessments. All other suspected sites of disease should be evaluated at each assessment. Disease response will be assessed in accordance with RECIST 1.1 (Eisenhauer-2009). Appendix 2 provides guidance in using the response criteria and includes a modification to RECIST 1.1 to address potential temporary treatment effects such as tumor lesion cavitation. Assessments will be performed until objective disease progression is documented by the investigator, or subsequent anti-cancer therapy is begun.

Patients experiencing tumor response (Partial Response [PR] or Complete Response [CR]) should undergo confirmatory assessment at least 4 weeks after initial documentation of response. It is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol. Bone scan is required as an element of the assessment of PR or CR response confirmation if bone lesions were identified at the baseline assessment. When bone scans are not protocol-specified, assessment for time point response will be based on assessment of all other lesions with imputation of Non-CR/Non-PD for bone lesions recorded as non-target lesions.

The investigator's assessment of disease response and progression will be the basis for patient management and study expansion decision making. Potential exists for individual tumor lesions to cavitate or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis and cavitation may result in minor increase in overall individual lesion size or unclear tumor margins prior to recovery to a smaller lesion, development of scar tissue, or complete resolution. For this reason, investigators may delay reaching the conclusion of disease progression until subsequent on-study disease assessments are performed.

Central radiology review for disease response and progression will be performed in this study and will be the basis for the primary statistical analysis used to estimate the objective response rate and its confidence interval as well as the duration of response and PFS. Materials to be forwarded for independent review will be all imaging studies performed at screening and on study, preferably in digital format, using an electronic transfer through a portal to the review vendor or transfer on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films. Further information on materials to be forwarded for independent review is provided in the core imaging laboratory Study Manual.

7.4 Safety Assessments

7.4.1 Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.03]), timing, seriousness, and relatedness to study treatment.

Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present at baseline will be recorded in the CRF as adverse events. Treatment-emergent adverse events will be reported separately from signs and symptoms of the patient's cancer diagnosis and/or comorbidities that are present at Day 1. The actual date of onset should be recorded in all cases. Ongoing AEs that change in attribution or severity should have the date of change entered as the "end date" and a new AE record should be opened with the changed details.

7.4.2 Physical Examination and Vital Signs

A physical examination including all major body systems is mandated at Screening and End of Treatment Visits only. During study treatment, symptom directed physical examinations will be performed.

Vital signs to be assessed include weight, body temperature, blood pressure, and pulse rate. Height will be recorded at screening only. On days when both vital signs and PK sampling are scheduled, the vital signs should be assessed prior to blood sampling.

Clinically significant findings noted during screening will be reflected on the medical history CRF, while those noted during study treatment will be collected on the AE CRFs.

7.4.3 Laboratory Safety Assessments

Laboratory safety assessments for which data will be collected in this study will include hematology, coagulation, and chemistry parameters presented in Table 9.

Laboratory tests will be drawn at the time points described in the Schedule of Assessment table and analyzed at local laboratories. Additional laboratory tests may be performed per standard of care, at the investigator's discretion for the purpose of planning treatment administration, dose modification, following adverse events, or as clinically indicated.

Table 9: Laboratory Safety Parameters

Hematology Panel	Blood Chemistry Panel
Hemoglobin	Aspartate aminotransferase (AST)
Platelet count	Alanine aminotransferase (ALT)
White blood cell count (WBC)	Alkaline phosphatase
Neutrophil count	Total bilirubin
Lymphocyte count	Creatinine
Eosinophil count	Uric acid
Basophil count	Albumin
Monocyte count	Sodium
	Potassium
Coagulation	Chloride
International normalized ration (INR)	Total calcium
Partial thromboplastin time (PTT)	Phosphate
	Magnesium

Pregnancy Testing: For patients of childbearing potential, a serum or urine pregnancy test will be performed at screening. Pregnancy tests will also be done whenever pregnancy is suspected during the study. Additional pregnancy testing may be necessary if required by local practices or regulations.

7.4.4 Electrocardiogram (ECG)

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Assessments reported by automated read as prolongation of QTc > 480 msec should be over-read by a cardiologist to ensure accuracy of interpretation.

7.5 Laboratory Studies

Laboratory studies for which blood will be collected include evaluation of PK, PD and ctDNA. The schedules for sample collection are outlined in Table 2 and Table 3. Blood samples will be collected using an in-dwelling catheter or venipuncture into specified

vacutainer tubes. Full details on sample processing, storage and shipment are presented in the Study Laboratory Manual.

7.5.1 Pharmacokinetic Evaluation

The PK of MGCD265 will be determined using plasma samples collected at specified time points prior to and following study treatment dosing. Every effort will be made to collect these PK samples at the exact nominal times relative to dosing. A variation window is allowed for each time point as outlined in Table 3. The actual time of drug administration and each PK sample collection will be recorded in the patient's source document and the CRF.

At each PK time point, blood samples will be collected into 6-mL K2EDTA tubes. For PK analysis, a total of approximately 48 mL of blood will be collected from each patient. Analysis of plasma samples for MGCD265 will be performed using specific validated bioanalytical methods.

7.5.2 Pharmacodynamic Evaluation

Pharmacodynamic parameters that may be investigated in this study include but are not limited to plasma levels of hepatocyte growth factor (HGF) and shed-MET receptor, prior to and during treatment. At each PD time point, whole blood samples will be collected into 10-mL K2EDTA tubes. For PD analysis, a total of approximately 40 mL of blood will be collected from each patient.

7.5.3 Circulating Tumor DNA

Blood samples for ctDNA analysis will be collected at pre-screening or baseline, at the time of disease evaluation to confirm a disease response (PR or CR) and at the End of Treatment visit, as outlined in Table 2. For patients who are enrolled based on prospective ctDNA testing, an additional sample may be requested prior to dosing to ensure adequate amounts of blood have been received to complete the remainder of analyses required per protocol. Parameters that will be evaluated include but are not limited to *MET* mutations, *MET* gene amplification, *MET* gene rearrangement, and other genetic mutations or gene copy number changes associated with the pathogenesis of human cancers.

At each ctDNA time point, blood samples will be collected into two 10mL Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures. For ctDNA analysis, the total volume of blood to be collected between pre-screening and End of Treatment will be up to approximately 60 mL of blood.

7.6 Post-treatment Follow-up

Post-treatment follow-up for survival will be conducted by telephone contact or other methods every 2 months (± 14 days) until death or lost to follow-up. Treatments received subsequent to study participation will be collected and recorded in the CRF.

8 ADVERSE EVENT REPORTING

8.1 Sponsor Medical Monitor Personnel

The contact information for the sponsor's Medical Monitor personnel for this trial is available in the study contact list located in the Study Manual.

8.2 Adverse Events

An adverse event (AE) is any reaction, side effect or other undesirable medical event that occurs during participation in a clinical trial, regardless of treatment group or suspected causal relationship to study treatment. All observed or volunteered AEs will be recorded in source documents and reported in the CRF. The best available medical terminology should be used to describe AEs in source documents and CRFs. Terms describing the diagnosis are preferred over individual signs and symptoms of the diagnosis. If determination of the diagnosis is delayed, record signs and symptoms and add the diagnosis as an additional AE when available; follow all recorded AEs to resolution. Examples of AEs include but are not limited to:

- Signs or symptoms of co-morbidity, illness, or toxicity of study treatment;
- Signs or symptoms of worsening malignancy under study (disease progression assessed by measurement of malignant lesions should not be reported as an AE).
- Laboratory abnormalities (see Section 8.2.1 for guidance for reporting in CRF);
- Hypersensitivity;
- Drug abuse, dependency, overdose, withdrawal or misuse;
- Signs or symptoms of drug interactions;
- Extravasation;
- Exposure during pregnancy or via breastfeeding;
- Medication error; or
- Occupational exposure.

8.2.1 Laboratory Abnormalities

An abnormal laboratory test results should be reported as an AE in the CRF only if it is associated with one or more of the following:

- Clinical symptoms;
- Requires additional tests (beyond repeats), treatment or intervention;
- Results in change in study treatment dosing;
- Requires discontinuation from study treatment; and/or
- Considered by the investigator or Sponsor to be an AE.

Hy's Law

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × ULN concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's Law and raises the concern for drug-induced liver injury when no other cause of the abnormal laboratory results is identified. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Cases meeting Hy's Law should be reported as SAEs. Study drug should be permanently discontinued for a Hy's Law case.

8.2.2 Severity Assessment

AEs occurring during this study will be graded in accordance with the NCI CTCAE Version 4.03. Documentation of AE grading in the source documents and CRF should be consistent with provided definitions.

8.2.3 Causality

For each AE, the investigator should determine and document whether there exists a reasonable possibility that the study treatment caused or contributed to the AE. The investigator's assessment should be recorded in the source document. The CRF will provide the options for attribution to study treatment as "related" and "not related." If the investigator's causality assessment is "unknown but not related to investigational product," this should be recorded in the CRF as "not related." If the investigator does not know whether or not the study treatment is causally-related to the event, reporting for study purposes will be as "related" to study treatment.

Collection of causal relationship for AEs associated with study procedures (e.g., tumor biopsy) is provided for separately in the CRF.

8.3 Serious Adverse Events

8.3.1 Definition of a Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/permanent damage (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

Progression of the malignancy under study, including any signs or symptoms of progression that may require hospitalization, should not be reported as an SAE unless the outcome is fatal within the safety reporting period.

Definition of Terms

Life threatening: An AE is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalization: Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not

worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/permanent damage: An AE is disabling or caused permanent damage if it resulted in a substantial disruption of a person's ability to conduct normal life functions, e.g., a significant, persistent or permanent change, impairment, damage or disruption in body function/structure, physical activities and/or quality of life.

8.3.2 Exposure During Pregnancy

Exposure during pregnancy (i.e., exposure in-utero [EIU]) may occur in a female study participant, the female partner of a male study participant or study site personnel working with the investigational product (e.g., occupational exposure) if:

- A female becomes or is found to be pregnant during treatment or within 6 months after discontinuing treatment or having been directly exposed to the investigational product;

- A male is exposed to the investigational product prior to or around the time of conception or during the pregnancy of his partner.

If exposure in-utero occurs, the investigator must submit an SAE form and an EIU Supplemental Form within 24 hours of awareness of the exposure, regardless of whether an AE or SAE has occurred.

In the event of pregnancy in a female study participant, if the pregnancy is continued, study treatment will be immediately discontinued.

In the event of exposure of the pregnant partner of a male study participant, the study participant should be asked to deliver an EIU Pregnant Partner Release of Information Form to his partner. The Investigator must document on the EIU Form that the patient was given this letter to provide to his partner.

Follow-up to obtain pregnancy outcome information is to be conducted for all EIU reports. In the case of a live birth, the health of the neonate should be assessed at the time of birth and for up to 3 months after birth. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the event the pregnancy is terminated, the reason(s) for

termination should be reported and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection.

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), an SAE report should be submitted to the Sponsor.

8.4 Reporting of SAEs and AEs

8.4.1 Reporting Period

The active reporting period for SAEs begins from the time that the patient provides main study informed consent (i.e., prior to undergoing any study-specific procedure or assessment) and continues until all SAEs have resolved or stabilized to a chronic condition, whichever is later. Death must be reported if it occurs during the active reporting period for SAEs regardless of whether a subsequent anticancer therapy is administered. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them and if the investigator assesses at least a reasonable possibility of being related to study drug.

The reporting period for non-serious AEs begins from the day of first dose of study treatment and continues until at least 28 days after last administration of study treatment and/or until recovery from all acute toxicities associated with the drug administration to a chronic condition, whichever is later. If a patient begins a subsequent anticancer therapy, the AE reporting period ends at the time the new treatment is started.

8.4.2 Reporting Requirements

All SAEs must be reported within 24 hours of Investigator/site knowledge of the event, irrespective of the extent of available AE information, by faxing the SAE report to the Sponsor's pharmacovigilance representative designated in the Study Manual. The 24-hour timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports and to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. The need for an expedited report to regulatory authorities will be determined by the Sponsor and necessary reporting will be performed by the Sponsor. The Sponsor will notify study investigators of all Suspected, Unexpected (as judged against the Investigator Brochure) Serious Adverse Reaction (SUSAR) reports. The investigator is responsible for reporting all SUSARs to the IRB/EC.

All AE (including SAEs) must be documented in source documents and reported in the CRF. Please note that the CRF and SAE report forms may collect information in somewhat different formats. Where the requested data overlap in different formats, the information should be consistent between the two forms.

9 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1 Hypothesis and Sample Size

This Phase 2, parallel-arm study will use a Bayesian Predictive Probability Design (Lee-2008) that minimizes the number of patients enrolled to test the hypothesis. The design will be applied separately and using the same assumptions in each of four treatment arms. As many as 45 patients are planned for inclusion in the primary analysis for each treatment arm. The study also provides for the addition of up to 55 patients to each of two treatment arms to provide sufficient safety and/or efficacy data to support an accelerated approval market application in two study populations. Thus, the ultimate sample size for this study could include as many as 290 patients.

ORR in accordance with RECIST v1.1 is the primary endpoint. With currently available treatments, ORR is assumed to be 20% (p_0), thus this rate is considered uninteresting. The target ORR using MGCD265 in this study is 40% (p_1). The trial will monitor the number of observed responses continuously after evaluating the first on-study disease assessments of the first 10 patients in each treatment arm in the mITT population. In creating the statistical design, the Type 1 error (α) is constrained to < 0.05 and Power ($1-\beta$) is constrained to ≥ 0.90.

Using the parameters identified, the ultimate sample size for each treatment arm is as many as 45 patients in the mITT population. The stopping rules (rejection regions), expressed as number of responses per patients treated, are 0/10, 1/14, 2/18, 3/22, 4/26, 5/29, 6/32, 7/35, 8/37, 9/39, 10/41, 11/43, 12/44, and 13/45. Thus, if more than 13 responses are observed among the first 45 patients enrolled who meet the criteria for the mITT population, the drug will be declared efficacious. If the true ORR is 20% (null hypothesis), the probability of early termination (under H_0) during the study is 0.92 and the expected sample size prior to termination is 28 patients. The Type 1 error is equal to 0.0499 and Power equal to 0.9065. If the true ORR is 40%, the probability of rejecting the hypothesis at each evaluation of the stopping rules varies, but cumulatively is 0.0935. If the true ORR is 40% and N=45, the exact 95% confidence interval (Clopper-Pearson) around the point estimate for ORR will be (25.7, 55.7). If the outcome in a treatment arm is promising and the option is taken to enroll up to 100 patients in the mITT in a specific treatment arm (45 patients in the initial arm plus 55 patients), to narrow the confidence interval around the ORR point estimate and to increase the size of the safety database, the exact 95% confidence interval around a true ORR of 40% will be (30.3, 50.3). Data collected in patients enrolled beyond the planned Phase 2 sample size will be used in secondary and supportive analyses. The primary analysis includes independent

evaluation of each of the four treatment arms in the first 45 patients; study expansion enables confirmation of the results of the primary analysis. The use of the Bayesian Predictive Probability Design within each arm effectively controls the overall Type I error to a maximum of 5% for each population of interest.

9.2 Data Handling

Listings of all patient data will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, by the four groups of patients having genetic tumor alterations activating *MET*, where appropriate. If some (or all) of those four groups of patients show similar objective response rate, data summaries (efficacy and safety) will also be presented for those groups combined as supportive analyses. Response rates will be considered similar between groups, if they are within ± 10%. Further details of planned analyses will be described in the SAP.

For all variables, only the observed data from patients will be used in the statistical analyses; there is no plan to estimate missing data. Patients without a valid clinical response assessment will be assigned a best overall response of not evaluable (NE). Data from patients who are lost to follow-up or have missing observations before reaching an endpoint in any of the time-to-event analyses will be treated as censored with specific rules defined in the SAP.

9.3 Analysis Populations

9.3.1 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population is defined in each arm as all patients who receive treatment at least one dose of MGCD265 on this study.

The primary efficacy analyses of the primary and secondary efficacy endpoints will be performed in the mITT population.

9.3.2 Safety Population

The Safety population is defined as all patients who received at least 1 dose of MGCD265 and will be equivalent to the mITT population for this study. The Safety population will be used for all safety analyses.

9.3.3 Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients in the mITT population for whom results of gene alteration tests in tumor tissue and/or ctDNA are available.

9.3.4 Pharmacokinetic Evaluable Population

The Pharmacokinetic evaluable population will consist of all patients in the mITT population who had sufficient concentration-time data to permit population PK analysis for MGCD265. For patients who were noncompliant with respect to administration of MGCD265, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

9.3.5 Pharmacodynamic Evaluable Population

The Pharmacodynamic evaluable population will consist of all patients in the mITT population for whom PD samples are collected.

9.4 Efficacy Endpoint Definitions and Analyses

9.4.1 Objective Response Rate

Objective disease response will be categorized in accordance with RECIST v1.1 (Appendix 2). Objective Response Rate (ORR) is defined as the percent of patients documented to have a confirmed Complete Response (CR) or Partial Response (PR), as reported by the central review laboratory. The primary analysis will be conducted approximately 12 weeks after the last patient is enrolled, allowing for observation of an early disease response and confirmation of PR or CR. ORR as reported by the investigator in the CRF will be used in secondary and supportive analyses as well as by the Internal Data Monitoring Committee for purpose of decision making using the Bayesian Predictive Probability Design.

Descriptive statistics (frequency and percentage) for ORR, CR, and PR will be presented. The exact 95% confidence interval of these response rates will be constructed. An exact test for single proportion (two-sided α=5%) will be performed to test H0: ORR $\leq$ 20% against H1: ORR > 20%. Other details will be described in the SAP.

9.4.2 Duration of Response

Duration of Response (DR) is defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of Objective Progression of Disease (PD) or to death due to any cause in the absence of documented PD. Censoring for the DR endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified by the central radiology review and the patient does not die while on study. DR will only be calculated for the subgroup of patients with an objective response. The Kaplan-Meier method will be used to obtain the estimate of median DR.

9.4.3 Progression Free Survival

Progression-free survival (PFS) is defined as the time from date of first study treatment to first PD or death due to any cause in the absence of documented PD. Censoring for the PFS endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified by the central radiology review and the patient does not die while on study. For patients in whom two or more sequential assessments are missed, followed by the finding of tumor progression, the PFS endpoint will be censored on the date of the last tumor assessment before the gap. Patients lacking an evaluation of disease after first study treatment will have their PFS time censored on the date of first dose with duration of 1 day. Patients who start a new anti-cancer therapy prior to documented PD will have the endpoint censored at the date of the last tumor assessment prior to the start of the new therapy. The Kaplan-Meier method will be used to obtain the estimate of median progression-free survival time.

9.4.4 Overall Survival

Time to death is defined as the time from date of first study treatment to death due to any cause. Censoring for the survival endpoint will be assigned on the date of the last on-study follow-up that the patient is reported to be alive. The Kaplan-Meier method will be used to estimate the median OS and 1-year Survival Rate; the 95% confidence interval of the 1-year survival rate will also be reported.

9.5 Safety Data Presentations and Summaries

9.5.1 Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Listings will include the verbatim term, preferred term, and system organ class (SOC). The number of patients with AEs and the incidence of AEs by SOC and preferred term will be summarized. AEs will be summarized by maximum intensity and relationship to study therapy. Separate summaries will be provided for AEs, SAEs, treatment-related AEs, treatment-related SAEs, and other significant AEs (e.g., AEs leading to study discontinuation).

9.5.2 Prior and Concomitant Medications

Collected prior and concomitant medications will be coded by WHO medical dictionary; patients who received these medications will be listed and summarized.

9.5.3 Clinical and Laboratory Assessments

Clinical and laboratory assessments include clinical laboratory tests (hematology, coagulation, and chemistry), vital signs, and 12-lead ECGs.

Clinical laboratory results will be listed by patient and, as appropriate, summarized descriptively, which will include a display of change from baseline. Selected parameters will be presented in shift tables of baseline against worst grade test result. Laboratory values outside of the normal ranges will be identified. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE v.4.03 will be listed and summarized.

ECG assessments will be evaluated for change of QTc from baseline as an exposure: response analysis. The investigator's interpretation of QTc will be used in the clinical management of patients. The study analysis will use Fridericia's formula applied programmatically to the ECG data collected in CRFs.

Vital signs and ECG measurements will be listed for each patient at each visit. Descriptive statistics of observed values and changes from baseline will be summarized by treatment group.

9.5.4 Patient Demographics, Baseline Characteristics and Disposition

Presentations of patient characteristics will include a summary of the following for all patients enrolling in the study:

- Demographics
- Baseline disease characteristics
- Pre-existing conditions/concurrent illness
- Prior therapies/surgeries

A summary of patient enrollment and disposition will include reasons for study discontinuation.

9.5.5 Analysis of MGCD265 Dosing

MGCD265 administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

9.6 Other Study Endpoints

9.6.1 Pharmacokinetic/Pharmacodynamic Analysis

The PK exposure and PD data from this study may be used in the development of population PK and PK/PD models for MGCD265. Additional PK parameters may be defined and described in the Pharmacokinetic Analysis Plan. Plasma concentrations will be listed by subject for the PK Population. Summary statistics of MGCD265 concentrations will be reported by Day and Cycle. Only samples with acceptable PK

(as defined in the Pharmacokinetic Analysis Plan) will be included in the summary statistics and a listing of individual data points or subjects excluded from the analysis will be presented.

9.6.2 Gene Alterations in Tumor DNA

Tumor tissue and ctDNA genetic alterations activating *MET* will be presented descriptively, by treatment arm. Moreover, change-from-baseline in ctDNA will be presented by visit and treatment arm to assess change in genetic alteration status in ctDNA with MGCD265 treatment over time.

A concordance analysis will be conducted between target gene alterations identified in tumor tissue versus ctDNA in individual patients at prescreening/baseline. Cohen's Kappa, sensitivity and specificity will be estimated for ctDNA as well as Spearman's correlations between tumor tissue and ctDNA.

An analysis of covariance will be performed on changes in ctDNA through time including Time and Treatment as fixed effects and ctDNA at baseline as covariate.

Further details of the analyses will be presented in the SAP.

9.7 Interim Analysis

No interim statistical analysis is planned during this study. However, ORR will be evaluated throughout the study as per the Bayesian Predictive Probability Design in order to decide whether or not a group should be stopped for lack of tumor response.

9.8 Internal Data Management Committee

Interim data will be reviewed for the purpose of study expansion decision making. The Internal Data Monitoring Committee (IDMC) will be comprised of a limited group of Sponsor representatives not directly involved in the conduct of the study. The IDMC will review emerging data in accordance with a separate charter. Investigators will be informed of enrollment decisions but details of efficacy results will be protected until communication points specified in the IDMC charter.

9.9 Evaluation of Enrollment Stopping Rules

Disease response and progression as documented by the investigator in the CRF will be the basis for evaluation of the enrollment stopping rules. The following guidelines will apply to each treatment arm when determining number of events in the numerator and denominator in the stopping rules:

1. The numerator will include patients with objective responses (PR or CR) at any time prior to disease progression as assessed by the investigator and documented in the CRF. Unconfirmed responses will be included until sufficient time has elapsed to allow confirmation of response; if the response is not confirmed, the response will be excluded from the numerator during subsequent reviews.

2. The denominator will include:

    a. Patients included in the numerator;

    b. Patients discontinued from treatment;

    c. Patients at the second or subsequent on-study disease assessment (scheduled after 4 treatment cycles, at Week 13) without PR, CR or PD (i.e., patient has Stable Disease [SD] or Not Evaluable [NE]).

3. The denominator will exclude:

    a. Patients on treatment that have not yet reached the first on-study disease assessment;

    b. Patients on treatment with SD or NE at the first on-study disease assessment (scheduled after 2 treatment cycles, at Week 7).

At each evaluation of stopping rules, the contribution of each participant's experience to the numerator or denominator will be updated based on current data. For example, a patient having SD at Week 13 may contribute only to the denominator at one evaluation, but be included also in the numerator at the next evaluation based on new data documenting PR or CR at Week 19.

A degree of discordance is expected between investigator assessments of disease response/progression and central review of disease response/progression. No attempt will be made to retrospectively apply the later emerging central review assessments to the enrollment stopping rules.

The IDMC may elect to apply the Bayesian Predictive Probability Design only to those patients taking the SDD formulation in order to mitigate the potential confounding effects from formulation change. These details are outlined in the IDMC charter.

10 ETHICS AND RESPONSIBILITIES

10.1 Ethical Conduct of the Study

This study will be conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization [ICH] 1996), and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

10.2 Obligations of Investigators

The Investigator is responsible for complying with the protocol and all applicable regulations and guidelines governing clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

All Investigators must provide the sponsor with a current *curriculum vitae*. Only Investigators and designated Sub-Investigators are permitted to sign CRFs and examination findings (e.g., laboratory results or ECGs).

The Investigator or designee is responsible for informing the patient of all available information relevant to his/her safety and obtaining signed, written consent from all participating patients. Additionally, the Investigator is responsible for monitoring patient safety and providing periodic and requested reports to the IRB/EC.

The Investigator is responsible for the accuracy and completeness of all study records including CRFs, source documents, and the Site Trial Master File. The Investigator will allow the study monitor, Sponsor, auditor, regulatory agencies, and IRB/EC full access to the study and source documents.

10.3 Institutional Review Board/Ethics Committee/Research Ethics Board (IRB/EC)

Prior to the shipment of clinical supplies or initiation of the study, the clinical trial protocol along with the informed consent form (ICF), Investigator's Brochure, and any other written information or instructions for the patient must be submitted to the IRB/EC for written approval. The Investigator will provide the Sponsor with a copy of the IRB/EC's written approval, as well as the membership list or a compliance statement

from the IRB/EC. The Investigator is responsible for notifying the IRB/EC of any Sponsor-approved amendments to the protocol or ICF, SAEs occurring in patients treated at the study site in accordance with local IRB/EC practice, and all expedited safety reports from SAEs occurring at other study sites participating in the drug development program.

10.4 Informed Consent Form

The ICF must contain all elements required by the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) Part 50 and the ICH GCP guidelines (ICH E6) in addition to any other elements required by applicable national, state, provincial, and local regulations, or institutional policies.

All patients who choose to participate in the study must provide written consent after having had adequate time to consider whether they will participate in the study. The written consent must be obtained prior to any protocol-related procedures that are not part of the patient's normal medical care. The patient must be advised of his/her right to withdraw from the study at any time.

Written documentation of consent must be recorded in the patient's source documents, study records and CRF indicating the date the consent was signed. The patient should receive a signed copy of the consent form according to GCP guidelines.

10.5 Confidentiality

All information generated in this study is considered confidential, is subject to applicable privacy rules and regulations, and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor and otherwise except in accordance with applicable law or regulations. However, authorized regulatory officials, IRB/EC personnel, the Sponsor and its authorized representatives (as and to the extent authorized in the patient's ICF) are allowed access to the records.

Identification of patients in CRFs shall be by study assigned patient numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

10.6 Reporting of Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction (i.e., clinical hold) imposed by an applicable Regulatory Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor must be informed immediately. In addition, the investigator will inform the Sponsor immediately of any serious breaches of this protocol or of ICH GCP of which the investigator becomes aware.

11 RECORDS MANAGEMENT

11.1 Source Documentation

Source documents include hospital or clinical patient charts, pertinent historical medical records, laboratory test reports, ECG tracings, pathology reports, radiographs, etc. All source documents must be legible. Data reported in CRFs and evidence of patient's informed consent must be documented in source documents.

11.2 Study Files and Records Retention

A CRF must be completed for each patient for whom informed consent for the study is obtained. The CRFs must be maintained by properly trained and delegated site representatives. The Principal Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF. CRFs must be signed by the Principal Investigator or by an authorized Sub-Investigator to attest that the information included is true.

The study site will maintain a Site Trial Master File in accordance with GCPs.

The Investigator shall retain all records for the longest of the following periods: (i) 15 years; (ii) the period of time that conforms to ICH GCP guidelines; (iii) the period of time required by applicable law or regulations, or (iv) the period of time specified in the Clinical Research Agreement.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring Procedures

Sponsor appointed Site Monitor(s) must be allowed access to all study records, original source documents, and investigational products throughout the duration of the study. These personnel are responsible to assess compliance with the protocol, appropriate health authority regulations, ICH GCP guidelines, and Sponsor requirements.

The study monitor is responsible for complying with the monitoring guidelines established by the Sponsor for the study, assessing the site's needs, and liaising with the assigned Sponsor staff.

Source documents are defined as all medical records, medical notes, pathology or radiology reports, laboratory results, ECG tracings, and any additional documents that have original patient information contained within it.

If the Investigator withdraws from the study and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the Sponsor in writing so arrangements can be made to properly store the study materials.

12.2 Auditing and Inspection Procedures

The Sponsor's Quality Assurance representatives, IRB/EC reviewers, or inspectors from regulatory agencies may perform an audit or inspection at any time during or after completion of the clinical study. All study-related documentation must be made available to the designated auditor. In addition, representatives of applicable regulatory health authorities may choose to inspect a study. A Sponsor representative will be available to assist in the preparation for such an inspection.

13 CHANGES IN STUDY CONDUCT

13.1 Protocol Amendments

Changes to the study protocol, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/EC is notified within 5 days. Any urgent safety measures taken by the investigator to protect the study patients against any immediately life threatening hazard must be reported immediately to the Sponsor.

Any permanent change to the protocol must be handled as a protocol amendment. The change and the justification will be documented in writing by the Sponsor, as an Administrative Letter or amended protocol. Protocol amendments will be provided with a separate document describing each change and rationale. The written Administrative Letter or amendment must be submitted to the IRB/EC and the investigator must await approval before implementing the changes. The Sponsor will be responsible for submitting protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/EC, the investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consents (revised as appropriate to address protocol amendments) will be obtained for patients enrolled in the study before continued participation.

13.2 Protocol Deviations

Prospective permission to deviate from the eligibility criteria for this protocol will not be provided by the Sponsor. Study specified assessments should not be omitted and the study treatment regimen should not deviate from protocol specifications. Minor,

occasional adjustments in the clinic visit schedule may be necessary for logistical reasons (e.g., due to weather conditions) but must not become routine or systematically alter the study schedule. The IRB/EC should be informed of any deviations that may affect a patient's treatment or informed consent, especially those increasing potential risks, which must receive prior written approval by the IRB/EC.

14 END OF TRIAL

14.1 End of Trial in a European Union Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA)) and ethics application in the Member State.

14.2 End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the investigator or designee.

14.3 Premature Termination

Premature termination of this study may occur at any time because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety concerns, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of MGCD265 at any time. If termination becomes necessary, the Sponsor will inform the appropriate regulatory authorities of the termination and the reason. The Principal Investigator will inform the IRB/EC of the same. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 STUDY REPORT AND PUBLICATION POLICY

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication of study results will be governed by the applicable Clinical Research Agreement between the Sponsor and the Study Site and Investigator (as applicable).

16 REFERENCES

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APPENDIX 1. ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

APPENDIX 2. ABBREVIATED PRESENTATION OF RECIST VERSION 1.1 GUIDELINES

A modification to RECIST 1.1 has been made to account for the possibility of temporary changes resulting from the potentially beneficial treatment response of tumor necrosis and cavitation.

Categorizing Lesions at Baseline

Measurable Lesions

- Accurately measured in at least one dimension.
- When assessed by CT or MRI, longest diameter at least 10 mm or greater (slice thickness 5-8 mm), measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other lesions.

Non-Measurable Disease

- Lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) or truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, and abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.
- Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previously irradiated lesions (or those subjected to other local treatment) are non-measurable unless they have progressed since completion of treatment.

Normal Lesions

- Non-malignant simple cysts should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above.
- Lymph nodes with short axis < 10 mm are considered normal and should not be followed as disease.

Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. All required scans must be done within the window of time specified in the Schedule of Assessments prior to treatment. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

The determination of whether lesions are measurable is performed only at baseline. "Measurable" at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the trial. Once selected as a target lesion, a lesion remains target throughout the trial.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to look for partial response at later assessments.

- If 2 target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.
- When nodal lesions decrease to < 10 mm (normal), the actual measurement should still be recorded.

Non-Target Lesions

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather qualitative evaluations of status will be recorded. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (e.g., 'multiple liver metastases').

Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast. If not, subsequent objective statuses may be indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.
- Indeterminate: Progression has not been documented, and
    - one or more target lesions have not been assessed,
    - or assessment methods used were inconsistent with those used at baseline and impaired assessment,
    - or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure),
    - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Lesion Changes That May Be Transient

Potential exists for individual tumor lesions to develop necrosis, to cavitate, have a flair response to treatment or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis, cavitation or flair may result in increase in overall size of individual lesions or unclear tumor margins prior to recovery to smaller lesions, development of scar tissue, or complete resolution. The true tumor measurements of lesions should be recorded but the conclusion of progressive disease may be suspended until continued assessment clarifies the nature of the tumor change. If repeat assessments indicate progression of disease, then PD should be recorded on the date of the first assessment giving the impression of progression. If repeat assessments indicate that the change was a process of transition, then NE (not evaluable) should be recorded during the period of transition, and PR or CR may be recorded for subsequent evaluations. The CRF will collect information on the observations during the period of transition to support the assessment conclusions.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

Best Objective Response

Target Lesions	Non-Target Lesions	New Lesion	Point in Time Response	Best Response
CR	CR	No	CR	CR and PR require confirmation at least 4 weeks after first observation
CR	Non-CR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	SD requires an on-study assessment after at least 6weeks on treatment. Unconfirmed PR or CR are reported as SD.
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Subjective Progression

Patients requiring discontinuation of treatment due to worsening health status attributable to advancement of the malignancy under study but without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status.