Protocol H9H-MC-JBAS(a)

A Randomized Phase 2 Study of LY2157299 versus LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

NCT02178358

Approval Date: 18-Dec-2017

1. Protocol H9H-MC-JBAS(a)
A Randomized Phase 2 Study of LY2157299 versus LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

LY2157299 monohydrate

Phase 2 study of LY2157299 in patients with hepatocellular carcinoma who have not received prior systemic treatment for advanced disease. Patients will be randomly assigned to 1 of 3 treatment arms: LY2157299, LY2157299 plus sorafenib, or sorafen b plus placebo.

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Protocol Electronically Signed and Approved by Lilly on: 18 November 2013
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 18-Dec-2017 GMT

2. Synopsis

Study Rationale

Transforming growth factor beta (TGF-β) is an important protein that regulates the immune response to tumor cells and metastatic spread of tumor cells. TGF-β is also an important regulator of neoangiogenesis. LY2157299 is a small molecule designed to selectively inhibit the serine/threonine kinase of the TGF-β receptor type I (RI). Thus, the antitumor effect of a TGF-β inhibitor such as LY2157299 is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis. The role of TGF-β inhibitors in hepatocellular carcinoma (HCC) was investigated in several in vitro and in vivo studies. For example, the TGF-β RI inhibition by LY2109761 produced several different antitumor activities in HCC preclinical models. The spread of HCC cells in the surrounding tissue is inhibited by the up-regulation of E-cadherin (Fransvea et al. 2008). LY2109761 inhibits invasion of HCC cells (Fransvea et al. 2009) and also inhibits tumor growth thanks to inhibition of neoangiogenesis by reducing vascular endothelial growth factor production (Mazzocca et al. 2009). These effects are selectively dependent on the TGF-1/SMAD-2 pathway (Melisi et al. 2008; Zhang 2009). Finally, LY2109761 inhibits the production of connective tissue growth factor, interrupts the cross talk between tumor and stroma, and blocks the progression of HCC (Mazzocca et al. 2010). Inhibition of TGF-β RI activation using LY364947 inhibits TGF-β-dependent cell signaling and reduces cell motility and invasion in parental and multikinase-resistant HCC cells (Garbay et al. 2010).

The scientific justification of investigating LY2157299 in HCC is compelling based on the role of TGF-β in the process of fibrosis and cirrhosis leading to HCC. The evidence of antitumor effects in several preclinical models with TGF-β-dependent tumor growth and their inhibition by other TGF-β inhibitors, such as LY2109761 and LY364947, suggest that LY2157299 will have activity in HCC. Preclinical data of the combination of LY2157299 and sorafenib shows the potentiation of sorafenib activity in vitro and ex vivo study and implies the possibility that this combination may be more effective than sorafenib alone. In addition, clinical data from HCC patients who have progressed on sorafenib and were treated with LY2157299 had antitumor activity (Study H9H-MC-JBAK [JBAK]). Based on recent interim analysis including 106 patients from Study JBAK, which studied LY2157299 in HCC, treatment resulted in a median time-to-tumor progression (TTP) of 12 weeks (18.3 weeks in patient without previous sorafenib treatment) and alpha fetoprotein (AFP) responses (as defined by >20% reduction from baseline) in 22% of patients.

The present Phase 2 study will further explore the safety and efficacy of LY2157299 alone or in combination with sorafenib in Asian patients with HCC who have not received prior systemic treatment for advanced disease.

Clinical Protocol Synopsis: Study H9H-MC-JBAS

Name of Investigational Product: LY2157299 Monohydrate (hereafter referred to as LY2157299)	
Title of Study: A Randomized Phase 2 Study of LY2157299 versus LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma	
Number of Planned Patients: Entered: Approximately 150 patients Enrolled/randomly assigned: 120 patients Completed: 100 deaths	**Phase of Development:** 2
Length of Study: approximately 30 months Planned first patient visit: April 2014 Planned last patient visit: January 2017 Planned interim analyses: #1: approximately 10 patients complete Cycle 1 in LY2157299 monohydrate (hereafter referred to as LY2157299) plus sorafenib arm; #2: 32 patients are randomized and complete 3 cycles of treatment, discontinue from study drug, or die; #3: 70 total deaths	

Objectives: The primary objective of this study is to compare the overall survival (OS) distributions between LY2157299 plus sorafenib therapy and sorafenib plus placebo therapy (control arm) in patients who have not received prior systemic treatment for advanced disease.

The secondary objectives of the study are:

- to estimate the hazard ratio (HR) from the OS distributions between LY2157299 monotherapy and sorafenib plus placebo
- to evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib in HCC patients
- to evaluate the population pharmacokinetics (PK) of LY2157299 as monotherapy and in combination with sorafenib in HCC patients
- to characterize other time-to-event distributions, such as TTP and progression-free survival (PFS), based on Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1
- to estimate antitumor efficacy using objective response rate (ORR, based on RECIST version 1.1 and modified RECIST [mRECIST]) for each treatment arm
- to assess patient-reported outcome (PRO) measures of disease-specific symptoms, time to symptomatic progression, and health-related quality of life questionnaires such as the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-30 and QLQ HCC-18 for each treatment arm

The exploratory objectives of this study are:

- to explore markers associated with EMT transformation and the TGF-β-associated signaling pathway presence in the original diagnostic tumor tissue and optional posttreatment tumor tissue and the correlation of this with both clinical efficacy endpoints and biomarker response
- to explore TTP, PFS, and ORR by immune response RECIST (irRECIST)
- to explore tumor volume changes of measurable lesions on CT/MRIs obtained for tumor response as an assessment of treatment effects on biological growth rate
- to explore the relative effects of LY2157299 versus LY2157299 plus sorafenib versus sorafenib plus placebo on antiangiogenesis as assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) metrics and on tumor cellularity/cell death as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI) metrics. These exploratory magnetic resonance imaging (MRI) techniques will only be performed at clinical sites where the associated MR imaging center scanner has been qualified prior to patient enrollment by the imaging core laboratory designated by the sponsor.
- to explore fibrosis-related tests, such as fibrotest
- to assess healthcare resource utilization including transfusions and hospitalizations

Study Design: This is a 3-arm, 1:2:1 randomized, multicenter, global (Asia), Phase 2 study of LY2157299 monotherapy or LY2157299 plus sorafenib therapy compared to sorafenib plus LY2157299-matched placebo therapy in patients with relapsed or progressed HCC. Patients who receive sorafenib and investigators will be blinded to the LY2157299 or placebo assignment for those arms.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Inclusion Criteria:

- have histological evidence of a diagnosis of HCC not amenable to curative surgery.
- have Child-Pugh Class A
- have the presence of measurable disease as defined by RECIST version 1.1. A lesion that has been previously treated by local therapy at least 3 weeks prior to the baseline scan will qualify as a measurable or evaluable lesion if there was demonstrable progression following locoregional therapy
- be aged ≥18 years
- have adequate organ function
- have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale
- have available diagnostic or biopsy tumor tissue

Exclusion Criteria:

- have received previous systemic treatment for advanced disease
- have known HCC with fibro-lamellar or mixed histology
- have presence of clinically relevant ascites
- have had liver transplant
- have moderate or severe cardiac disease
- have known hypersensitivity to sorafenib or its excipients
- have active or uncontrolled clinically serious hepatitis B virus or hepatitis C virus infection
- have experienced any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 gastrointestinal bleeding or any variceal bleeding episode in the 3 months prior to enrollment requiring transfusion or endoscopic or operative intervention
- have esophageal or gastric varices that require immediate intervention (eg, banding, sclerotherapy) or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist

Test Product, Dosage, and Mode of Administration

LY2157299 will be administered orally by daily dosing morning and evening (twice daily [BID]). The monotherapy dose will be 150 mg BID (300-mg daily dose) for 14 days, followed by 14 days with no study drug. The LY2157299 dose used in combination with sorafenib will be determined based on the results of the H9H-MC-JBAK (JBAK) study Part C (dose will either be 80 mg or 150 mg BID [160 mg or 300 mg daily dose]) for 14 days, followed by 14 days with no study drug.

LY2157299-matched placebo will be administered orally by daily dosing morning and evening (BID) for 14 days, followed by 14 days with no placebo.

Sorafenib will be administered orally by daily dosing morning and evening (BID) at 400 mg per dose (total dosage of 800 mg daily) for 28 days.

One cycle is defined as 28 days in all treatment arms.

Planned Duration of Treatment Per Patient: Patients will receive LY2157299 until their disease has progressed, the patient has died, or the patient discontinues for adverse events, investigator's judgment, or other reasons.

Wash-out period: none.

Planned Follow-up Observation Period Per Patient: Patients who have discontinued study treatment without progression will continue to be followed for progression. Every attempt should be made to gather all information every 2 months (radiological scans and survival), even if a patient starts a new anticancer therapy. All patients will be followed until death. Patients who have entered the treatment extension period will be followed for just 30 days after treatment discontinuation.

Criteria for Evaluation:

Efficacy: OS, TTP, PFS, and ORR using RECIST version 1.1, mRECIST, and irRECIST

Safety: International CTCAE, version 4.0

Health Outcomes: PRO measures of disease-specific symptoms and health-related quality of life (EORTC QLQ-30 and QLQ HCC-18)

Bioanalytical: Plasma LY2157299/sorafenib concentrations will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry.

Statistical Methods:

Statistical: Approximately 120 patients will be randomly allocated to treatment in a 1:2:1 ratio (LY2157299 monotherapy/LY2157299 plus sorafenib therapy/sorafenib plus placebo therapy). This will provide about 83% power (strong prior) to detect a significant treatment difference in terms of OS between the LY2157299 plus sorafenib and sorafenib plus placebo using a Bayesian-augmented control design with a 1-sided alpha of 0.14 under the assumption that the true HR is 0.667 in favor of the LY2157299 plus sorafenib arm.

Efficacy: The primary analysis is to compare the OS between LY2157299 plus sorafenib with sorafenib plus placebo using a Bayesian OS model that augments current control data with additional information from historical data. The same Bayesian OS model will be used to estimate the HR between LY2157299 monotherapy and sorafenib plus placebo. HRs between the 3 treatment arms will also be estimated for TTP and PFS using proportional hazards models. ORR based on the RECIST v1.1 and mRECIST criteria will be calculated.

Safety: Summary statistics, plots, and listings for all safety data collected will be provided by arm.

Health Outcomes: Summary descriptive statistics by study part will be provided for the PRO data (ie, EORTC QLQ-30 and QLQ HCC-18) at each time point and change from baseline. Time to symptomatic progression will also be evaluated.

Pharmacokinetics: A population PK analysis will be performed on all patients receiving LY2157299. A PK analysis will be performed for sorafenib as well. This analysis will explore the impact of covariates such as demographic factors and markers on the relevant PK parameters.

Pharmacodynamics: Changes in response biomarkers, such as phosphorylated SMAD in tumor tissue (or other TGF-β-related biomarkers), AFP L3, and E-cadherin in serum will be estimated and may be correlated with clinical efficacy. Exploratory population PK/pharmacodynamic analyses may be conducted to identify the exposure-biomarker response relationship.

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AFP	alpha fetoprotein
ALT	alanine aminotransferase
$AUC_{0-\infty}$	area under the curve from time zero to infinity
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures, GCP, and the applicable regulatory requirement(s).
BID	twice daily
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock.
CL/F	clearance
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, GCP requirements, and the applicable regulatory requirements.
CR	complete response
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

CYP	cytochrome P450
DCE-MRI	dynamic contrast-enhanced MRI
DCSI	Development Core Safety Information
DW-MRI	diffusion-weighted MRI
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EMT	epithelial-to-mesenchymal transition
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the ICF directly or through their legally acceptable representatives.
EORTC	European Organisation for Research and Treatment of Cancer
ERB	ethics review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
EU	European Union
extension period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met.
F344	Fischer 344
FFPE	formalin-fixed paraffin-embedded
GBCA	gadolinium-based contrast agent
GBM	glioblastoma
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GnRH	gonadotropin-releasing hormone

HCC	hepatocellular carcinoma
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
irRECIST	immune response RECIST
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
LV	left ventricular
LVEF	left ventricular ejection fraction
MAP	multi-analyte panel
MedDRA	*Medical Dictionary for Regulatory Activities*
mRECIST	modified RECIST
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOEL	no-observed-effect level
NONMEM	nonlinear mixed-effect modeling
OR	overall response

ORR	objective response rate
OS	overall survival
patient	a study participant who has the disease or condition for which the investigational product is targeted
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PH	proportional hazards
PIVKA II	prothrombin induced by vitamin K absence
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PS	performance status
pSMAD	phosphorylated SMAD
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
rescreen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	system organ class
study completion	This study will be considered complete after the final analysis of the primary endpoint (100 deaths) is performed.

SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TGF-β	transforming growth factor beta
TGF-β RI	TGF-β receptor type I
TTP	time-to-tumor progression
ULN	upper limit of normal
US	United States

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5. Introduction

Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide with a still increasing incidence (Parkin et al. 2005). Patients with chronic liver disease and cirrhosis are at high risk for HCC; thus the prognosis, which is usually poor, is related to underlying liver function in addition to disease stage.

Patients with HCC considered to have noncurable disease include those for whom liver transplant, resection, tumor embolization, or other percutaneous ablation are not suitable. For these patients, the median survival time with no treatment ranges from 40 months for patients with multinodular asymptomatic tumors to about 5 months for those with cancer-related symptoms, vascular disease, or extrahepatic spread. Survival differences were noted between patients in the United States (US)/European Union (EU)/Japan versus patients in East Asia. East Asian patients have shown shorter overall survival (OS) because of the enrollment of patients with poorer prognosis after aggressive surgery or loco-regional therapy: median OS for patients without standard treatment (reflecting natural history of the disease) was 3.57 ± 1.88 months in Asian trials and 5.96 ± 1.46 months in non-Asian trials (Hsu et al. 2010). For this patient population, sorafenib is the only option with survival impact. In the recently presented Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol trial (Phase 3) conducted in US and EU, which compared sorafenib with placebo in patients with advanced liver cancer with no prior systemic treatment, performance status (PS) 0 to 2, and a Child-Pugh status A, the hazard ratio (HR) for OS was 0.69 (95% confidence interval [CI]: 0.55, 0.87; p=.0006) in favor of sorafenib, representing a 44% improvement in OS compared with placebo. The median OS was 10.7 for sorafenib and 7.9 months for placebo with an HR for time-to-tumor progression (TTP) of 0.58 (95% CI: 0.45, 0.74; p=.000007). The median TTP was longer (5.5 vs 2.8 months) with sorafenib than with placebo (Llovet et al. 2008).

In the East Asia (China, Taiwan, and South Korea) ASIAN-Pacific trial, which compared sorafenib with placebo in patients with advanced liver cancer with no prior systemic treatment, median OS was 6.5 months (95% CI: 5.56, 7.56) in patients treated with sorafenib, compared with 4.2 months (95% CI: 3.75, 5.46) in those who received placebo (HR: 0.68 [0.50–0.93]; p=.014). Median TTP was 2.8 months (95% CI: 2.63, 3.58) in the sorafenib group compared with 1.4 months (95% CI: 1.35–1.55) in the placebo group (HR: 0.57 [0.42–0.79]; p=.0005). The most frequently reported grade 3/4 drug-related adverse events (AEs) in the 149 assessable patients treated with sorafenib were hand-foot skin reaction (16 patients [10.7%]), diarrhea (9 patients [6.0%]), and fatigue (5 patients [3.4%]) (Cheng et al. 2009).

Given these results, sorafenib is the first-line standard of care for patients with advanced liver cancer who are not candidates for surgical or local treatment. However, if the treatment with

sorafenib failed, there is no approved second-line therapy. Available results of sorafenib in the Asian population are summarized in Table JBAS.5.1.

Table JBAS.5.1. Sorafenib in Asian Populations

Study	Sample Size (Number of Patients)	Median OS (Months)	Reference
Sorafenib versus placebo	150	6.5	Cheng et al. 2009
Sorafenib versus sunitinib	410 (Asian Pacific subgroup)	8.8	Cheng et al. 2011
Sorafenib versus brivanib	372 (Asian subgroup)	8.9	Johnson et al. 2013

Abbreviation: OS = overall survival.

Transforming growth factor beta (TGF-β) has been shown to be a tumor promoter in advanced, metastatic cancer; while in normal tissue, TGF-β inhibits epithelial cell proliferation (de Caestecker et al. 2000; Massagué et al. 2000; Derynck et al. 2001; Wakefield and Roberts 2002). Because of this tumor-promoting activity, TGF-β inhibition is currently being considered as a treatment option in patients with advanced cancer (Yingling et al. 2004).

TGF-β signals into the cell by engaging TGF-β receptor type I (RI) and type II and inducing phosphorylation of the TGF-β receptor kinases (Shi and Massagué 2003). The TGF-β RI kinase phosphorylates SMAD2 and SMAD3, resulting in the formation of SMAD complexes, which are subsequently translocated into the nucleus to stimulate gene transcription of TGF-β responsive genes (Derynck et al. 2001). Therefore, assessment of phosphorylated SMAD (pSMAD) after TGF-β activation can be used to determine the ability of the host to respond to TGF-β activation.

Several mechanisms have been proposed to explain the tumor-promoting activity of TGF-β, such as increased neovascularization of the tumor causing increased nourishment to the tumor cells, immunosuppression leading to the escape of tumor immune surveillance, and increased migration and invasion resulting in metastasis (Akhurst and Derynck 2001; Derynck et al. 2001; Siegel and Massagué 2003). These combined effects on the tumor microenvironment by TGF-β promote tumor progression, and therefore a TGF-β RI kinase inhibitor is expected to cause arrest of tumor growth and metastasis in patients.

It has been reported that TGF-β1 is increased in HCC patients and correlates with worst prognosis. In addition, plasma TGF-β1 levels are elevated in HCC patients with alpha-fetoprotein (AFP) levels above 10 IU/mL (Sacco et al. 2000).

TGF-β, a profibrotic cytokine, induces HCC progression through a paracrine mechanism, which is abrogated by inhibition of TGF-β/SMAD signaling in hepatocytes (Gressner et al. 2002; Mikula et al. 2006). HCC progression is also frequently associated with an epithelial-to-mesenchymal transition (EMT) of hepatocytes that may be caused by the cooperation of laminin 5 and TGF-β (Giannelli et al. 2005). TGF-β stimulation induces EMT and invasion in HCC, while its inhibition is associated with decrease of invasion (van Zijl et al. 2009).

A recent review integrating the gene expression data from 9 different human genetic expression studies across various geographies and stages of HCC was able to propose 3 distinct genetic patterns associated with disease outcome (Hoshida et al. 2009). In this genetic expression assessment, the β-catenin and TGF-β-induced gene expression was associated with poor survival. AFP was found to differentiate between the proposed 3 clusters (S1 to S3).

LY2157299 monohydrate (hereafter referred to as LY2157299) has been studied to a limited extent in HCC; however, surrogate compounds, such as LY2109761, have been used to elucidate the antitumor effect of the TGF-β inhibition in several in vitro and in vivo studies. TGF-β RI inhibition by LY2109761 produced several different antitumoral activities in HCC preclinical models. The spread of HCC cells in the surrounding tissue is inhibited by the up-regulation of E-cadherin (Fransvea et al. 2008). LY2109761 blocks both invasion of HCC cells (Fransvea et al. 2009) and tumor growth by inhibiting neoangiogenesis via reduction in vascular endothelial growth factor production (Mozzacca et al. 2009). These effects are selectively dependent on the TGF-β1/SMAD-2 pathway (Zhang 2009; Melisi et al. 2008). Finally, LY2109761 inhibits the production of connective tissue growth factor, interrupts the cross-talk between tumor and stroma, and blocks the progression of HCC (Mazzocca et al. 2010). Inhibition of TGF-β RI activation using another surrogate compound, LY364947, also inhibits TGF-β-dependent cell signaling and reduces cell motility and invasion in parental and multikinase-resistant HCC cells (Garbay et al. 2010). TGF-β/TGF-β RI inactivation using LY2157299 inhibits TGF-β–dependent cell signaling in HCC cell lines with either antiproliferative or anti-invasive effects depending on the model. In tumor samples from patients, inhibition of TGF-β signaling was associated with decreased AFP levels, inhibition of proliferation, and apoptosis induction (Serova et al. 2013).

Preclinical data of a combination of LY2157299 with sorafenib show potentiation of sorafenib activity in vitro, and ex vivo studies imply the possibility that this combination may be more effective than sorafenib alone.

These data support the study of TGF-β inhibitors in HCC. LY2157299 is a small molecule designed to selectively inhibit the serine/threonine kinase of the TGF-β RI. Thus, the antitumor effect of LY2157299 is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis.

5.1. LY2157299 – Nonclinical and Clinical Experience

5.1.1. Nonclinical Pharmacokinetics of LY2157299

Nonclinical pharmacokinetic (PK) studies were performed in 2 species, rat and dog. LY2157299 exposure was examined in rats following daily oral doses of 15, 50, and 150 mg/kg after 1 dose and 28 doses. The PK of LY2157299 were linear, but female rats had a consistently higher (approximately 2-fold) exposure over the course of the study. LY2157299 is rapidly absorbed and eliminated with a half-life ($t_{1/2}$) of approximately 4 to 8 hours.

As determined by metabolism studies in rats, most of LY2157299 was excreted in feces. Three metabolites have thus far been identified. The function and activity of these metabolites have not been defined at this time.

In the nonrodent studies using dogs, a gastric pH-dependent variability was observed suggesting that at an acidic pH, LY2157299 had a less variable exposure. To reduce possible PK variability, LY2157299 will be administered on an empty stomach.

Male and female Fischer 344 (F344) rats were given daily oral doses of LY2157299 monohydrate at 0, 15, 50, or 150 mg/kg for 1 month. Male and female beagle dogs were given daily oral doses of LY2157299 monohydrate at 0, 50, 250, or 500 mg/kg for 1 month. The potential for induction of hepatic microsomal drug-metabolizing enzymes was evaluated by quantitating total cytochrome P450 (CYP) content in liver samples collected at necropsies. Slight but variable changes in total CYP content were observed in treated male rats; while no significant changes were observed in treated female rats. No statistically significant changes in total CYP content were observed in treated beagle dogs. The magnitude of the changes observed in male rats and the lack of significant change in female rats and male and female dogs suggest that LY2157299 is not an inducer of overall CYP content under the conditions of these studies.

The ability of LY2157299 to inhibit CYP-mediated metabolism in vitro was examined. The data show that LY2157299 would not be expected to inhibit metabolism mediated by CYP2D6, CYP2C19, CYP2C9, and CYP1A2. LY2157299 was found to competitively inhibit the biotransformation of midazolam to 1'-hydroxymidazolam, a marker activity for CYP3A4, yielding an inhibition constant value of 44 μM. LY2157299 was found to competitively inhibit the biotransformation of testosterone to 6β-hydroxytestosterone, a marker activity for CYP3A4, yielding an inhibition constant value of 290 μM.

Based on the nonclinical metabolism studies, LY2157299 is not anticipated to have the potential to accumulate in patients or have a risk of high hepatic metabolism.

For details on the nonclinical PK of LY2157299, please see the Investigator's Brochure (IB).

5.1.2. Nonclinical Pharmacokinetic/Pharmacodynamic Model

Because regular assessment of pSMAD in tumor tissue in patients is both too invasive and likely to produce variable results given the heterogeneous nature of tumor tissue, a specific bioassay was developed to determine pSMAD levels in a surrogate tissue, peripheral blood mononuclear cells (PBMCs) (data on file, Eli Lilly; Farrington et al. 2007). To compare the effect of LY2157299 between the surrogate and tumor tissue, the pSMAD level changes measured in both PBMCs and 4T1 tumor tissue in rats treated with LY2157299 was investigated. A significant relationship between pSMAD modulation in tumor cells and in peripheral blood was observed at 30- and 300-mg/kg doses (p-values were .002 and .059 in the 30- and 300-mg/kg groups, respectively, and <.0001 for the combined data), which suggests that the pSMAD modulation in human PBMCs should be a useful surrogate of the pharmacodynamic (PD) effect of LY2157299.

A PK/PD model was developed to characterize the relationship between drug concentrations and pSMAD levels. This PK/PD model integrated the time course of the PK of the compound, the

inhibition of pSMAD in tumor and PBMCs, as well as the nonclinical tumor growth delay of 3 tumor animal models. This model was used to predict an anticipated dose range that is likely to be biologically effective in patients with cancer. The simulations from the rat and the mouse suggest that a range of 200 to 500 mg (total daily dose), administered twice daily (BID) is expected to produce the required percentage inhibition of pSMAD that has been associated with tumor-growth delay in the preclinical studies.

For details refer to the IB.

5.1.3. Clinical Pharmacokinetics of LY2157299

As of 07 September 2012, based on 5 dose-escalation cohorts (40-, 80-, 160-, 240-, and 300-mg doses), a total of 717 plasma concentration observations from 37 patients from Study H9H-MC-JBAH (JBAH) were obtained. LY2157299 was rapidly absorbed with plasma concentrations measurable for at least 48 hours. No accumulation upon multiple dosing of LY2157299 in the 5 cohorts was observed over the 14-day BID dosing regimen. The median $t_{1/2}$ ranged between 6 to 8 hours across dose levels. On Day 14, the median time to maximum concentration at steady state ranged from 0.5 to 2 hours postdose, independent of dose. Both the maximum observed concentration at steady state and exposure approximately doubled with a 2-fold increase in dose. The population PK of LY2157299 was best described by a 2-compartment model with first-order absorption and elimination. LY2157299 was rapidly absorbed into the systemic circulation with an absorption rate constant of 2.2/h . The mean population apparent clearance (CL/F) of LY2157299 was 38 L/h, and the steady state volume of distribution was 193 L. The between-patient variance for plasma total CL/F and exposure was moderate (46%), and between-occasion variance was low (18%). Systemic exposure to LY2157299 was not influenced by age, smoking status, alcohol consumption, body mass index, or ethnicity in this model developed mainly from glioblastoma (GBM) patient data.

Preliminary simulations of the median exposures (20th-80th percentile) following administration of 160 mg and 300 mg in patients with HCC (Study H9H-MC-JBAK [JBAK]) (n=137) were 3.8 (1.7-7.3) and 7.0 (3.5-13.6) mg*h/L, respectively (Raymond et al. 2013). Between-patient variability on apparent CL/F was moderate (at 42%) in HCC patients. Preliminary PK data suggest that some patients at the 300-mg dose might reach higher exposures than previously observed for the same dose level in patients with GBM. LY2157299 will be fully eliminated after a 14-days-off period.

For additional information, see Section 6.1 in the IB.

5.1.4. Nonclinical Toxicology of LY2157299

The toxicity of LY2157299 has been characterized in repeat- and intermittent-dose, nonclinical safety studies up to 6 months duration in the rat and dog. The following paragraphs summarize the major findings in rats and dogs.

The heart and great vessels are major target organs for toxicity in both F344 rats and beagle dogs following treatment with LY2157299. These effects include valvulopathy and vascular lesions of multiple blood vessels at the base of the heart in rat and dog, which in the rat appear to be

partially reversible. In the rat, a continuum of changes in the gastrointestinal (GI) tract have been described, including inflammation of the mucosa, simple mucosal hyperplasia, and adenocarcinoma following 6 months of continuous treatment. Based on safety pharmacology studies, administration of LY2157299 produced increases in hexobarbital-induced sleep time. Administration of LY2157299 may produce dose-dependent hemodynamic side effects, measured by decreased blood pressure and increases in heart rate, which can be easily monitored in the clinic and are reversible upon cessation of treatment. The nonclinical data do not reveal any substantive clinical risk of QT/corrected QT prolongation at doses that result in total plasma concentrations of at least 3.3 μg/mL.

LY2157299 was negative in a bacterial mutation test (Ames test) and an in vivo mammalian test (mouse micronucleus). However, LY2157299 was positive in an in vitro mammalian test (chromosome aberration) with and without S9 activation. This positive finding is considered acceptable in the intended patient population.

Rats were dosed up to 3 months intermittently or 6 months continuously at 50, 150, and 250 mg/kg. Dogs have been dosed with up to 500 mg/kg for 1 month and 8, 20, and 60 mg/kg daily for 6 months. LY2157299 caused mortality in the rat at progressively lower doses as the duration of treatment increased. In shorter-duration studies, mortality was observed in rats administered 1200 mg/kg of LY2157299 in a 14-day pilot study, and in the 3- and 6-month rat studies, mortality occurred in animals receiving daily doses of 150 (6-month study) and 250 mg/kg (3- and 6-month study) beginning on Days 83 and 54, respectively. All preterminal deaths in rats were attributed to compound-related inflammation of the aorta and distributing arteries at or near the base of the heart, except for 1 male for which the cause of death was undetermined and 1 male that died of an intestinal adenocarcinoma (6-month study). One female dog in the high-dose reversibility group (500 mg/kg) died shortly after the treatment phase ended in the 1-month study; death was attributed to bile peritonitis. There was no mortality observed in the 6-month dog study. Vascular lesions in the rat were characterized by minimal to severe inflammation of multiple blood vessels at the base of the heart, including the ascending aorta, coronary arteries, and distributing arteries of the aortic arch. These changes were described in the 3-month (150 and 250 mg/kg) and 6-month (≥50 mg/kg) continuous-dose groups. The vascular damage in rats administered ≥150 mg/kg continuously for 3 and 6 months and 2 weeks on/2 weeks off correlated with serum chemistry and hematologic responses typical of chronic hemorrhage and inflammation. In rats given 150 and 250 mg/kg (mid and high dose, 6 months and ≥3 months, respectively), vascular inflammation was, in some animals, associated with vascular rupture resulting in acute hemorrhage into the thoracic cavity and death.

The no-observed-effect level (NOEL) for vascular damage in the rat is 50 mg/kg administered on a 2-week-on/2-week-off schedule. Changes in the base of the ascending aorta, characterized by minimal-to-marked degeneration, disorganization, and separation of intramural elastic laminae without an accompanying inflammatory response, were observed in the dog administered daily doses of 8, 20, or 60 mg/kg for 6 months. The aortic mural degeneration was focally extensive or multifocal with no compound-related microscopic changes in the descending aorta. Although the microscopic changes likely compromised regional aortic structural integrity, there were no

diagnostic changes of an aortic aneurysm—no gross dilation, no effects in the intimal layer, and a lack of free blood within the wall of the aorta. A cardiac valvulopathy, characterized by endothelial/stromal cell proliferation, inflammation, and increases in smooth muscle actin immunolabeling and hemorrhage, was identified in rats and dogs given high doses of LY2157299 for ≤30 days. In the 3- and 6-month studies, compound-related valvulopathy of similar character occurred at lower doses than previously described in studies ≤30 days in duration (150 and 250 mg/kg [intermittent 2 weeks on/2 weeks off and continuous groups] in the 3-month study; and at all doses [50, 150, and 250 mg/kg] in the rat 6-month study; and at the mid and high doses [20 and 60 mg/kg] in the dog). The cardiac valvulopathy observed in rats and dogs given LY2157299 were observed but have not been associated with extracardiac evidence of valvular insufficiency or dysfunction. The NOEL for valvulopathy in the rat is 50 mg/kg administered on a 2-week-on/2-week-off schedule and 8 mg/kg in the dog in the 6-month study. In an effort to characterize the reversibility of cardiovascular lesions, a non–good laboratory practice (GLP) study in rats administered 250 mg/kg daily for 8 weeks followed by a 6-week recovery period was conducted. Data indicate that vascular lesions are partially reversible when rats are administered a dose known to induce a high incidence of cardiovascular lesions (vasculitis and valvulopathy) with daily dosing. After the 6-week recovery period, a decrease in both incidences in severity of cardiovascular lesions was observed. However, at the end of this recovery period, a few animals still were observed with minimal to moderate inflammation at the base of the aorta, coronary arteries, or valves and with minimal stromal hyperplasia of the atrioventricular valves. These lesions were still considered adverse.

Treatment with LY2157299 results in a continuum of changes characterized by inflammation in the mucosa of mid- and high-dose (150 and 250 mg/kg) rats dosed either daily or intermittently for 3 months to proliferative changes at the mid and high dose (150 and 250 mg/kg) in the 6-month daily-dosing rat study. The proliferative changes included simple mucosal hyperplasia that progressed to include adenomatous hyperplasia, adenoma, and, in 2 males at the high dose, adenocarcinoma.

In the rat, additional important compound-related findings affecting the skeletal system, consisting of proliferation of trabecular bone or sternal cartilage, altered endochondral ossification, and slightly increased degeneration of articular cartilage were observed. Consistent with literature predictions (Lahn et al. 2005), administration of LY2157299 in a pilot embryo-fetal study resulted in increased resorptions and alterations in fetal skeletal morphology at 20 and 200 mg/kg. A NOEL for embryo-fetal effects was established at 2 mg/kg in this pilot study. In the dog, corneal edema and episcleritis were noted in the eyes of dogs at the high dose (60 mg/kg) during a scheduled ophthalmologic examination of all dogs on Day 176. Corneal endothelitis (inflammation of the most posterior cell layer of the cornea) was considered to be the primary change. Histologic evaluation of the eye was unremarkable. Additional important compound-related findings in the dog consisted of atrophy and/or inflammation of the mucosa of the stomach and large intestine, proliferation of sterna cartilage, and gallbladder mucification.

For additional information, see Section 5 in the IB.

5.1.4.1. Overall Conclusions

Collectively, the findings in the continuous 3- and 6-month daily-dosing toxicity studies, particularly the degeneration of the large blood vessels, imply that long-term, daily dosing of LY2157299 may carry a risk in patients for developing aneurysms. Reversibility was not assessed in the 3- or 6-month toxicity studies, but in a non-GLP reversibility study in rat, data indicate the cardiovascular lesions are partially reversible; but those lesions that are still present following the recovery period are still adverse. The intermittent-dosing regimen in patients is based on the safety demonstrated in the rat and dog following 1 month of continuous daily dosing in which the NOELs for any effects in the heart were 150 and 20 mg/kg in the rat and dog, respectively, and a 3-month intermittent-dosing study in the rat in which the NOEL for any effects in the heart was 50 mg/kg (see Table JBAS.5.2 for margin-of-safety calculations). Although the likelihood of occurrence or the extent and timing of such a risk observed after daily dosing is not known in humans, LY2157299 will be administered as an intermittent-dosing regimen in this patient population that has a poor prognosis and rapidly advancing cancer.

Table JBAS.5.2. CCI

5.1.5. Clinical Experience

As of 01 September 2013, 6 clinical studies and 2 clinical pharmacology studies were ongoing. In total, approximately 406 patients have received LY2157299 either alone (n=201) or in combination with chemotherapy or chemoradiation (n=205).

Safety data are available for 230 patients (as reported in the 2012 and 2013 LY2157299 IBs). As of 01 September 2013, all trials were ongoing, and regular safety reviews between 07 September 2012 and 01 September 2013 have not detected a change in the risk-benefit profile for LY2157299. A comprehensive benefit-risk analysis will be conducted when Phase 2 studies achieve their primary endpoints (pending) or futility assessments or if any unexpected safety

concerns arise during regular safety reviews. At this time, no clear or definitive drug-related toxicity profile has emerged.

The most common treatment-emergent adverse events (TEAEs) related to LY2157299 monotherapy were fatigue, nausea, and vomiting. All other events occurred in <5% of the patient population. Most TEAEs were of mild or moderate severity.

A total of 155 serious adverse events (SAEs) have been reported in the clinical and safety databases. Forty-five SAEs considered to be related to LY2157299 have been reported among 26 patients. Of these, 18 patients receiving LY2157299 monotherapy reported a total of 31 treatment-related SAEs, and 8 patients receiving LY2157299 combination therapies reported a total of 14 treatment-related SAEs. For the monotherapy, the most common treatment-related SAEs (occurring in 2 or more patients) included anemia, thrombocytopenia, neutropenia, GI hemorrhage, and diarrhea. None of the treatment-related SAEs occurring with the combination therapies occurred in 2 or more patients.

A total of 15 deaths due to causes other than study disease have been reported. Infection-related deaths were observed in 4 cases, and GI-related deaths were reported in 3 cases. Additionally, not-yet-determined or unknown causes of death were reported in 6 cases; 2 deaths, occurring with monotherapy, were reported by investigators to be potentially associated with study drug. However, in reviewing the specific cases, the rationale for causality with LY2157299 appears to be uncertain.

Study H9H-MC-JBAN, to evaluate the safety of LY2157299 in Japanese patients, has been initiated. The first cohort (150 mg/day, 3 patients) completed Cycle 1 without significant toxicity. The second cohort (300 mg/day) is currently ongoing with the first 2 patients having completed Cycle 1 without significant toxicity.

Due to the preclinical cardiovascular toxicity findings, comprehensive cardiovascular monitoring has been conducted for all patients receiving LY2157299 (echocardiography/Doppler, cardiac markers [brain natriuretic peptide {BNP}, troponin I], electrocardiogram [ECG], chest magnetic resonance imaging [MRI] or computed tomography [CT] with contrast). To date, no cardiovascular toxicity has been observed in the 218 patients enrolled in the LY2157299 clinical trials.

In summary, LY2157299 shows a toxicity profile that justifies its use as monotherapy and in combination with radiochemotherapy and with chemotherapy.

For additional information, see the IB.

5.1.5.1. Brief Summary of Patients Treated in Study JBAK (LY2157299 Monotherapy in Patients with Advanced Hepatocellular Carcinoma Who Failed or Were Not Eligible to Receive Sorafenib)

In Study JBAK, patients with advanced HCC who progressed on sorafenib or were ineligible to receive sorafenib; patients were eligible if they had advanced Child-Pugh A/B7 HCC, Eastern Cooperative Oncology Group (ECOG) PS ≤1, measurable disease (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), and ≤1 prior systemic regimen. LY2157299 was

administered as intermittent dosing of 14 days on/14 days off (28 days = 1 cycle). Patients were randomized to either 160 mg/day (Arm A) or 300 mg/day (Arm B) LY2157299.

An interim analysis for Study JBAK was conducted after enrollment of 106 patients with elevated AFP levels (AFP ≥1.5 times the upper limit of normal [ULN]).

One hundred six patients were enrolled (Arm A=37; Arm B=69) and included 92% non-Asians. Baseline characteristics (Arm A/B) were a median age of 61/66 years; PS of 0, 60%/51%; Child-Pugh A, 97%/86%; and etiology: hepatitis C (30%/33%), hepatitis B (24%/25%), and alcohol (22%/22%). Overall, 78%/83% of patients had received prior sorafenib; 64%/58% of patients had AFP levels ≥400 ng/mL. Median TTP was 12.0 weeks (90% CI: 7.1, 12.6) in the overall population (Arm A, 12.6 weeks; Arm B, 10.9 weeks). In 20 sorafenib-naive patients, TTP was 18.3 weeks (90% CI: 6.3, nonestimable). Disease control rate was 34.9%. In sorafenib-naive patients, disease control rate was 45%. AFP decline of >25% occurred in 21/106 patients (20%). Four patients discontinued treatment due to a drug-related TEAE. The most common Grade 3/4 related TEAEs in patients were neutropenia (n=3), GI bleeding (n=2), fatigue (n=2), and anemia (n=2) (Faivre et al. 2013).

Of the information collected to monitor the potential for cardiac toxicity during treatment (ECG, echocardiograph, troponin I, and BNP), none were considered of clinical significance.

Among 137 patients with evaluable PK in Study JBAK (both patients with AFP ≥1.5x ULN and AFP <1.5x ULN), there was a dose-proportional increase in exposure (area under the curve from time zero to infinity [$AUC_{0-\infty}$] = 3.8 mg*h/L for the 160-mg dose, and $AUC_{0-\infty}$= 7.0 mg*h/L for the 300-mg dose) (Raymond et al. 2013). There were higher exposures in HCC patients than previously observed for exposures in GBM patients (Rodon et al. 2011). PK data suggested that total CL/F of LY2157299 in HCC patients (25.4 L/hr) is lower than the previously reported CL/F in GBM patients (38.4 L/hr). Moderate between-patient variability on exposure was observed in HCC patients, which was similar to GBM patients. LY2157299 appears to be fully eliminated at the end of the 14-day off period of a cycle. Administration of 300 mg/day to patients with HCC may result in higher exposures than in patients with GBM. These increased exposures did not result in increase of toxicities.

Study JBAK has been amended to include assessment of sorafenib LY2157299 combination. The study is ongoing to define the recommended dose to be used with this combination.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of LY2157299 may be found in the IB. Information on AEs expected to be related to the study drug may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

5.2. Rationale for the Study

In most geographies, sorafenib is the approved first-line systemic treatment for patients with advanced HCC. Despite several efforts to improve first-line treatment in HCC, there has been no

progress in first-line treatment. In the past, Phase 3 studies compared a new agent head-to-head with sorafenib. Therefore, it is important to evaluate the activity of LY2157299 compared to sorafenib in a randomized Phase 2 prior to designing a future Phase 3.

The scientific justification of investigating LY2157299 in HCC is compelling based on the role of TGF-β in the process of fibrosis and cirrhosis leading to HCC. The evidence of antitumor effects in several models with TGF-β inhibitors, such as LY2109761 and LY364947, suggest that LY2157299 will have activity in HCC.

Based on recent interim analysis including 106 patients from Study JBAK, LY2157299 treatment resulted in a median TTP of 12 weeks (18 weeks in patients without previous sorafenib treatment) and AFP (as defined by >20% reduction from baseline) responses in 22% of patients.

Based on:

- Preclinical data of combination of LY2157299 with sorafenib showing potentiation of sorafenib activity in vitro and ex vivo study and implying the possibility that this combination may be more effective than sorafenib alone.
- The favorable safety and PK profile of LY2157299 thus far observed in HCC suggest that a combination with sorafenib may not add additional toxicity to the known toxicity of sorafenib.

Furthermore, the PK profile for LY2157299 will be documented for patients receiving the combination treatment and will be compared with the PK profile for patients who received the monotherapy.

Study JBAK is currently investigating the combination of LY2157299 with sorafenib in patients with first-line HCC and Child-Pugh A status.

Safety

The favorable safety and PK profile of LY2157299 thus far observed in HCC suggest that a combination with sorafenib may not add additional toxicity to the known toxicity of sorafenib. Furthermore, the PK profile for LY2157299 will be documented for patients receiving the combination treatment and compared with the PK profile for patients who received the monotherapy.

Antitumor Activity of LY2157299 in First-Line Patients

Preliminary results from 20 sorafenib-naive patients (3 of whom had received brivanib as a first-line treatment and 17 who had not received any systemic treatment) who were considered ineligible to receive sorafenib were treated with LY2157299 monotherapy. These patients had an estimated median TTP of 18.3 weeks, higher than TTP in second-line HCC patients. Such patients who are ineligible to receive sorafenib generally have a reduced prognosis than do patients who are physically fit to receive sorafenib. Together with the preclinical information, this justifies the evaluation of the combination in first-line HCC.

It is anticipated that LY2157299 will increase immunocompetence in HCC patients and show increased antitumor activity due to a reduction in fibrogenesis, remodeling, neoangiogenesis, and invasiveness.

The proposed immunomodulatory as well as anti-invasive properties of LY2157299 suggest that a clinical investigation in the first-line setting of patients with HCC is promising. Hence, it may be acceptable to treat patients with LY2157299 even before they are considered to receive sorafenib or other antivascular agents.

In summary, the combination of a well-tolerated agent such as LY2157299 in a disease with high unmet medical need, justifies the evaluation of this agent in the first-line treatment of HCC. Thus, the overall benefit/risk profile is acceptable in this setting.

5.2.1. Rationale for Amendment (a)

The rationale for this amendment was to update the study schedule for patients on extension period. Specifications were added to clarify the cardiovascular monitoring for patients receiving galunisertib. Consistent with the study schedule, the frequency of cardiac assessments is corrected from each cycle to every other cycle. Other minor corrections and clarifications were made within the study schedule for patients on extension period.

Attachment 19 lists changes made in the protocol amendment.

6. Objectives

6.1. Primary Objective

The primary objective is to compare the OS distributions between LY2157299 plus sorafenib therapy and sorafenib plus placebo therapy (control arm) in patients who have not received prior systemic treatment for advanced disease.

6.2. Secondary Objectives

- to estimate the HR from the OS distributions between LY2157299 monotherapy and sorafenib plus placebo
- to evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib in HCC patients
- to evaluate the population PK of LY2157299 as monotherapy and in combination with sorafenib
- to characterize other time-to-event distributions, such as TTP and progression-free survival (PFS), based on RECIST version 1.1
- to estimate antitumor efficacy using objective response rate (ORR, based on RECIST version 1.1 and modified RECIST [mRECIST]) for each treatment arm
- to assess patient-reported outcome (PRO) measures of disease-specific symptoms, time to symptomatic progression, and health-related quality of life questionnaires such as the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-30 and QLQ HCC-18 for each treatment arm

6.3. Exploratory Objectives

- to explore markers associated with EMT transformation and the TGF-β-associated signaling pathway presence in the original diagnostic tumor tissue and optional posttreatment tumor tissue and the correlation of this with both clinical efficacy endpoints and biomarker response
- to explore TTP, PFS, and ORR by immune response RECIST (irRECIST)
- to explore tumor volume changes of measurable lesions on CT/MRIs obtained for tumor response as an assessment of treatment effects on biological growth rate
- to explore the relative effects of LY2157299 versus LY2157299 plus sorafenib versus sorafenib plus placebo on antiangiogenesis as assessed by dynamic contrast-enhanced MRI (DCE-MRI) metrics and on tumor cellularity/cell death as assessed by diffusion-weighted MRI (DW-MRI) metrics. These exploratory MRI techniques will only be performed at clinical sites where the associated MRI center scanner has been qualified prior to patient enrollment by the imaging core laboratory designated by the sponsor.
- to explore fibrosis-related tests, such as fibrotest
- to assess healthcare resource utilization including transfusions and hospitalizations

7. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] have histological evidence of a diagnosis of HCC not amenable to curative surgery

[2] have Child-Pugh Class A

[3] have the presence of measurable disease as defined by RECIST version 1.1 (Eisenhauer et al. 2009) (see Attachment 9). A lesion that has been previously treated by local therapy at least 3 weeks prior to the baseline scan will qualify as a measurable or evaluable lesion if there was demonstrable progression following locoregional therapy

[4] are aged ≥18 years

[5] have given written informed consent prior to any study-specific procedures

[6] have adequate organ function including:

- Hematologic: absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥60 x 10^9/L, and hemoglobin ≥8 g/dL

- Hepatic: bilirubin ≤2.5x ULN; alanine aminotransferase (ALT) and aspartate aminotransferase ≤5x ULN. Prothrombin time (PT) international normalized ratio (INR) ≤2.3 or PT 6 seconds above control

- Renal: serum creatinine ≤1.5x ULN or calculated creatinine clearance >45 mL/min (see Attachment 10)

Note: Small differences from the outlined laboratory values will be deemed as consistent with the protocol requirements provided that the following criteria are met. The differences must be isolated, transient, and not reflective of a medical condition in the opinion of the investigator. Such differences are often a result of biological or laboratory equipment variability. To confirm that these results are within biological or laboratory equipment variability, repeat laboratory/hematological tests should be done prior to dosing the patient on Cycle 1 Day 1.

[7] have a PS of ≤1 on the ECOG scale (see Attachment 4)

[8] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[9] if male or female with reproductive potential, must agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug

[10] if females with childbearing potential, must have had a negative serum pregnancy test ≤7 days prior to the first dose of study drug

[11] are able to swallow capsules or tablets

[12] have available diagnostic or biopsy tumor tissue

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[13] are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the study drug/device used in this study) or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[14] have received previous systemic treatment for advanced disease

[15] have known HCC with fibro-lamellar or mixed histology

[16] have presence of clinically relevant ascites

[17] have had a liver transplant

[18] have moderate or severe cardiac disease:

a) have the presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension (see Attachment 13)

b) have documented major ECG abnormalities, at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle-branch blocks, ventricular hypertrophy, or recent myocardial infarction)

c) have major abnormalities documented by echocardiography with Doppler (for example, moderate or severe heart-valve-function defect and/or left ventricular ejection fraction (LVEF) <50%, evaluation based on the institutional lower limit of normal). For additional details, refer to the echocardiography protocol guidelines (see Attachment 14).

d) have predisposing conditions that are consistent with the development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, Marfan Syndrome, bicuspid aortic valve, evidence of damage to the large vessels of the heart documented by CT scan with contrast)

[19] have serious preexisting medical conditions that, in the opinion of the investigator, cannot be adequately controlled with appropriate therapy or would preclude participation in this study

[20] have active or uncontrolled clinically serious hepatitis B virus or hepatitis C virus infection:

- Patients with acute exacerbation or flare of hepatitis B or reactivation of hepatitis B or positive hepatitis C RNA are excluded.

- Patients with stable and chronic viral hepatitis are eligible.

[21] have experienced any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 GI bleeding or any variceal bleeding episode in the 3 months prior to enrollment requiring transfusion or endoscopic or operative intervention. (Patients with any bleeding episode considered life-threatening during the 3 months prior to enrollment are excluded, regardless of transfusion or intervention status.)

[22] have esophageal or gastric varices that require immediate intervention (eg, banding, sclerotherapy) or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist

[23] had herbal therapy for the purpose of anticancer treatment up to 21 days prior to the study randomization

[24] had major surgery within 4 weeks prior to the study randomization

[25] are females who are pregnant or lactating

[26] have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission and off all therapy for that disease for a minimum of 3 years

At the discretion of the investigator, hormone-sensitive prostate cancer patients who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.

[27] have active infection that would interfere with the study objectives or influence study compliance

[28] have known hypersensitivity to sorafenib or its excipients

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [13] and [23] eliminates drugs that cannot be mapped to a standard drug dictionary or for which little data are known to analyze the potential relationship of AEs or drug interactions.

Exclusion Criterion [14] prevent inclusion of patients who have received previous treatment and are thus no longer in first-line setting.

Exclusion Criterion [18] excludes patients with compromised cardiac function that could be at risk when receiving LY2157299. Based on the nonclinical toxicology assessment, patients with

cardiac insufficiency or damage to large vessels of the heart will be carefully screened. All moderate and severe cases of cardiac insufficiency will be excluded. Because of the average age of most patients eligible for this study, mild or minimal cardiac disease is commonly present, and therefore, these patients will not be excluded (Singh et al. 1999). If CT scan of the chest cannot be performed, MRI can also be used as an alternative imaging procedure.

Exclusion Criterion [25] excludes patients who are pregnant or breastfeeding. This is appropriate as there are no data available that can provide safety estimates for fetal development or the impact of LY2157299 on infants.

Exclusion Criteria [15] to [18], [20], [24], [26], [27], and [28] provide for patient safety.

Exclusion Criterion [21] and [22] exclude patients who have high bleeding risk and may have early discontinuation due to bleeding.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor's clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

In addition, patients will be discontinued from the study drug in the following circumstances:

- patient has evidence of symptomatic progression or confirmed objective progressive disease (radiological assessments by RECIST version 1.1). The important decision in determining whether a patient can continue on study drug should be based on his/her clinical symptoms, even if the patient has progressive disease based on radiological evidence. The investigator may also take into consideration biomarker responses, such as AFP elevations.
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
    - The investigator decides that the patient should be discontinued from the study or study drugs. If this decision is made because of an SAE or a clinically significant

laboratory value related to the study drug, the study drug is to be discontinued, and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the new agent.
- patient decision
    - the patient requests to be withdrawn from the study or study drug.
- sponsor decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- patient is significantly noncompliant with study procedures and/or treatment.
- unacceptable toxicity: patients who discontinue sorafenib because of toxicity may continue LY2157299 or placebo treatment.
- patient becomes pregnant or fails to use adequate birth control (for women with reproductive potential)

The reason for and date of discontinuation will be collected for all patients. All randomly assigned patients who discontinue regardless of whether or not they received study drug, will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethics review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

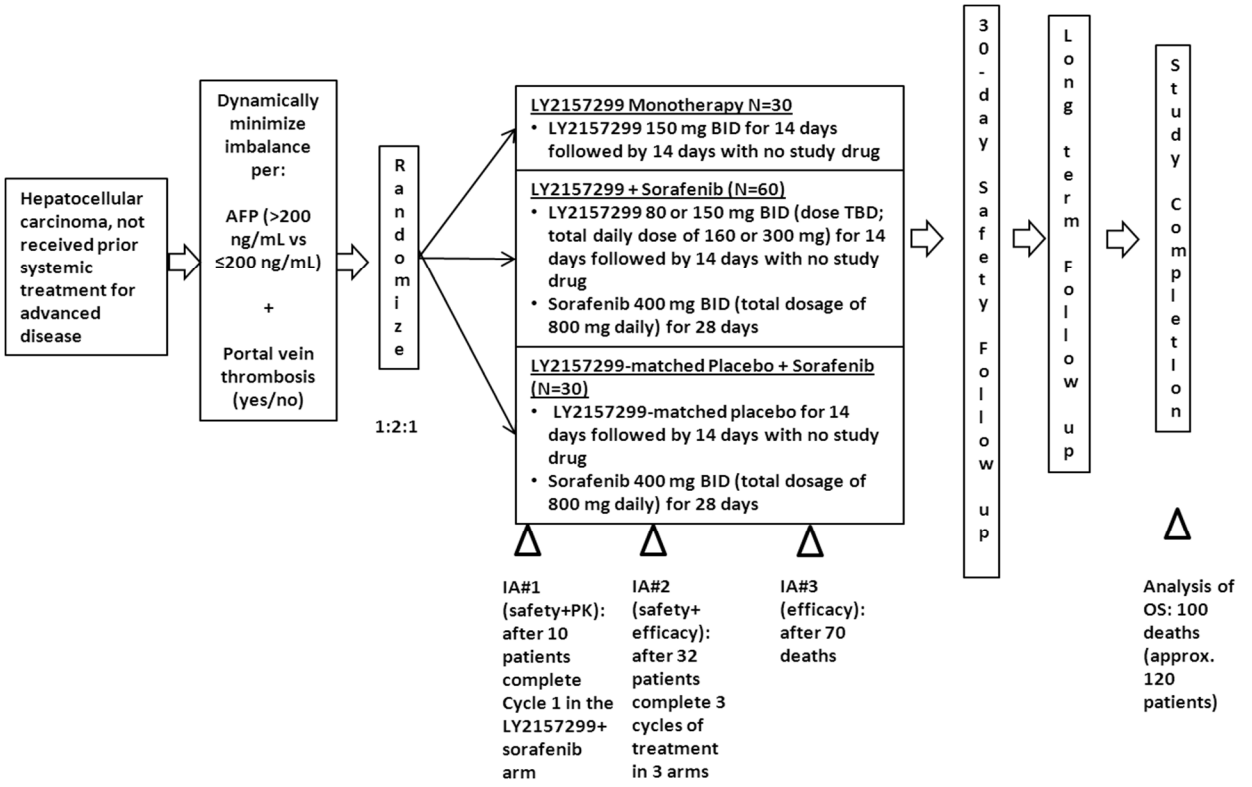
Study H9H-MC-JBAS is a 3-arm, randomized, multicenter, global (Asia), Phase 2 study of LY2157299 plus sorafenib therapy or LY2157299 monotherapy compared to sorafenib plus LY2157299-matched placebo therapy in patients with relapsed or progressed HCC. Patients who receive sorafenib and investigators will be blinded to the LY2157299 or placebo assignment for those arms.

Approximately 120 patients will be randomly assigned in a 1:2:1 fashion to 1 of 3 treatment arms: LY2157299 monotherapy, LY2157299 plus sorafenib 400 mg BID, or sorafenib 400 mg BID plus LY2157299-matched placebo (Figure JBAS.8.1). The monotherapy dose will be 150 mg BID (300-mg daily dose) for 14 days, followed by 14 days with no study drug. The LY2157299 dose used in combination with sorafenib will be determined based on the results of the JBAK study – Part C (dose will either be 80 mg or 150 mg BID [160-mg or 300-mg daily dose]). LY2157299 and matched placebo will be given for 14 days followed by 14 days of rest; sorafenib will be given each day during the cycle. A cycle is defined as 28 days in duration (a minimum of 26 days and a maximum of 31 days). The treatment period for LY2157299 must be a minimum of 10 days and a maximum of 14 days.

Patients may receive treatment until they met at least one of the discontinuation criteria (Section 7.3.1).

This Phase 2 study will be considered complete after 100 deaths for OS analysis have occurred. Patients still on treatment at the time that the study is considered complete may enter the treatment extension period and continue with the study treatment (see Section 8.1.1).

End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule (Attachment 1) for the last active patient in the study. Consult regional standard operating procedures for further information.



Abbreviations: AFP = alpha fetoprotein; BID = twice daily; IA = interim analysis; OS = overall survival; TBD = to be determined.

Figure JBAS.8.1. JBAS study period design.

8.1.1. Extension Period

At the time of study completion (ie, study objectives met, see Section 6), patients receiving study treatment and having clinical benefit may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (Section 7.3.1).

Patients who are no longer on study treatment at the time of study completion and who have completed at least the 30-day safety follow-up visit (Visit 801) will be discontinued from long-term follow-up and therefore reach the end of the study, unless they are being followed due to unresolved safety concerns. Lilly will notify investigators when the extension period begins.

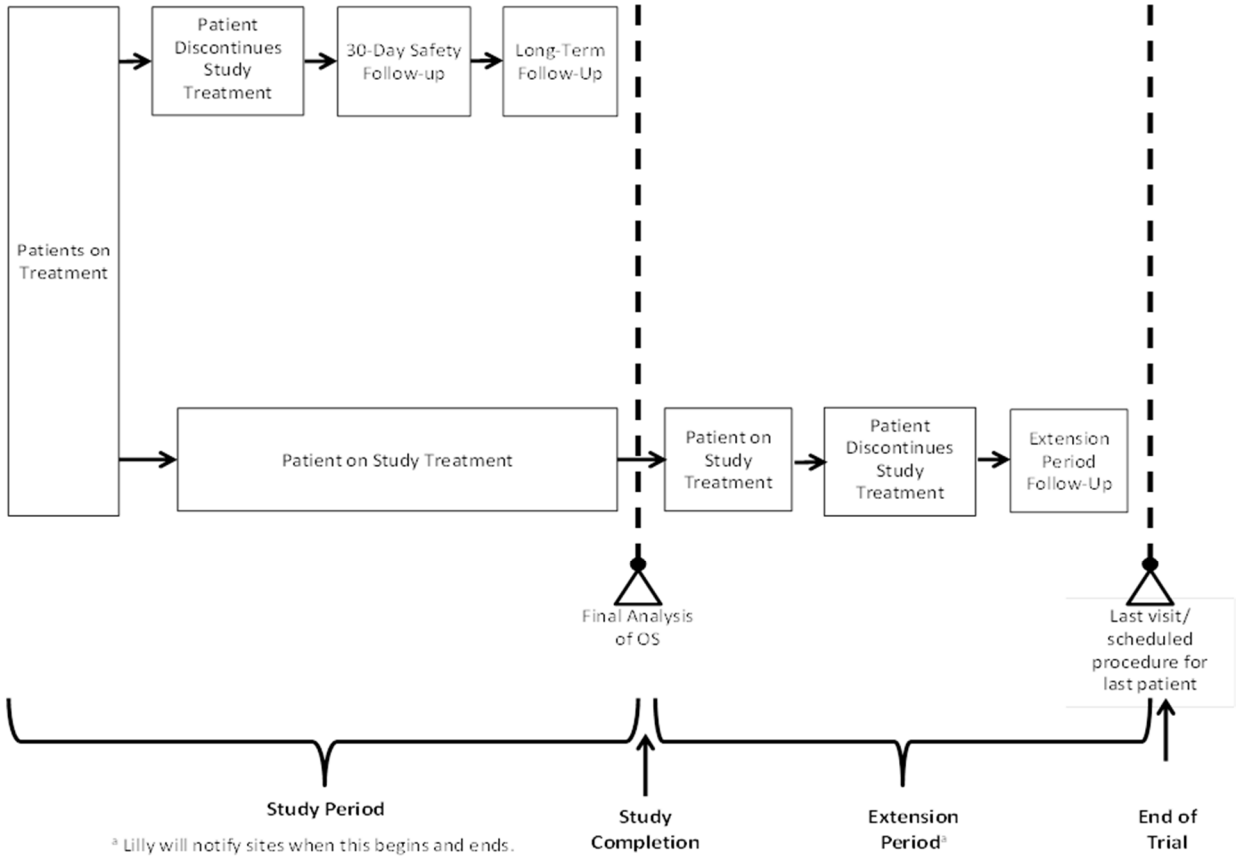
All AEs and study drug exposure will be reported on the case report form (CRF). SAEs will also be reported on the CRF and to Lilly Global Patient Safety (see Section 10.3.1.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) to evaluate the reported SAE.

All patients in the extension period will be treated following the Study Schedule (see Attachment 1). This will ensure that appropriate risk-benefit assessment is conducted for all patients.

The patient's participation in the extension period will end after study drug(s) is discontinued (Figure JBAS.8.2). The date and reason for treatment discontinuation will be collected on the CRF. Data will be collected until 30 days after the patient has been discontinued from study

treatment, and, at this point, the patient will have ended the study. If the patient dies within the 30-day safety follow-up period, the reason for study discontinuation will be "Death," and the date of death will be recorded. Otherwise, the reason for study discontinuation will be noted as "Completed." There will be no long-term post-discontinuation follow-up period for these patients unless any safety concerns have not resolved. Requests for updates of survival may be requested.

After the last patient in the extension period has completed the 30-day safety follow-up period, an addendum report will be written listing the details of data collected from all patients entered on this phase. The addendum report will not be delayed because of any patients being in long-term follow-up but will note those patients who are still in long-term follow-up due to unresolved safety issues.



Abbreviation: OS = overall survival.

Figure JBAS.8.2. JBAS extension period design.

8.2. Discussion of Design and Control

Approximately 150 patients will be entered in order to randomly assign 120 patients to 1 of 3 treatment arms using a 1:2:1 allocation ratio in favor of the LY2157299 plus sorafenib arm. A randomized, controlled design is being used in this study. Randomization minimizes systematic

bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. The study will use a dynamic allocation method, introduced by Pocock and Simon (1975) (and extended for unequal treatment group sizes by Han et al. [2009]) to minimize imbalance between treatment arms according to factors such as AFP and portal vein thrombosis. Using an appropriate concurrent control arm (which is sorafenib in combination with placebo) enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. The rationale behind favoring the combination arm in the randomization is that this is the primary treatment of interest to compare with sorafenib alone. However, based on the longer time to progression observed in Study JBAK patients in whom LY2157299 was administered as a monotherapy in a first-line setting, there is medical need of getting more information for efficacy and safety of LY2157299 monotherapy. Therefore, a monotherapy arm is also included and will inform future Phase 3 development. The purpose of the monotherapy arm is to provide a comparison to assess the safety of LY2157299 compared to sorafenib. This is especially important because LY2157299 has shown preclinical cardiac toxicity, which, thus far, has not confirmed in clinical studies. However, sorafenib has known cardiac toxicity in patients. The 3-arm study will provide a better differentiation between the various safety profiles and inform the design of Phase 3. Since OS is not affected by pseudoprogression evaluations, OS is a preferred primary endpoint over TTP or PFS. A Bayesian design can be used to leverage survival data for sorafenib alone from historical clinical trials to benefit from the 2:1 randomization of the combination arm relative to sorafenib alone with the goal of increasing power over an otherwise similar design.

9. Treatment

9.1. Treatments Administered

Patients will be randomly assigned to one of the following arms shown in Table JBAS.9.1.

Table JBAS.9.1. Treatment Regimens

	Daily Dose	Schedule	Time of Day
Arm 1	150 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] and then paused for 14 days
Arm 2	80 or 150 mg BID LY[c] plus	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] with sorafenib and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening for 28 days
Arm 3	LY-matched placebo plus	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] with sorafenib and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening for 28 days

Abbreviations: BID = twice daily; LY = LY2157299; PK = pharmacokinetic.

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.

a In extenuating circumstances, the "on-study-drug" window for LY2157299 is allowable from Day 10 to Day 14.

b Both study drugs should be taken on an empty stomach, at least 1 hour before a meal.

c LY2157299 dose will be defined based on the results of the H9H-MC-JBAK study. Dose will either be 80 or 150 mg BID.

The investigator or his/her designee will be responsible for the following:

- explaining the correct use of the investigational agent to the patient,
- verifying that instructions are followed properly,
- maintaining accurate records of study-drug dispensing and collection, and
- returning or destroying all unused medication to Lilly or its designee at the end of the study as requested

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

Patients will keep a study diary to document that they are taking study treatment correctly.

A treatment delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.

All patients should be started on a standard dose of sorafenib, but a subsequent reduction in dose appears to be justified to reduce long-term toxicity. A dose reduction from the start will not be considered a protocol violation.

Patients who have toxicity with sorafenib that cannot be managed by dose reduction may continue on LY2157299 or placebo if they are randomly assigned to 1 of the 2 arms receiving sorafenib.

9.2. Materials and Supplies

9.2.1. LY2157299

LY2157299 or placebo will be supplied in open-label or blinded blister packs or other appropriate packaging of film-coated, paracapsule-shaped tablets that are light yellow/yellow in appearance (eg, 80 or 150 mg). All materials must be stored at room temperature within temperature range specified on the material label. The material will be labeled according to regulatory requirements of the country. Should the type of clinical trial material packaging change, it will adhere to country-specific regulations.

The tablet should remain in the blister pack until just prior to administration.

9.2.2. LY2157299-Matched Placebo

Placebo provided for this study will be identical in appearance to that of the LY2157299 tablets.

9.2.3. Sorafenib

Sorafenib will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements.

9.3. Method of Assignment to Treatment

For this study, approximately 120 patients with advanced HCC who have not received prior systemic treatment and who meet all criteria for enrolment will be randomly assigned by the interactive web-response system (IWRS) to receive LY2157299 monotherapy, LY2157299 plus sorafenib, or sorafenib plus LY2157299-matched placebo in a 1:2:1 ratio after completing the screening at Visit 0. Additionally, patients who receive sorafenib and investigators will be blinded to the LY2157299 or placebo assignment for those arms (Arms 2 and 3).

A dynamic allocation method, introduced by Pocock and Simon (1975) (and extended for unequal treatment group sizes by Han et al. [2009]), will be adopted to minimize imbalance between treatment arms according to the following factors:

- AFP (>200 ng/mL vs ≤200 ng/mL)
- portal vein thrombosis (yes vs no)

The randomization parameter P will be set at 0.9 to maximize the benefit of the allocation procedure while keeping treatment assignments unpredictable. Randomization will be monitored periodically, and the randomization parameter will be modified if necessary.

Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS.

The IWRS will be used to assign blister packs containing study drug to each patient. Site personnel will confirm that they have located the correct blister packs by entering a confirmation number found on the blister packs into the IWRS.

9.4. Selection and Timing of Doses

Room-temperature storage condition is recommended for the tablet drug products. The tablets should remain in the primary packaging until just prior to administration.

At the discretion of the investigator, if a patient vomits within 30 minutes of taking a dose of LY2157299 or sorafenib, the dose should be repeated 1 time only that same day, if nausea/vomiting permits.

LY2157299/LY2157299-matched placebo and sorafenib will be dosed BID, in the morning and evening approximately 10 to 12 hours apart in relationship to meal times and should be taken at approximately the same time every day. Patients should take the study drug on an empty stomach, preferably 1 hour before breakfast and 1 hour before dinner, and should preferably not consume food for at least 1 hour after taking study drug.

Tablets should be swallowed whole and not split, crushed, or dissolved for administration.

A cycle is defined as an interval of 28 days (a delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not counted as a protocol deviation).

A patient may continue to receive study drug until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3.1).

9.4.1. Dose Adjustments and Delays

9.4.1.1. LY2157299

Table JBAS.9.2 summarizes dose adjustment for patients experiencing the following events that are considered possibly related to LY2157299. LY2157299 will be omitted until the event resolves:

Table JBAS.9.2. Doses Adjustments for LY2157299

Events Possibly Related to LY2157299	Adjustment
ANC <0.5 x 10^9/L for longer than 7 days, or ANC <1.0 x 10^9/L with a single temperature of >101°F/38.3°C or a sustained temperature of >100.4°F/38°C for >1 hour	LY2157299 will be omitted until the event resolves
Platelet count <25 x 10^9/L	LY2157299 will be omitted until the event resolves
CTCAE Grade 3 or 4 nonhematologic toxicity	LY2157299 will be omitted until the event resolves

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

- Nonhematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).
- Hematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.

If dosing is delayed for >2 weeks for treatment-related AEs, the patient should be withdrawn from the study treatment. Patients who do recover within the 2-week time frame may have the dosage reduced to 160 mg/day (or 80 mg/day if selected dose for the combination is 160 mg/day).

In case of a dose delay of LY2157299, patients can continue sorafenib treatment (at investigator discretion).

No patient will have his/her LY2157299 dose reduced more than once. Reescalation to the previous LY2157299 dose is acceptable in the absence of continuing or cardiac toxicities. If subsequent LY2157299 dose reduction is required after reescalation, the patient must be maintained at the reduced dose level for all remaining cycles.

If moderate or severe heart valve toxicities are observed, the patient must immediately be discontinued from the treatment (for definitions see Attachment 14, including references on the echocardiographic assessment based on the Guidelines of the American and European Societies of Cardiac Echocardiography). Exceptions to this rule must be approved by the ERBs and Lilly.

9.4.1.2. Sorafenib

As a guidance of toxicity relationship for sorafenib, please refer to Attachment 18 (safety profile for sorafenib).

Doses will be delayed or reduced for clinically significant hematologic and other toxicities (Table JBAS.9.3; see Table JBAS.9.4 for modifications due to skin toxicity) that are related to sorafenib. In case of a dose omission/delay of sorafenib, patients can continue LY2157299 or placebo treatment up to total of 14 days (at the investigator's discretion).

In case of discontinuation of sorafenib treatment, patients can still revive LY2157299 or placebo as per protocol (at investigator discretion).

When dose reduction is necessary, sorafenib dosage may be reduced using the predefined dose levels:

- Dose level 1 (no reduction): 400 mg (2 x 200 mg) administered orally BID daily
- Dose level 2: 400 mg (2 x 200 mg) daily
- Dose level 3: 400 mg (2 x 200 mg) every other day
- If further dose reduction is required, the patient should be discontinued from sorafenib treatment.

At the discretion of the investigator, the dose may be reescalated to the previous dose level 400 mg BID after the resolution of the AE.

Table JBAS.9.3. Sorafenib Dose Modifications for Hematologic and Nonhematologic Toxicities (Except Skin Toxicity and Hypertension)

Grade	Dose Delay	Dose Modification
Hematologic toxicities		
Grades 0-2	Treat on time	No change
Grade 3	Treat on time	Decrease 1 dose level
Grade 4	Delay[a] until ≤ Grade 2	Decrease 1 dose level
Nonhematologic toxicities (except skin toxicity)[b]		
Grades 0-2	Treat on time	No change
Grade 3	Delay[a] until ≤ Grade 2	Decrease 1 dose level[c]
Grade 4	Discontinue sorafenib treatment	Discontinue sorafenib treatment

[a] If no recovery after 30-day delay, treatment will be discontinued unless patient is deriving clinical benefit.

[b] Also excludes nausea/vomiting that has not been premedicated and diarrhea.

[c] If >2 dose reductions are required, treatment will be discontinued.

Source: Llovet et al. 2008 supplementary material

Table JBAS.9.4. Suggested Sorafenib Dose Modifications for Skin Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modifications
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet that does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by 1 dosage level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue sorafenib treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grades 0-1. When resuming treatment, decrease sorafenib dose by 1 dosage level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue sorafenib treatment

Source: Nexavar (sorafenib) package insert

Suggested Management of Hypertension (adapted from Izzedine et al. 2009)

- Blood pressure should be checked regularly in patients on sorafenib therapy. Hypertension should be managed in accordance with standard medical practice for sorafenib individualized to the patient's clinical circumstances (refer to local institutional guidance, other available guidelines, or Izzedine et al. 2009).
- For hypertension >140/90 mm Hg and ≤160/100 mm Hg: Continue sorafenib. Consider adding or adjusting antihypertensive medications.
- For persistent (>160/100 mm Hg) or symptomatic hypertension: Interrupt sorafenib. Resume when blood pressure improves to ≤160/100 mm Hg. If persistent hypertension with optimal treatment consider decrease sorafenib by 1 dose level.
- In case of hypertension crisis (Grade 4), sorafenib should be withheld.

9.5. Blinding

Arm 1 is open label. Patients on Arms 2 and 3 and investigators will be blinded to the LY2157299 or placebo assignment for those arms.

Upon overall study completion, investigators may unblind patients in Arms 2 and 3 to LY2157299/LY2157299-matched placebo assignment.

Efficacy information will not be shared between sites until the study is completed.

Treatment assignment will be scrambled in the reporting database until the database lock for data analysis. This will ensure unblinded aggregate efficacy results are not available until the time of final data analysis.

9.5.1. Emergency Unblinding in Arms 2 and 3

Emergency unblinding for AEs may be performed through an IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

9.5.2. Inadvertent Unblinding in Arms 2 and 3

Every effort will be made to blind both the patient and the investigator to the identity of LY2157299 or LY2157299-matched placebo in Arms 2 or 3, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

Except for GnRH-agonist therapy and antiestrogen therapy (if patients are stable on these therapies), no other anticancer therapy, immunotherapy, hormonal cancer therapy, herbal treatment as anticancer treatment or experimental medications will be permitted while the patients are participating in this study. Palliative radiation therapy to nontarget lesions is allowed. Any disease/symptomatic progression requiring other forms of specific antitumor therapy will be cause for early discontinuation of study therapy.

The use of antiviral therapy should be considered in accordance with local guideline or American Association for the Study of Liver Diseases practice guidelines or in consultation with hepatitis experts (Lok and McMahon 2009).

During the first-in-human Study JBAH, patients received enzyme-inducing anti-epileptic drugs, such as carbamazepine, phenobarbital, or phenytoin. No apparent drug-drug interaction has been observed, consistent with the nonclinical absorption, distribution, metabolism, excretion properties of this agent.

When sorafenib is administered, avoid concomitant use of strong CYP3A4 inducers (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort),

when possible, because inducers can decrease the systemic exposure to sorafenib. Warfarin is not recommended for coadministration with sorafenib.

9.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning, review of diary, and counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the "Study treatment: modifications" form.

For patients who are significantly noncompliant (<80% or >120% of expected study drug taken in a visit interval), investigative sites must counsel patients on the importance of study drug compliance and drug accountability. Patients who are consistently out of the compliance range may be discontinued. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

The following procedures will be employed to ensure appropriate drug accountability:

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study-drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all unused study drug for all patients.

Patients will keep a study diary to document that they are taking LY2157299/ LY2157299-matched placebo and sorafenib correctly.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Terms used to describe the periods during the study are defined below:

- **Baseline (Visit 0):** From the time of screening to the first study treatment (or discontinuation, if no treatment is given)
- **Treatment Start**: First day of study treatment
- **Treatment Period:** Time from treatment start to discontinuation from study treatment
    - During the study period, cycle number will correspond to visit number (eg, Cycle 1 = Visit 1).
    - During the extension period, cycle number will correspond to extension visit number (eg, Cycle 1 = Visit 501).
- **Discontinuation from Study Treatment**: The day the patient discontinues study treatment (summary visit)
    - applies to patients in extension period, too
- **30-Day Safety Follow-Up Period (Visit 801)**: The time after the patient discontinues study treatment during which follow-up data are collected. Visit 801 starts 1 day after discontinuation from study treatment and lasts 30 days (±3 days).
    - applies to patients in extension period, too. However, for patients in the extension period, the end of the 30-day safety follow-up period is also the end of their study participation (unless further follow-up is required for cardiac toxicities).
- **Long-Term Follow-Up Period (Visits 802, 803, etc):** Visit 802 starts 1 day after the 30-day Safety Follow-up (Visit 801) and lasts 60 days (±7 days). All subsequent long-term follow-up visits will occur at 60-day intervals (±7 days) (for example, Visit 803, Visit 804, etc.) for as long as the patient remains alive or until the required number of deaths have been observed.
    - not required for patients in extension period unless there are cardiac toxicities

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection and testing assessments and their timing are described in the sections below and are shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

All patients will be followed for progression and OS. Patients who come off therapy due to objective progressive disease will be followed for survival every 2 months. Patients may continue on study treatment even if they have objective progression or if they are clinically asymptomatic (see Section 7.3). However, it is important that the cycle response records

objective progressive disease in the cycle that it occurred in order to estimate TTP, PFS, and response rate without bias. These patients will then be discontinued from study treatment because of overall symptomatic deterioration (including biomarker response) or other causes. Patients who come off therapy and do not have objective progressive disease should be followed every 2 months after discontinuation from study treatment until death, including radiologic examinations every 6 weeks until objective progressive disease is determined (using the same radiological scans as at baseline). Patients who progress should then be followed for survival every 2 months. Every attempt should be made to gather all information every 2 months (radiological scans and survival), even if a patient starts a new anticancer therapy. Evaluation of survival can be accomplished by telephone contact if necessary. The date any new anticancer therapy starts, either during the 30-day safety or long-term follow-up periods, needs to be collected. This will enable a better estimate of time-to-event data to inform future decisions in this indication as it will be based on more mature data.

It is important that protocol procedures related to collection of these data, both during the active study treatment phase and follow-up period, are followed and that dates of data collection are recorded accurately.

10.1.1. Clinical Efficacy Measures

While RECIST version 1.1 is the primary efficacy measure, other radiographic assessments will be used in the study. RECIST version 1.1 (see Attachment 9) and mRECIST (Attachment 16) will be used for response assessment; RECIST version 1.1 will also be used for TTP, and PFS. irRECIST (Wolchok et al. 2009; see Attachment 17) may be used for explorative response assessment and time-to-event variable determination.

Each patient will be assessed by 1 or more of the following radiologic tests for tumor measurement at the times specified in the Study Schedule (Attachment 1): CT scan or MRI. In addition, for final study report analyses, a central review of all radiographic examinations will be conducted, and assessments of progression will be based on RECIST v1.1 and, if applicable, irRECIST.

Radiologic assessments will be collected at the times shown in the Study Schedule. MRI and/or CT scans will be collected and stored centrally.

Changes in biomarkers response (collected as specified in the Study Schedule [Attachment 1] and detailed in Section 10.4.2.2) are measures of progressive disease response, and the relationship to clinical efficacy measures will be explored.

10.1.2. Primary Efficacy Measure

The primary efficacy endpoint is OS, defined as the time from the date of randomization to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS time will be censored at the last contact date the patient was known to be alive prior to the cut-off date.

10.1.3. Secondary Efficacy Measures

The following secondary efficacy measures (Table JBAS.10.1) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JBAS.10.1. Secondary Efficacy Endpoints

Endpoint	Definition
TTP	The time from the date of study randomization to the date of first observation of objective progression. For patients who are not known to have progressed as of the data-inclusion cut-off date, TTP will be censored at the date of the last objective progression-free disease assessment
PFS (based on RECIST v1.1)	The time from the date of study randomization to the date of first observation of objective progression or death from any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the date of the objective progression-free disease assessment
ORR (based on RECIST v1.1)	The proportion of patients who achieved a best overall response of either complete or partial response defined by RECIST v1.1. The ORR for each treatment group will be estimated by dividing the total number of confirmed responders by the number of patients who received at least 1 dose of study treatment

Abbreviations: ORR = objective response rate; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TPP = time-to-tumor progression; v = version.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

The assessment of PROs, including disease-specific symptoms and health-related quality of life, will be assessed using the EORTC QLQ-30 and QLQ HCC-18.

EORTC QLQ-30

The EORTC QLQ-C30 is a general measure of quality of life in cancer patients (Aaronson et al. 1993). It is a self-reported instrument consisting of 30 items covered by 1 of 3 dimensions: global health status/quality of life (2 items); functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning); symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact) (Attachment 11).

EORTC QLQ HCC-18

To assess disease-specific symptoms of HCC patients, the HCC-specific module (EORTC QLQ HCC 18) will be used. The EORTC QLQ HCC18 is an 18-item HCC-specific supplemental module developed to augment QLQ-C30 and to enhance the sensitivity and specificity of HCC-related QOL issues (Blazeby et al. 2004) (Attachment 12).

Both the EORTC QLQ-30 and QLQ HCC-18 will be administered at baseline, at every cycle starting from Cycle 2, and at discontinuation (see Study Schedule for details [Attachment 1]).

PRO instruments should be completed at the beginning of office visits, before any extensive contact and consultation with the clinician/study investigator or staff. Consultation with the clinician may bias perceptions about quality of life and symptoms and thus affect assessments.

The EORTC QLQ-30 and QLQ HCC-18 will only be completed by patients for whom there is a validated language translation in which the patient is fluent.

10.2.2. Resource Utilization

Investigators will be asked to document the use of best supportive care measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day safety follow-up visit.

10.3. Safety Evaluations

Investigators will be responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator will be responsible for the appropriate medical care of patients during the study.

The investigator will remain responsible for following, through an appropriate healthcare option, AEs that are serious, that are considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JBAS.10.2 describes AE and SAE collection with regard to the type of events to be reported during each period of the study.

Table JBAS.10.2. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported
Baseline (pretreatment)	Preexisting conditions All AEs SAEs related to protocol procedures
Study treatment period	All AEs and SAEs
30-day safety follow-up	All AEs and SAEs
Long-term follow-up	All SAEs related to protocol procedures or study drugs
Extension period	All AEs and SAEs
Extension period follow-up	All AEs and SAEs
After the patient is no longer participating in the study (that is, no longer receiving study therapy and no longer in follow-up)	All SAEs related to protocol procedures or study drugs that the investigator becomes aware of

Abbreviations: AE = adverse event; SAE = serious adverse event.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, laboratory values, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record in the electronic CRF (eCRF) any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or its designee via eCRF.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via eCRF.

Any clinically significant findings from ECGs, laboratory tests, vital-sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and/or study drug via eCRF.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study-site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

The investigator will interpret the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related:** a direct cause-and-effect relationship between the study treatment and the AE is likely
- **Possibly related:** a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related:** without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-CTCAE version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE version 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class (SOC) and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the *Medical Dictionary for Regulatory Activities* (MedDRA) dictionary.

10.3.1.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on 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.

SAE collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

SAEs occurring after a patient has taken the last dose of study drug will be collected for 30 days after the discontinuation from study treatment, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either the study drug, the drug delivery system, or a protocol procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

SAEs due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the DCSI in the IB and that the investigator identifies as related to the investigational product or study procedure. US 21 Code of Federal Regulations 312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiography

For each patient, 12-lead digital ECGs will be obtained as single ECGs according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near

syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee will be responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study-report purposes.

It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

Other safety measures include assessments of physical examinations, preexisting conditions, transfusions and hospitalizations, and AEs. Patients will be assessed before each visit by using the CTCAE version 4.0.

For patients in the extension period, monitoring should be performed at predose on Day 1 of every other cycle for patients receiving galunisertib. The standard care of treatment should be followed for patients receiving sorafenib.

10.3.2.2. Echocardiographs with Doppler and Chest Computed Tomography Scans

Because of the cardiotoxicity monitoring in this study, echocardiographs with Doppler and chest CT scans are being performed (see Attachment 1, Attachment 14, and Attachment 15). Echocardiography with Doppler will be locally assessed at screening for enrollment and throughout the study according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. The individual must be identified at each site. A central reading will be performed for the data used in the study report.

Chest CT scan with contrast of thorax and abdomen to evaluate the large vessels of the heart will be locally assessed at screening for enrollment and every 6 months throughout the study and at the end of study visit (Visit 801) according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

Chest CT scan with contrast of thorax and abdomen for tumor assessment will be locally assessed at screening for enrollment and every 6 weeks starting Cycle 2 Day 14 until radiological disease progression according to the Study Schedule (Attachment 1) by a physician or a person

who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography, ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and 805).

If there are no clinically significant cardiac findings at discontinuation (Visit 801), 1 more echocardiography, ECG, and ECG chemistry will be performed after 2 months (Visit 802). If a patient receives another treatment, Visit 802 cardiac assessments will not be performed.

For cardiac monitoring of patients in the extension period, chest CT scan or MRI will be locally assessed every 6 months for patients receiving galunisertib. Tumor and radiological assessments are recommended at regular intervals during the extension period. The rest of the monitoring described in the previous 2 paragraphs will also be applicable for patients in the extension period. Therefore, for these cases, the patient does not discontinue from the study at the end of the 30-day safety follow-up period but after the cardiac findings have either resolved or, if not resolved after 6 months, after discussions between the Lilly CRP and investigator.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and will review:

- trends in safety data
- laboratory analytes
- AEs
- If a patient experiences elevated ALT >5x ULN and elevated total bilirubin >2x ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3x ULN, monitoring should be triggered at ALT >2x baseline.
- Details for hepatic monitoring depend on the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

For the purpose of this study, in which survival is a primary endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly Global Patient Safety representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections and exploratory imaging biomarkers in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

With the exception of samples for PK testing, all samples should be collected prior to study drug dosing unless otherwise specified in Attachment 1 or Attachment 5. In extenuating circumstances, blood can be drawn up to 3 days before Day 1, but the appropriate central laboratory kit for the respective new visit must be used.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood, urine, and tissue samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. A serum pregnancy test will be performed (if applicable). Other clinical laboratory tests will be analyzed by central and local laboratories. Attachment 2 lists the specific tests that will be performed for this study. Patient eligibility is based on local laboratory results only, unless the investigator chooses to use the central laboratory for such a purpose. Central laboratory results are used for study report purposes and where appropriate for safety analyses.

At screening, pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue will be collected (paraffin blocks or approximately 10 unstained slides cut from that block) for correlation studies of molecular markers and for confirmatory diagnosis. Due diligence should be used to make sure that a tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, it is acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Pharmacodynamics and/or Tailoring Biomarkers

10.4.2.1. Pharmacogenomic Evaluations

There is growing evidence that DNA variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; the mechanism of action of the drug; the disease etiology; and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis. It is a 1-time collection, as noted in the Study Schedule (Attachment 1).

It is recommended that the blood sample be taken before study treatment commences but may be taken at any time while the patient is participating in the clinical study. Genes related to safety, efficacy, PK, and/or the mechanism of action of LY2157299 may be tested. Patients will not have the option to request test results and will not receive the genetic test results.

Samples will be stored and analysis may be performed on genetic variants thought to play a role in cancer and targets related to LY2157299 and other administered medicines including genetic changes associated with metabolism and response genes to evaluate their association with observed response to LY2157299.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped, and analysis may be performed to evaluate a genetic association with response to LY2157299. These investigations may be limited to a focused-candidate gene study, or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The sample will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator-site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.4.2.2. Nonpharmacogenetic Biomarker Evaluation and Patient Tailoring

Collection of samples for measurement of biomarker responses (including E cadherin; TGF-1; platelet factor-4 and T regulatory cell counts; AFP; AFP L3; prothrombin induced by vitamin K

absence [PIVKA II]; urine C-terminal telopeptides of type 1 collagen; immunophenotype; fibrotest; multi-analyte panel [MAP] panel; and other biomarkers related to LY2157299, sorafenib, and HCC) is required for this study. Refer to the Study Schedule (Attachment 1) for timing of sample collection.

An optional tumor biopsy may be taken by core needle biopsy/surgical biopsy at screening, at Cycle 2, and at the time of disease progression. Due diligence should be used to ensure that a tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying the tissue may also be requested.

The research on stored samples from this study may look at the proteins or other biochemical markers to learn more about compound-specific disease states or how patients respond to or tolerate treatment with LY2157299, sorafenib, or other compounds/medications administered during this study. Stored samples may also be used in validating diagnostic tools or assay(s) related to patient tailoring and disease state.

At baseline, before the patient receives study drug, the following samples will be collected:

- mandatory: pretreatment FFPE tumor tissue (paraffin blocks or approximately 10 unstained slides cut from that block)
- optional tumor biopsy
- plasma

At Cycle 1, the following samples will be collected:

- plasma

At Cycle 2, an optional tumor biopsy will be collected.

At Cycle 2, at each cycle after Cycle 2, and at the time of disease progression, the following samples will be collected:

- plasma

The samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Blood, serum, and plasma samples must be collected and shipped according to instructions provided in the central laboratory manual.

Samples will be shipped by the local laboratory to the designated research laboratories, according to the instructions in the central laboratory manual. Designated research laboratories are associated with Lilly and are located in the US and EU.

Samples will be destroyed according to a process consistent with local regulations.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

Sparse samples for PK evaluation will be collected from all patients in the study as indicated in Attachment 5. The actual time of dosing on the day of sampling and the actual time of sampling for each of the samples must be collected. Dose information (dose time and amount of dose) must be collected for the day of sampling and the 2 days prior to the sampling day. This information can be obtained from the patient at the visit for blood sampling.

The sampling times in the schedule are approximate, and the actual sampling time should be recorded. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Plasma PK samples will be collected and analyzed for LY2157299 and sorafenib using a validated method. PK samples for the LY2157299-matched placebo may be collected but will not be analyzed. A maximum of 8 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Lilly.

Drug concentration information will not be reported to investigative sites or blinded personnel.

Bioanalytical samples collected to measure study-drug concentration will be retained for a maximum of 2 years following the last patient visit for the study.

10.4.4. Exploratory Imaging Biomarkers for Pharmacodynamic Assessments

Tumor volume measurements will be performed by the imaging core laboratory for measurable lesions on the CT/MRI scans done for tumor response and will be used to assess the effect of treatments on biological growth rates for each arm.

DCE-MRI and DW-MRI will be performed at clinical sites that have access to an MRI center whose MRI scanner is qualified and approved in advance of patient scanning by the imaging core laboratory designated for this study by the sponsor. Patients who are able to undergo MRI scanning with a gadolinium-based contrast agent (GBCA) will undergo noncontrast DW-MRI and then DCE-MRI in a single scanning session at 2 time points: the first scan at baseline within 10 days of first dose of study drug and the second scan at Cycle 2 Day 22 ± 3 days. The estimated glomerular filtration rate (eGFR) obtained from the creatinine value obtained in Cycle 2 Day 14 will be used to ensure that the patient has maintained an acceptable eGFR for GBCA use in the Cycle 2 Day 22 scan. The metrics obtained from the DCE-MRI scans will include the volume transfer constant between the plasma and the extracellular extravascular leakage space and the initial area under the contrast enhancement curve, typically between 0 seconds and 60 and/or 90 seconds and will be used to compare the antiangiogenic effect across treatment arms. The DW-MRI will typically be obtained for the body areas (abdomen, chest) containing tumor lesions, and the SW-MRI metric(s) that are used to assess the effect of treatment will include the apparent diffusion coefficient obtained across arms.

Details of the imaging acquisitions will be provided in an MRI scanning manual provided by the imaging core laboratory.

10.5. Appropriateness of Measurements

There are no surrogate endpoints used in this study. All efficacy and safety assessments used in this study are standard and appropriate for an oncology study.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The sites will maintain a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

CRF data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, ECG data, or CT and MRI images and their analysis results, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary, PRO measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Approximately 150 patients will be entered into this study in order that 120 patients will be randomly assigned to 1 of 3 treatment arms. The randomization will be in a 1:2:1 allocation ratio with 30 patients in LY2157299 monotherapy, 60 patients in LY2157299 plus sorafenib therapy, and 30 patients in sorafenib plus placebo therapy.

The primary objective is to compare the OS distributions between LY2157299 plus sorafenib therapy (combination arm) with sorafenib plus placebo (control arm) using a Bayesian augmented control design. By incorporating historical information regarding the control group into the Bayesian model, it is possible to improve the operating characteristics compared to a standard (frequentist) analysis. The primary objective will be considered to be met if, after 120 patients have completed at least 2 years of follow-up, the posterior probability is >84% that the HR for OS of the combination arm versus control arm is <1.

The study is designed to observe approximately 100 deaths. Simulations (FACTS version 3.2) were carried out using below assumptions:

- Exponential survival model using summary hazard rates from 2 previous sorafenib trials in Asia-Pacific population (see Table JBAS.12.1), along with data from the sorafenib plus placebo arm in this study;

Table JBAS.12.1. Summary of Historical Trials

Trial Name	Sample Size	Median OS (Months)	Hazard Rate (per Week)
Cheng et al. 2009	150	6.5	0.02666
Cheng et al. 2011	410 (Asian Pacific subgroup)	8.8	0.0197
Weighted overall	560	8.2	0.0216

Abbreviation: OS = overall survival.

- A fixed prior distribution for the sorafenib plus placebo hazard rate following a gamma distribution with a mean of 0.0216/week and a weight of 10 (strong prior) and a weight of 1 (weak prior);
- The prior distribution of the log HR between the combination arm and the control arm is assumed to be normally distributed with a mean of 0 and a standard deviation of 100 (weak prior);
- True HRs between the combination arm and the control arm, LY2157299 monotherapy arm and the control arm, are 0.667 and 1, respectively;
- The accrual rate is 10 patients/month (1.7 patients/week);
- The minimum follow-up for the last patient is approximately 2 years (104 weeks).

The simulations indicate that, by randomizing 120 patents, the posterior probability of concluding superiority of the combination arm over the control arm is approximately 83%

(strong prior) and 74% (weak prior) (Table JBAS.12.2). Assuming an HR of 1, the posterior probability of concluding superiority of the combination arm over the control arm (ie, type I error) is approximately 14% to 15%. For comparison purpose, a frequentist analysis using the log-rank test would give a power of 73% assuming the HR = 0.667 and type I error = 14% (one-sided).

Table JBAS.12.2. Simulation Results for Final Analysis

N (Deaths)	Control Rate Prior	Timing of Analysis	Type I Error	Posterior Probability (HR <1) > 0.84
120 (100)	Strong prior for final analysis	FPV + 32.7 months	14%	83%
120 (100)	Weak prior for final analysis	FPV + 32.7 months	15%	74%

Abbreviations: FPV = first patient visit; HR = hazard ratio.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

All patients who receive at least 1 dose of study drug will be evaluated for safety, efficacy, toxicity, and progressive disease endpoints. The progressive disease responses will especially focus on the AFP kinetics and the TGF-β1 levels but also include the assessments of EMT-associated markers (for example, E-cadherin) and fibrosis-related blood markers.

Patients with measurable disease will be included in summaries of tumor response. Tumor response will only be tabulated for patients who received at least 1 dose of study drug and have measurable disease at baseline.

Safety analyses will be based on the safety population, defined as all randomized patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

Patients from all sites will be pooled for the purposes of analysis. Inference about survival will be made using a Bayesian posterior probability for the superiority of LY2157299 plus sorafenib arm survival over sorafenib plus placebo arm. The remaining analyses of this study will estimate differences between arms where appropriate, including exploratory analyses.

Results of descriptive analyses and estimates from inferential analyses will be presented by treatment arm. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Any missing longitudinal data will not be imputed, but rather will be estimated from an appropriate random mixed-effects model. Transformations will be applied where assumptions behind any analysis are better satisfied by data being transformed onto an alternative scale. All results from any of these

analyses will be back transformed to the original scale. Alternatively, nonparametric methods will be applied.

Any change to the data-analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data-analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as the number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- historical illness
- prior therapies
- concomitant drugs

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be listed and may be summarized by the World Health Organization preferred name for the safety population.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm. A summary of treatment compliance will be generated using information from drug accountability records and the patient diary. The number of tablets taken relative to the number expected to be taken will be summarized by cycle and treatment arm.

12.2.6. Primary Outcome and Methodology

OS duration will be measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the

data inclusion cut-off date. (Contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date.) A method of analysis for comparing OS between the treatment arms will use a Bayesian exponential-likelihood model with possibly a hierarchical random-effects distribution on treatment effects. The model incorporates historical data from 2 studies with a sorafenib plus placebo arm to augment the prospective control arm data. If the Bayesian posterior probability of superiority of the combination arm over the control arm (ie, HR <1) exceeds 0.84 under a strong prior, then it will be concluded that the combination arm is superior. The same analysis will be repeated using the weak prior. A similar Bayesian analysis will be carried out to provide 90% predictive intervals of the HR between the control arm and LY2157299 monotherapy.

12.2.7. Secondary Efficacy Analyses

In addition to the above primary Bayesian analyses for OS, OS curves for each treatment arm will also be analyzed using the Kaplan-Meier product-limit method (Kaplan and Meier 1958). Two-sided, 95% CIs for median OS will be computed by the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). OS rates at 6 and 12 months will also be estimated using Kaplan-Meier estimates on the OS curve for each treatment arm. Associated 2-sided 95% CIs will also be calculated. Pairwise HRs along with 95% CIs between the 3 arms may be estimated using proportional hazards (PH) models. Additional exploratory analyses using PH models to control for other factors may be performed. Details will be specified in the statistical analysis plan.

TTP and PFS curves and TTP/PFS rates will be summarized (at 3 months, 6 months, 9 months,12 months) using Kaplan-Meier estimates of the median survival times (including 95% CIs). Pairwise HRs along with 95% CIs between the 3 arms will also be provided. Additional exploratory analyses using PH models to control for other factors may be performed.

ORR based on RECIST version 1.1 and mRECIST will be estimated by dividing the total number of responders (complete response [CR] or partial response [PR]) by the number of who received at 1 dose of study treatment and had measureable disease at baseline. Exact 95% CIs by the method of Clopper and Pearson (Clopper and Pearson 1934) for each treatment arm will be provided.

12.2.8. Pharmacokinetic Analyses

The plasma-concentration-versus-time data together with information on dosing and patient characteristics will be pooled and analyzed using a population PK analysis approach. Nonlinear mixed-effect modeling (NONMEM) will be used for the estimation of the population PK parameters of LY2157299. Sorafenib PK will be assessed against a published sorafenib population PK model.

All patients who have completed at least 2 days of sampling will be included in the PK analysis. LY2157299 PK will be modeled using NONMEM. These population parameters will describe the average dose-concentration relationship in the target population, the influence of fixed effects

(such as weight or age) on a PK parameter of interest, the interindividual variation in the PK parameter, and the residual variation in the observed concentration.

For the purposes of the JBAS clinical study report, plasma-concentration data will be illustrated graphically and summarized descriptively. If data is sufficient, then data from patients in this study will be modeled using the population approach for characterizing LY2157299 PK.

Exploratory PK/PD analyses will be conducted to identify the exposure-response (biomarker) relationship in this study. The PK and PK/PD analyses may be reported as separate stand-alone reports for this study. Additional analyses such as exposure-response using TTP and/or other appropriate clinical endpoints may be explored, if data warrant.

The version of any software used for the analysis will be documented, and the program will meet Lilly requirements for software validation. It is possible that other validated equivalent PK software programs may be used if appropriate, warranted, and approved by global PK management.

12.2.9. Pharmacodynamics Analyses

PD parameters (eg, E-cadherin, pSMAD) will be analyzed using PD data from all patients who underwent PD assessments. The association between changes in PD parameters and clinical endpoints will be explored to determine their value as predictive biomarkers of drug effect on clinical outcome.

12.2.10. Health Outcome/Quality of Life Analyses

Questionnaire compliance rates will be ascertained at each measurement time point until the end of study therapy including at discontinuation (Visit 801).

Summary descriptive statistics will be provided for the PRO data (ie, EORTC QLQ-30 and QLQ HCC 18) at each assessment. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline. Scores will be evaluated both in aggregate (that is, median values for each study arm at a given time point) and individually, in which each patient's score on study is evaluated relative to his/her baseline score. Time to symptomatic progression will also be evaluated, and longitudinal analyses, such as repeated measures, will be performed. Other exploratory longitudinal analyses may be performed.

12.2.11. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study medication and will be repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test.

Safety analyses will include, but are not limited to, the following:

- all reported AEs, including seriousness, severity, and possible relationship to study drug, using CTCAE terminology and grades
- TEAEs, including seriousness, severity, and possible relationship to study drug, using CTCAE terminology and grades
- dose adjustments for any study therapy
- physical examination and other safety observations, including those specifically targeting the monitoring of cardiac safety
- laboratory measures

AE terms and severity grades will be assigned by the investigator using CTCAE version 4.0. MedDRA version 16 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA lower level term will be used in the treatment-emergent computation. A TEAE, defined as an event that first occurred or worsened in severity after baseline, will be summarized by SOC and by decreasing frequency of preferred term within SOC.

Laboratory and nonlaboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grades 3 and 4. These summaries will be provided for events regardless of study drug causality and will be repeated for events deemed by the investigator to be possibly related to study medication.

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug. SAEs will be summarized by preferred term.

Hospitalizations and transfusions during the study treatment period or during the 30-day safety follow-up period will be summarized by treatment group.

12.2.12. Exploratory Analyses

Exploratory analyses/data mining will be carried out on imaging data, fibrotest data, gene-expression data, rules-based medicine MAP data and tumor-tissue data as appropriate, investigating links between these data and clinical and PD efficacy endpoints.

12.2.13. Interim Analyses

Three interim analyses are planned:

- The first interim assessment is planned when approximately 10 patients have completed Cycle 1 in the LY2157299 plus sorafenib arm. It aims to evaluate the PK and safety profiles in the combination arm. The plan is to continue enrolling patients during the interim assessment unless ongoing safety reviews have raised safety concerns. This

analysis is estimated to take place approximately 3 months from when the first patient is randomly assigned to a treatment arm.

- The second interim assessment is planned when approximately 32 patients are randomized and have completed either 3 cycles of treatment, discontinued from study drug, or died. It will aim to evaluate that patients treated with LY2157299 monotherapy are not at risk of receiving a treatment that is inferior to sorafenib. This analysis is estimated to take place approximately 6 months from when the first patient is randomly assigned to a treatment arm. Bayesian OS analysis will be carried out at this interim analysis. The LY2157299 monotherapy may be considered futile if the posterior probability of seeing HR <0.667 is <10%. Table JBAS.12.3 summarizes the likelihood of futility under different HRs. FACTS (version 3.2) was used for simulations.

Table JBAS.12.3. Simulation Results for Interim Analysis #2

n	Allocation	Control Rate Prior	Timing of Analysis	HR	Posterior Probability (HR <0.667) <10%
32	1:2:1	Strong prior for interim analysis #2	First patient visit+7.1 months	1	19%
				1.5	43%
				2	65%
32	1:2:1	Weak prior for interim analysis #2	First patient visit +7.1 months	1	21%
				1.5	40%
				2	61%

Abbreviation: HR = hazard ratio.

- The third interim assessment will be conducted for the purposes of detecting early efficacy signals as well as further evaluating safety observations. This interim analysis will be carried out after approximately 70 deaths have occurred in 3 arms and is projected to take place approximately 17 months after the first patient's visit. Bayesian OS analysis will be carried out at this interim analysis. No formal stopping rules for efficacy will be applied to the interim analyses so that no alpha adjustment will be made. summarizes simulation results for type I errors and statistical powers using FACTS (version 3.2).

Table JBAS.12.4. Simulation Results for Interim Analysis #3

N (deaths)	Control Rate Prior	Timing of Analysis	Type I Error	Posterior Probability (HR <1) >0.84
120 (70)	Strong prior for interim analysis #3	first patient visit +20.4 months	14%	74%
120 (70)	Weak prior for interim analysis #3	first patient visit +20.4 months	15%	65%

Abbreviation: HR = hazard ratio.

The safety/tolerability and efficacy results from the interim analyses will be reviewed only by an internal assessment committee consisting of the Lilly Medical Director, a Lilly CRP not in contact with study sites, a Lilly statistician, and a PK scientist, if needed. The assessment committee members will review unblinded safety and/or efficacy data at each interim analysis to determine whether there are sufficient safety or futility concerns to justify the termination of a study treatment arm. Results of the interim analyses will not be communicated to the study sites, unless the interim analyses show evidence of harm.

12.2.14. Criteria for Study Termination

This Phase 2 study will be considered complete following the completion of all data collection and/or when study objectives have been met (including any possible long-term "follow-up" survival analysis). The Lilly CRP will notify investigators in the event of study closure and the decision to stop collecting data.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator will be responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator will be responsible for ensuring that informed consent is given by each patient or his or her legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's ERBs should be provided with the following:

- the current IB or package labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics) and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2. the ICH GCP Guideline (E6)
3. applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most analyzable patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JBAS Study Schedule

Study Schedule, Protocol H9H-MC-JBAS – Study Period

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Follow-Up Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[c]	14[c,e]	22	1[c]	14[c,e]			
Procedures																
Informed consent	X															Informed consent must be signed prior to performing any study procedures.
Medical history		X														
Child-Pugh, BCLC, and CLIP staging			X[f]													
Physical exam including vital signs (heart rate, blood pressure, weight)		X		X		X			X	X		X		X		Starting in Cycle 3, to be performed once per cycle
CTCAE grading		X		X		X			X	X		X		X	X[g]	Starting in Cycle 3, to be performed once per cycle
Concomitant medications		X		X					X			X	X	X	X	During long-term follow-up collect only therapy provided to patient for HCC
ECOG performance status		X		X		X			X	X		X		X		Starting in Cycle 3, to be performed once per cycle
Survival data															X	Every 60 days ±7 days

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Follow-Up Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[c]	14[c,e]	22	1[c]	14[c,e]			
Tumor assessment, physical (palpable or visible)		X		X					X			X		X		
Imaging procedures																
Echocardiography with Doppler[h]	X								X			X		X[i]	X[i]	Cycle 2, 3, 4, and every other cycle (Cycle 6, Cycle 8, etc)
Chest CT scan or Chest MRI		X												X[j]		CT scan or MRI every 6 months (for cardiac assessment)
Tumor assessment, radiological		X								X		X		X[k]	X[k]	Chest CT scan with contrast of thorax and abdomen (with both arterial and portal phase imaging of the liver for mRECIST) or MRI for tumor assessment every 6 weeks (± 3 days) starting Cycle 2 Day 14
ECG		X							X			X		X[i]	X[i]	Cycle 2, 3, 4, and every other cycle (Cycle 6, Cycle 8, etc)

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Follow-Up Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[c]	14[c,e]	22	1[c]	14[c,e]			
DW-MRI and then DCE-MRI (performed sequentially in the visit)			X								X					Baseline scan to be performed within 10 days prior to first study drug dose. The second scan will be performed at Cycle 2 Day 22 ± 3 days. eGFR should be ≥30 mL/min/1.73 m^2 to allow safe use of GBCA, The creatinine needed to calculate the eGFR may be obtained from the serum chemistries at baseline for the first MRI and at Cycle 2 Day 14 for the second MRI at Cycle 2 Day 22.
Laboratory tests																Refer to Attachment 2
Pregnancy test			X													
ECG chemistry		X							X			X		X[i]	X[i]	Cycle 2, 3, 4, and every other cycle (Cycle 6, Cycle 8, etc)

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Follow-Up Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[i,c]	14[c,e]	22	1[c]	14[c,e]			
Special chemistry			X		X	X		X	X	X	X	X	X	X		Includes troponin and BNP
Hematology			X		X	X		X	X	X	X	X	X	X		
Serum chemistry			X		X	X		X	X	X	X	X	X	X		
Urinalysis		X							X			X		X		
Hepatitis B and C serology	X[l]								X[m]			X[m]		X[m]		
Urine C-terminal telopeptides of Type 1 collagen		X							X			X				
PK sampling				X		X	X	X	X			X				See Attachment 5 for timing of samples
Serum markers		X		X		X			X	X		X	X	X		AFP, AFP L3, E-cadherin, PIVKA II
Immunopheno-type				X					X			X		X		
TGF-β + PF4				X		X			X	X		X	X	X		
MAP				X		X				X			X	X		

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Follow-Up Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods.
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[c]	14[c,e]	22	1[c]	14[c,e]			
Fibrotest		X				X				X			X			
aPTT/PT/ INR		X		X					X			X				
Patient-reported outcomes																
EORTC QLQ-30		X							X			X		X		
EORTC QLQ-HCC 18		X							X			X		X		
Resource utilization									X			X		X		Document BSC measures, concomitant medications, transfusions, and treatment-related hospitalization days
Translational research																
Whole blood for PGx				X												

Cycle (Visit)	Baseline (Visit 0)			Patient on Study Treatment										Post Discontinuation Followup Periods		Comments
				Cycle 1 (Visit 1)					Cycle 2 (Visit 2)			Cycle 3, n[a] (Visit 3, etc)		30-Day Safety Follow-Up (v801)	Long Term Follow-Up[b] (v802, v803, etc)	Refer to Section 10 of the protocol for descriptions of the study periods.
Relative Day Within a Cycle	≤28	≤14	≤7	1[c,d]	8[c]	14[c]	15	22	1[c]	14[c,e]	22	1[c]	14[c,e]			
Optional tumor biopsy	X									X				X[n]		± 3 days Optional tumor biopsy to be obtained at baseline, cycle 2 and after end of treatment with LY2157299
Obtain diagnostic tumor tissue	X															Mandatory for study entry. Tumor tissue (tumor blocks or slides) must be located prior to randomization and sent to central laboratory after randomization

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; BCLC = Barcelona Clinic Liver Cancer; BNP = brain natriuretic peptide; BSC = best supportive care; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; DW-MRI = diffusion-weighted magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; EORTC = European Organisation for Research and Treatment of Cancer; exam = examination; GBCA = gadolinium-based contrast agent; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; INR = international normalized ratio; MAP = multi-analyte panel; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; PF4 = platelet factor 4; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; QLQ = quality-of-life questionnaire; RNA = ribonucleic acid; TGF-β = transforming growth factor beta.

a Patients on study for more than 1 year (before entering extension period) only need tests to be performed on Day 1 of each cycle.

b Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days).

c To be performed predose LY2157299 or sorafenib

d A delay at the start of a cycle (Day 1) of no more than 3 days because of holidays, weekends, inclement weather, or other justifiable events will be permitted and not counted as a protocol violation.

e In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14.

f Child-Pugh, BCLC, and CLIP assessment procedures can be found in Attachment 6, Attachment 7, and Attachment 8, respectively.

g If drug-related toxicity is present 30 days after the last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

h Echocardiography with Doppler can be performed up to 3 days prior to Day 1.

i If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography with Doppler and ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and V805). If there are no cardiac findings at discontinuation (Visit 801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (Visit 802) unless a patient is receiving another treatment (see Section 10.3.2.2).

j If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

k Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

l Within 60 days prior to randomization; includes HBsAg, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis B e antigen, hepatitis B e antibody, hepatitis B virus DNA, hepatitis C RNA.

m HBsAg carriers should be closely monitored with assessment of hepatitis B serology during the study treatment and 30-day safety follow-up period.

n ±3 days after end of treatment with LY2157299.

Study Schedule, Protocol H9H-MC-JBAS: Extension Period

Cycle (Visit)	Study Treatment (v501, v502, etc)[a]	Post Discontinuation Follow-Up Periods		Comments
		30-day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802)	Refer to Section 10 of the protocol for descriptions of the study periods
Procedures				
Physical exam	X	X		Performed once per cycle on Day 1 of each cycle in extension period
Vital signs (heart rate, blood pressure, weight)	X	X		Performed once per cycle predose on Day 1 of each cycle in extension period
CTCAE grading	X	X	X[c]	Performed once per cycle predose on Day 1 of each cycle in extension period
Concomitant medications	X	X	X	Performed once per cycle predose on Day 1 of each cycle in extension period
Performance status	X	X		Performed once per cycle predose on Day 1 of each cycle in extension period
Imaging procedures				
Echocardiography with Doppler[d]	X	X[e]	X[e]	For patients receiving galunisertib: Performed once per cycle predose on Day 1 of every other cycle in the extension period.
Chest CT scan or chest MRI	X	X[f]		For patients receiving galunisertib: CT scan or MRI every 6 months (for cardiac assessment).
Tumor assessment, radiological				Recommended at regular intervals during the extension period.
ECG	X	X[e]	X[e]	For patients receiving galunisertib: Perform predose on Day 1 of every other cycle in the extension period. For patients receiving sorafenib only, follow standard of care.

Cycle (Visit)	Study Treatment (v501, v502, etc.)[a]	Post Discontinuation Follow-Up Periods		Comments
		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802)	Refer to Section 10 of the protocol for descriptions of the study periods
Laboratory tests				
Hepatitis B serology	X[g]	X[g]		HBsAg carriers only. Can be done at local labs during the extension period.
ECG chemistry	X	X[e]	X[e]	For patients receiving galunisertib: Perform predose on Day 1 of every other cycle in the extension period. Can be done at local labs during the extension period. For patients receiving sorafenib only, follow standard of care.
Special chemistry	X	X		For patients receiving galunisertib: Perform predose on Day 1 of each cycle in the extension period. Can be done at local labs during the extension period. Includes troponin and BNP. For patients receiving sorafenib only, follow standard of care.
Hematology	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum markers	AFP only	X		As clinically indicated. Can be done at local labs during the extension period.

Abbreviations: BNP = brain natriuretic peptide; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; exam = examination; HBsAg = hepatitis B surface antigen; MAP = multi-analyte panel; MRI = magnetic resonance imaging; v = visit.

[a] A delay at the start of a cycle (Day 1) of no more than 3 days because of holidays, weekends, inclement weather, or other justifiable events will be permitted and not counted as a protocol violation.

[b] Follow-up consists of Visit 802 and all subsequent visits (60 days±7 days). For the patients in the extension period, long-term follow-up will not be conducted unless there are cardiac toxicities (Section 10.3.2.2).

[c] If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

[d] Echocardiography with Doppler can be performed up to 3 days prior to Day 1.

[e] If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography with Doppler and ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and V805). If there are no cardiac findings at discontinuation (Visit 801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (Visit 802) unless a patient is receiving another treatment (see Section 10.3.2.2).

[f] If there are no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

[g] HBsAg carriers should be closely monitored with assessment of hepatitis B serology during the study treatment and 30-day safety follow-up period.

Study Schedule, Protocol H9H-MC-JBAS – Study Drug Dosing

Cycle (Visit)	Study Period		Extension Period (Visits 501, 502, etc.)		Comments
	Cycle 1, n (Visit 1, n)				
Relative Day Within a Cycle	1-14	15-28	1-14	15-28	Refer to Section 10 of the protocol for descriptions of the study periods
LY2157299 dosing	X		X		The monotherapy dose will be 150 mg BID (300-mg daily dose) for 14 days, followed by 14 days with no study drug. The LY2157299 dose used in combination with sorafenib will be determined based on the results of the JBAK study – Part C (dose will either be 80 mg or 150 mg BID [160-mg or 300-mg daily dose]).
LY2157299-matched placebo dosing	X				Administered orally by daily dosing morning and evening (BID) for 14 days, followed by 14 days with no placebo. Not administered in the extension period
Sorafenib	X	X	X	X	Administered orally by daily dosing morning and evening (BID) at 400 mg per dose (total dosage of 800 mg daily) for 28 days

Abbreviation: BID = twice daily.

Attachment 2. Protocol JBAS Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]
Hemoglobin
Erythrocyte count (RBC)
Leukocytes (WBC)
Neutrophils, segmented + bands
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Immunophenotype[b]

Urinalysis[a]
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Leukocyte esterase

ECG chemistry[b]
Lipase
Thyroid stimulating hormone
Tri-iodothyronine
Thyroxine
Calcium[c]
Glucose, random (nonfasting)[c]
Albumin[c]
Phosphorus[c]
Sodium[c]
Potassium[c]
Magnesium[c]

Special chemistry[b]
Cystatin C
Troponin I
BNP
High-sensitivity C-reactive protein

Hepatitis B and C serology and panels[b]

Hepatitis B surface antigen

Hepatitis B surface antibody

Total hepatitis B core antibody

Hepatitis B e antigen

Clinical chemistry[b]
Serum concentrations of:
Total bilirubin
Direct bilirubin
Total protein
Alkaline phosphatase
LDH
Creatine kinase
Alanine aminotransaminase/serum glutamic pyruvic transaminase
Aspartate aminotransferase/ Serum glutamic oxaloacetic transaminase
Blood urea nitrogen
Creatinine
Uric acid
Calcium
Glucose, random (nonfasting)
Albumin
Cholesterol
Phosphorus
Sodium
Potassium
Magnesium

Serum markers [b]
AFP`
AFP L3
PIVKA II
E-cadherin

TGF-β+PF4[b]

aPPT/PT/INR[b]

Fibrotest[b]

Urine C-terminal telopeptides of Type 1 Collagen[b]

MAP[b]
Serum pregnancy test (females only)[a]

Hepatitis B e antibody

Hepatitis B virus DNA

Hepatitis C RNA

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; BNP = brain natriuretic peptide; ECG = electrocardiogram; INR = international normalized ratio; LDH = lactate dehydrogenase; MAP = multi-analyte panel; PF4 = platelet factor 4; PIVKA II = prothrombin induced by vitamin K absence; PT = prothrombin time; RBC = red blood cell; TGF-β = transforming growth factor beta; WBC = white blood cell.

[a] All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a local or investigator-designated laboratory, with the exception of immunophenotype.

[b] All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a Lilly-designated laboratory. Tests will be performed at a local laboratory if performed during the treatment extension period.

[c] Test not performed if both chemistry and ECG chemistry are required. See Attachment 1.

Attachment 3. Protocol JBAS Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly CRP.

Hepatic Monitoring Tests

Hepatic hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = International normalized ratio.

a Assayed by Lilly-designated central laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JBAS Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, 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 >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al. 1982.

Attachment 5. Protocol JBAS Pharmacokinetic Sampling Instructions

Sample Number	Cycle	Day	Sampling Windows for Pharmacokinetics
1	1	1	Predose[a]
2	1	1	0.5-2 hours
3	1	14	Predose[a]
4	1	14	0.5-2 hours
5[b]	1	14	3-5 hours
6[b]	1	15	Morning[b,c]
7	1	22	Morning
8	2	1	Predose[a]
9	3, n	1	Predose[a]

Abbreviation: n = cycle number ≥ Cycle 4.

[a] The predose sample has to be taken before the patients receive any LY2157299 and sorafenib.

[b] The evening dose of LY2157299/LY2157299-matched placebo and sorafenib on Day 14 should be omitted.

[c] The predose sample has to be taken before the patients receive sorafenib.

Attachment 6. Protocol JBAS Child-Pugh Score

Child-Pugh Score

Clinical and Biochemical Parameters	Points[a]		
	1	2	3
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL	>3.5	2.8-3.5	<2.8
Ascites	Absent	Moderate	Tense
Encephalopathy	Absent	Moderate (Stage I-II)	Severe (Stage III-IV)
Prothrombin time			
Sec prolonged	<4	4-6	>6
%	>60	40-60	<40
INR[b]	<1.7	1.7-2.3	>2.3
In case of primary biliary cirrhosis			
	1	2	3
Bilirubin (mg/dL)	<4	4-10	>10

Abbreviations: INR = international normalized ratio; Sec = second.

a Total points: 5 to 6: Child-Pugh class A; 7 to 9: Child-Pugh class B; 10 to 15: Child-Pugh class C.

b INR is an expression of prothrombin time, corrected by the sensitivity of the reactive to anticoagulants and should be validated as an alternative to prothrombin time in liver insufficiency.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-649.

Attachment 7. Protocol JBAS Barcelona Clinic Liver Cancer Classification Table

Barcelona Clinic Liver Classification Table

Stage	Performance Status Test	Tumor Stage	Okuda Stage	Liver Function Status
A	0	Single	I-II	Child-Pugh A-B
B	0	Large multinodular	I-II	Child-Pugh A-B
C	1-2	Vascular invasion/ extrahepatic spread	I-II	Child-Pugh A-B
D	3-4	Any	III	Child-Pugh C

Note: Stage A and B, all criteria should be fulfilled; Stage C and D, at least 1 criterion should be fulfilled.
Source: Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362(9399):1907-1917.

Attachment 8. Protocol JBAS Cancer of the Liver Italian Program Scoring System

CLIP Scoring System

Variable	Score
Child-Pugh stage	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension ≤50%	0
Multinodular and extension ≤50%	1
Massive or extension >50%	2
AFP	
<400	0
≥400	1
Portal vein thrombosis	
No	0
Yes	1

Abbreviations: AFP = alpha-fetoprotein; CLIP = Cancer of the Liver Italian Program.
Source: The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology*. 2000;31(4):840-845.

Attachment 9. Protocol JBAS RECIST Criteria Version 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New RECIST: Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (slice thickness ≤5 mm)
- 10-mm caliper measurement by clinical examination (nonmeasurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed-lytic blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable).
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated at a previously irradiated area or in an area subjected to other loco-regional therapy, are nonmeasurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Nontarget Lesion

Target Lesions

When >1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Nonnodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters or decimal fractions of centimeters).

Nontarget Lesions

All other lesions (or sites of disease) will be identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions is not required but should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm will be considered nonpathological and will not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never >4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical examination.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If, prior to enrollment, it is known that a patient is not able to undergo CT scans with intravenous contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (with or without intravenous contrast) should be used to evaluate the patient at baseline, and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-Ray

Chest CT is preferred over chest x-ray when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When a CT scan has a slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI will also be acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound

Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy

The use of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor Markers
Tumor markers alone cannot be used to assess tumor response. If markers are initially above the ULN, they must normalize for a patient to be considered in CR. Specific guidelines for both prostate-specific antigen response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology
These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

PET Scan (Fluorodeoxyglucose-PET, PET CT)
PET scan is not recommended for lesion assessment. If a new lesion is found by PET scan, another assessment must be done by CT scan, unless the PET CT scan is of diagnostic quality. If CT scan is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan
If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions
CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Tumor-marker results must have normalized.

PR: At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of ≥1 new lesion is also considered progression.

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline

Evaluation of Nontarget Lesions

CR: Disappearance of all nontarget lesions and normalization of tumor-marker level. All lymph nodes must be nonpathological or normal in size (<10-mm short axis).

Non-CR/Non-Progressive Disease: Persistence of ≥1 nontarget lesion and/or maintenance of tumor marker level above the normal limits

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of ≥1 new lesion is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs

Evaluation of Best Overall Response

The best overall response (OR) is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best OR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The best OR will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time-Point Response

It is assumed that at each protocol-specified time point, a response assessment will occur. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point.) Table 1 provides a summary of the OR status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time-Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease.

[a] Non-CR/non-PD is preferred over stable disease for nontarget disease.

Frequency of Tumor Reevaluation

A baseline tumor evaluation must be performed within 4 weeks before a patient begins study treatment. Frequency of tumor reevaluation while on and adapted to treatment should be protocol specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial-effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and nontarget sites will be evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoint, confirmation of response is not required. But elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from the first dose.

Duration of Overall Response

The duration of OR will be measured from the time that measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective

progression is observed (taking as reference for progressive disease the smallest measurements recorded during the study).

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

Duration of Stable Disease

SD will be measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of progressive disease).

Attachment 10. Protocol JBAS Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\textbf{CrCL} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85}\ (\text{if female}),\ \text{or} \times \textbf{1.0}\ (\text{if male})}{\textbf{72} \times \textbf{serum creatinine}\ (mg/dL)}\ (\text{mL/min})$$

For serum creatinine concentration in μmol/L:

$$\textbf{CrCL} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85}\ (\text{if female}),\ \text{or} \times \textbf{1.0}\ (\text{if male})}{\textbf{0.81} \times \textbf{serum creatinine}\ (\mu mol/L)}\ (\text{mL/min})$$

Abbreviations: CrCL = creatinine clearance; wt = weight.

a Age in years, weight in kilograms.

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

-OR-

$$GFR\ (mL/min/1.73m^2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$

$$\times\ [0.762\ \text{if patient is female}] \times [1.18\ \text{if patient is black}]$$

$$\times\ [SUN]^{-0.17} \times [Alb]^{+0.318}$$

Abbreviations: Alb= serum albumin in g/dL; GFR = glomerular filtration rate; PCr= plasma creatinine in mg/dL; SUN= serum urea nitrogen in mg/dL.

Source: Murray PT, Ratain MJ. Estimation of the glomerular filtration rate in cancer patients: a new formula for new drugs. *J Clin Oncol*. 2003;21(14):2633-2635.

Attachment 11. Protocol JBAS EORTC QLQ-30

CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]		[redacted]

EORTC QLQ-C30 (version 3)

ENGLISH

Please go on to the next page


CCI

Attachment 12. Protocol JBAS EORTC QLQ-HCC18

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ENGLISH

Attachment 13. Protocol JBAS New York Heart Association Functional Classification

The New York Heart Association Functional Classification classifies the extent of heart failure by placing patients in 1 of 4 categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown & Co; 1994.

Attachment 14. Protocol JBAS Echocardiography

The echocardiography protocol guidelines were created approximately 8 years ago for the first study with LY2157299 (Study JBAH). Since then, there have been minor changes in practice that have been incorporated into the guideline below. The collection of data in JBAS will be consistent with the previous studies and will allow the integration of all the centrally collected information.

Echocardiography

In this study, echocardiographic images will be acquired with the purpose of ascertaining that patients enrolled in the study have baseline (and maintain during the study) normal cardiac structure and function, normal pulmonary artery pressure, and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis). Repeated echocardiograms in each patient will be performed to establish the cardiac safety of LY2157299 by comparison with the initial studies. Determination of normalcy status requires objective evaluation of cardiac chamber size and function and attention to the use of appropriate techniques in the performance of the echocardiographic examinations, in particular the use of standardized settings during the acquisitions of color-flow Doppler imaging. Therefore, because quantitative echocardiography is the goal, stringent criteria for image quality and reproducibility are essential.

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh et al. 1999 and Zoghbi et al. 2003 (see below) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate, or severe, using mean and peak pressure gradient in mm Hg and orifice area in cm^2 as applicable), other echocardiographic parameters to be serially quantified are left ventricular (LV) cavity size (diameters, volumes). LVEF, LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial volume index, and extrapolation of pulmonary artery systolic pressure based on contrast-enhanced tricuspid regurgitation Doppler data.

An echocardiogram with no clinically significant abnormalities is one defined specifically as the LV internal dimension in diastole should be $\leq$2.8 cm/M^2 (Schiller et al. 1989) the left atrial end-systolic volume should be $\leq$36 mL/M^2 (Tsang et al. 2002), the LVEF should be $\geq$50% without regional wall motion abnormalities (Oh et al. 2006), 2-dimensional echocardiographic-derived LV mass index should be $\leq$115 g/M^2 for males and $\leq$99 g/M^2 for females (Schiller et al. 1989), the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity $\leq$2.5 ms and/or pulmonary valve flow acceleration time $\geq$120 ms), the LV diastolic function should be normal (screening: mitral deceleration time $\geq$150 ms and $\leq$250 ms, mitral E/A ratio $\geq$0.75 and

≤1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15) (Kouhri et al. 2004), and there should be no evidence for pericardial or congenital or heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be >2 cm^2, and aortic valve area should be >1.5 cm^2) and no evidence of more than mild mitral or aortic regurgitation (Singh et al. 1999 and Zoghbi et al. 2003). Patients enrolled in the study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild), or aortic (trace or mild) regurgitation by Doppler techniques (Singh et al. 1999 and Zoghbi et al. 2003).

References

Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. *J Am Soc Echocardiogr.* 2004;17(3):290-297.

Oh JK, Seward JB, Tajik AJ. The Echo manual. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2006.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. *J Am Soc Echocardiogr*. 1989;2:358-367.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* 1999;83(6):897-902.

Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90(12):1284-1289.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, for the American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

Echocardiographic Certification Process

To ensure protocol adherence, each study center will be required to submit an initial study for certification. The certification study will be performed on the first patient at the study site. Once a certification certificate is received from Biomedical Systems, the site may begin seeing additional study patients.

General Instructions for Echocardiography

- Allow 1 hour for the performance of the echocardiographic examination in each patient.

- Do not enter the patient's name in the initial video screen of the echocardiographic imaging system or protocol. Only the patient's screen and/or randomization number is to be entered and visible during the echocardiogram recording.
- Set the echocardiography imaging system (create preset "Lilly" and use in subsequent visits of patients in the study) to acquire and store digital 3 cardiac cycles loops for 2-dimensional echocardiographic image per screen and obtain at least 3 or more cardiac cycles per each M-Mode or Doppler spectral-image screen.
- This protocol calls for the use of both, harmonic imaging (for all views; native or tissue harmonics, using high [>1.3] mechanical index, with the appropriate highest transmitted frequency possible for that transducer) as well as fundamental imaging (this for limited views of the aortic and mitral valve on parasternal long axis).
- Obtain the patient's height and weight at the time of the examination and include with the study data.
- Obtain and record with the study data the patient's arterial blood pressure in the right arm while undergoing echocardiography in the recumbent left-lateral position.
- Display the ECG at all times during echocardiographic sequence recordings.
- Obtain all image sequences at held expiration (for up to 5 seconds at a time).
- Record images (2-dimensional and color-flow Doppler cine loops, frames for M-mode and Doppler spectral) in digital form and copy to a CD-ROM or MO-disk for each patient per visit.
- Choose the best transmit gain, TGCs, mechanical index, and compression setting for each patient. Record these settings and use them at all future visits for each specific patient.
- Always obtain all images (except subcostal) at held-end expiration with the patient lying on the left side (45 to 60 degrees) at a 16-cm depth of field. In the rare instance when the apical view silhouette of the heart (including the atria) exceeds 16 cm, then employ a 20-cm depth setting and make a note of this to employ 20-cm depth for that patient in subsequent visits.

- Employ Doppler color-flow imaging from all views (long axis, short axis, apical 4-chamber, apical 2-chamber, and apical long axis) and note presence of valvular regurgitation. For Doppler color flow, employ a Nyquist limit of 50 to 60 cm/sec, and set the color gain at a level that just eliminates random color speckle from nonmoving regions. Before recording Doppler color-flow image data for the first time in each patient at each visit, record continuously in videotape while the adjustment of color gain is performed to document in the videotaped data that gain settings have been properly obtained. Avoid using very high or very low levels of pulse-repetition frequency. Also, employ a color sector or color region of interest as narrow as possible for each valve examination, and with the least depth, to maximize lateral and temporal resolution.
- Spectral Doppler and M-mode echocardiography data are to be recorded at a display speed of 50 or 100 mm/s (use discretion considering heart rate; videotape) using optimal gain control and minimal filter setting (at least 3 beats), also at held expiration.
- Before starting the second or subsequent visit echocardiogram for a given patient:

  A. Retrieve the cine loop from the patient's first study digital data set and 2-dimensional images of the left ventricle (short axis) as acquired in the original study.

  B. Utilize this cine loop as part of a split screen to use as a guide to obtain the same imaging plane of the short axis again for this and subsequent visits of the same patient.

- After obtaining the current image, acquire a new image of both short-axis LV images. Keep a set of the digital images of each echocardiogram obtained for that particular patient into a "master" file to remain in the site's echocardiography laboratory and send via courier mail a CD-ROM or MO-disk copy of each study to the Core Echocardiography Laboratory at Biomedical Systems, St. Louis. Use the provided preprinted shipping forms included with this manual. If additional forms are required, please contact Biomedical Systems Echocardiography Laboratory in St. Louis.

Echocardiography Protocol; Required Views

Parasternal long-axis view, 16-cm depth

- Record 3 beats (held expiration) of the entire 2-dimensional image with harmonic imaging.
- Employ color-flow Doppler to evaluate for aortic and mitral regurgitation (using here and at each time that color-flow Doppler is used, the procedures described above regarding Nyquist limits, gain, and pulse-repetition frequency) and record 3 beats (held expiration).

- Obtain M-mode views of the LV as close as possible to the minor axis of the ventricle, avoiding the papillary muscle, and obtain a freeze-frame M-mode image (50 to 100 mm/s display).

Parasternal short-axis view, 16-cm depth

- Record 2-dimensional harmonic imaging views of the aortic, mitral valve, and papillary muscle level of the LV and record a sweep sequence of 5 beats.
- Employ color-flow Doppler to evaluate for aortic regurgitation (record 3 beats in held expiration), then for mitral regurgitation at the level of the aortic root/left atrium (record 3 beats in held expiration).
- Obtain pulsed spectral Doppler of the pulmonary valve flow at the level of the right-ventricular outflow tract; freeze and record spectral display of 3 to 5 beats at held expiration.
- If this is the second study in this patient, compare to previous image in the same patient (loop) to ensure obtaining the same LV papillary muscle level. This procedure entails retrieving from digital data of the site's laboratory master storage of the same patient's previous echocardiogram tape that contains the short-axis view.
- Once it has been ascertained that the same papillary muscle level is being obtained today, as before, acquire (end-expiration) and save "today's" short axis LV papillary muscle level; record both for 3 beats.

Apical 4-chamber view, 16- or 20-cm depth

- Avoid foreshortening of the image by maximizing the length of the LV cavity with the transducer placed as laterally and leftward as possible (toward the axilla and at a lower interspace in the left chest wall). Likewise, obtain the widest possible LV cavity to ensure optimal assessment of LV volumes.
- Pay special attention to optimal visualization of the endocardium of the lateral wall and septum and avoid visualization of the papillary muscle in this view. Record 5 beats with harmonic imaging at held expiration.
- Employ color-flow Doppler to evaluate for mitral and tricuspid regurgitation (using procedures described above for settings, etc) and record 3 beats for each valve.
- Record at least 3 beats of the pulsed Doppler transmitral-flow velocity with the sample volume (smallest size possible) positioned both at the mitral leaflet tips and at the mitral annulus level with the left atrium (displayed at 100 mm/s).
- Then measure the flow velocity across the mitral valve employing continuous-wave Doppler (3 beats, spectral display recording, 50 to 100 mm/s).

- Record at least 3 beats of the pulmonary venous-flow velocities (pulsed Doppler spectral) with the sample volume at the right upper pulmonary vein entrance into the left atrium.
- Record at least 3 beats of the pulsed Doppler transtricuspid-flow velocity with the sample volume positioned at the tips of the tricuspid valve.
- Then measure the flow-velocity spectra across the tricuspid valve employing continuous-wave Doppler (tricuspid-regurgitation peak-flow velocity; 3 beats, spectral display recording, 50 to 100 mm/s).
- For recording of the tricuspid regurgitation peak jet after saline enhancement, be prepared to quickly reduce the Doppler spectral gain to avoid noise-artifact blooming of the signal once the saline contrast effect is detected at the tricuspid-valve inlet. Using continuous-wave Doppler, obtain at least 3 beats with the enhanced Doppler signal; freeze the spectral display, and record for 5 seconds.
- Obtain by tissue-Doppler echocardiography (initially by real-time 2-dimensional color display to facilitate placement of the sample volume within the LV myocardium), the spectral data of myocardial velocities at the level of the mitral annulus (lateral wall or interventricular-septum site), freeze a spectral display (50 mm/s; at least 3 to 4 beats, held end expiration), and record (apply procedures for specific manufacturers regarding presets with optimal settings for map, gain, power, dark background in the display, etc). Ensure that the ECG is displayed above the Doppler tissue spectral data.

Apical 5-chamber view, 16-cm depth

- Record 3 beats of the apical 5-chamber view harmonic imaging color-flow Doppler (to evaluate for aortic regurgitation).
- Place a sample volume within 1 cm of the aortic valve in the LV outflow tract and record (at held expiration) at least 3 beats of spectral-pulsed Doppler of the flow velocity in the outflow tract (displaying the closing [but not the opening] valve clicks, at 50 or 100 mm/s spectral-display speed).
- Then measure the flow velocity across the aortic valve employing continuous-wave Doppler (3 beats, spectral-display recording, 50 to 100 mm/s) displaying both systolic- and any diastolic-flow velocity spectra (held expiration).

Apical 2-chamber view, 16- or 20-cm depth

- Obtain 3 beats at held expiration (or held inspiration, if necessary for this view only) of the harmonic imaging apical 2-chamber view. Avoid foreshortening of the view by obtaining the longest possible major-axis length displayed and the widest possible cavity.
- Employ color-flow Doppler to evaluate for mitral regurgitation and record 3 beats.

Apical long-axis view, 16- or 20-cm depth

- Record 3 beats of the harmonic imaging apical long-axis 2-dimensional examination employing held expiration. Again, avoid foreshortening the view by obtaining the longest as well as the widest possible LV cavity area.
- Employ color-flow Doppler to evaluate for mitral and aortic regurgitation and record 3 beats for each valve image.

Subcostal view, 20- or 24-cm depth (if necessary)

- Record 3 beats continuously with harmonic imaging of the inferior vena cava while asking the patient to abruptly sniff once.

Attachment 15. Protocol JBAS Qualitative and Quantitative Parameters for Grading Valvular Regurgitation

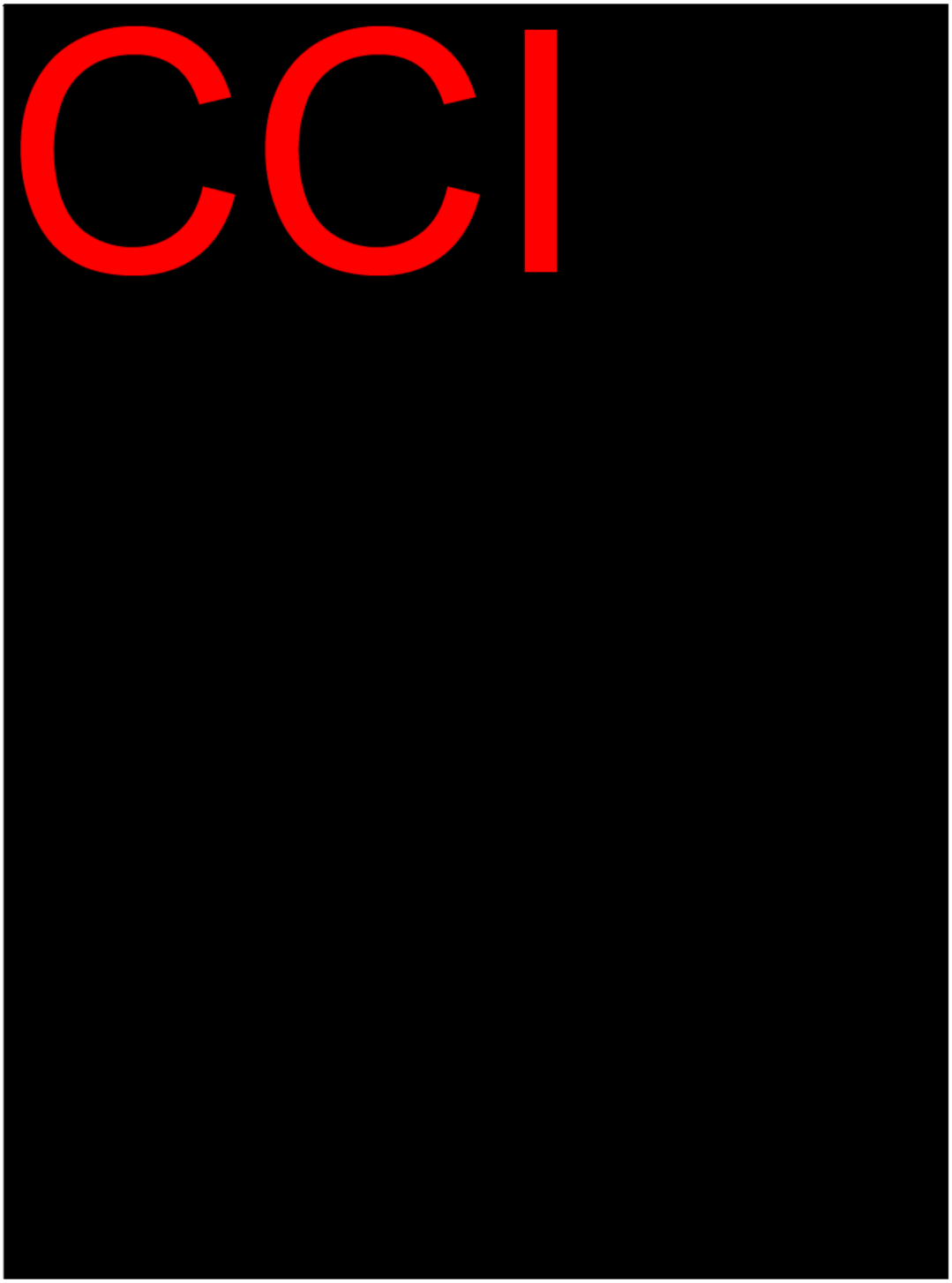
(Mitral and Aortic) Regurgitation Severity

Please refer to references below for information on qualitative and quantitative parameters for grading valvular (mitral and aortic) regurgitation severity.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol*. 1999;83(6):897-902.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, for the American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

Attachment 16. Modified RECIST Assessment for Hepatocellular Carcinoma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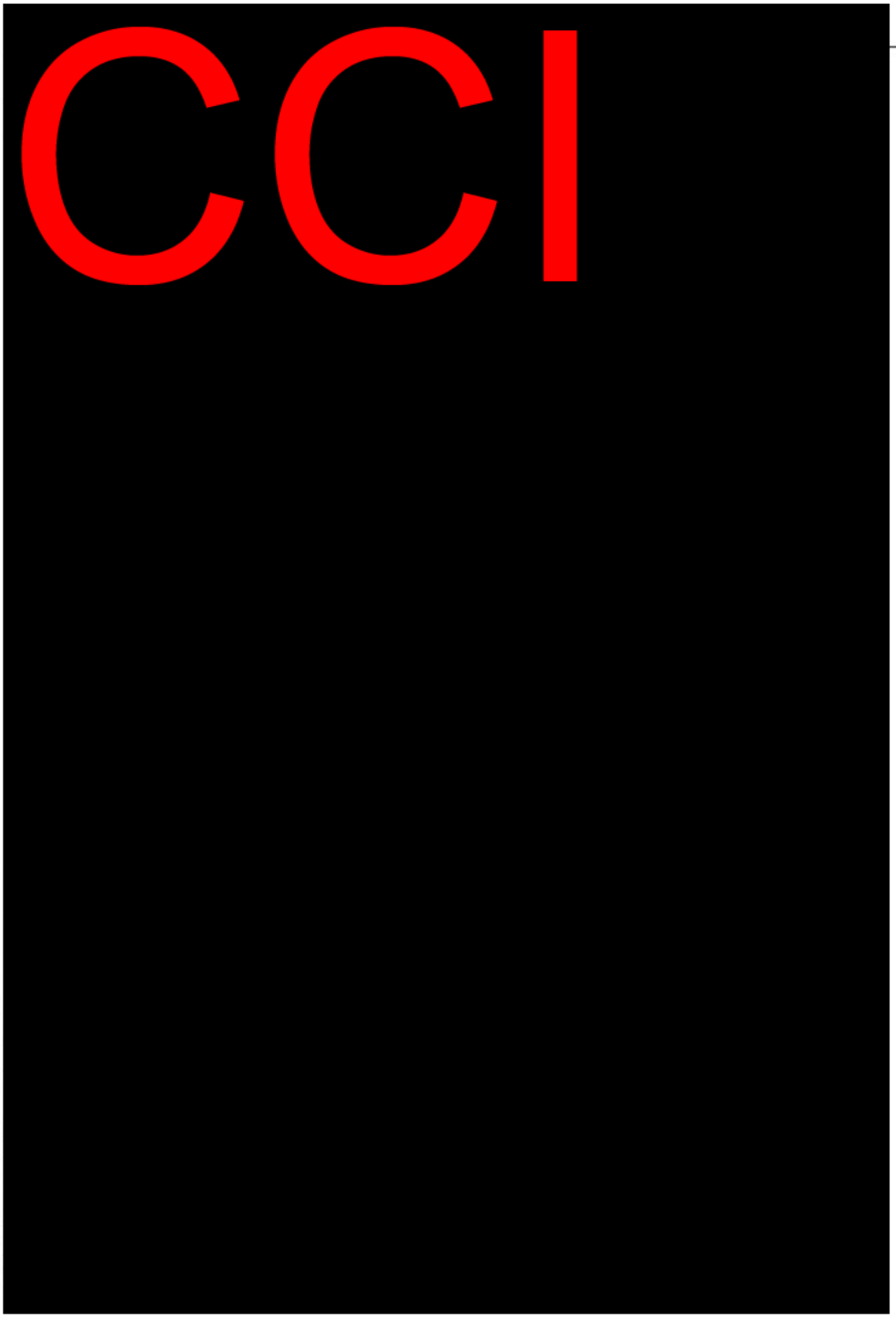

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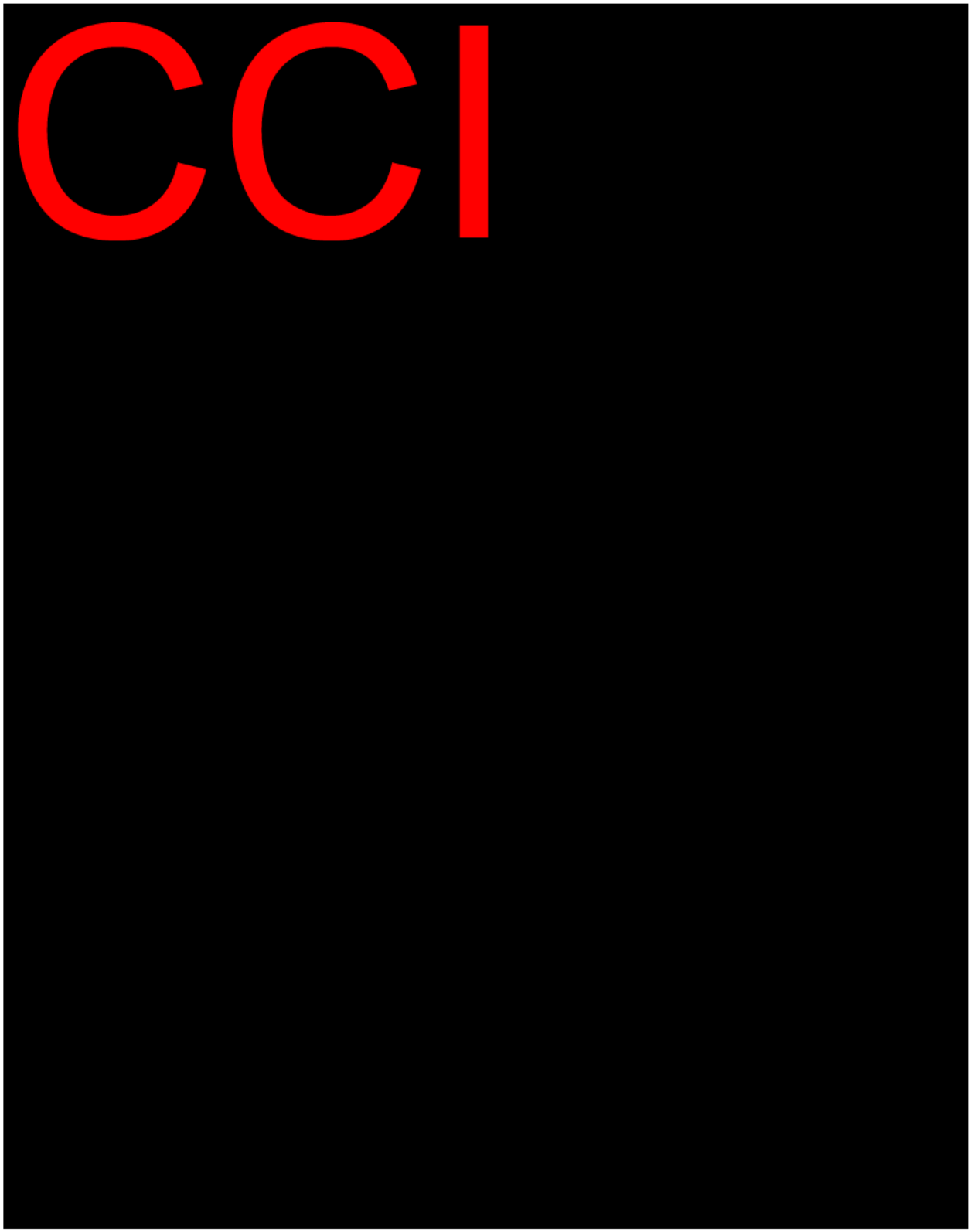
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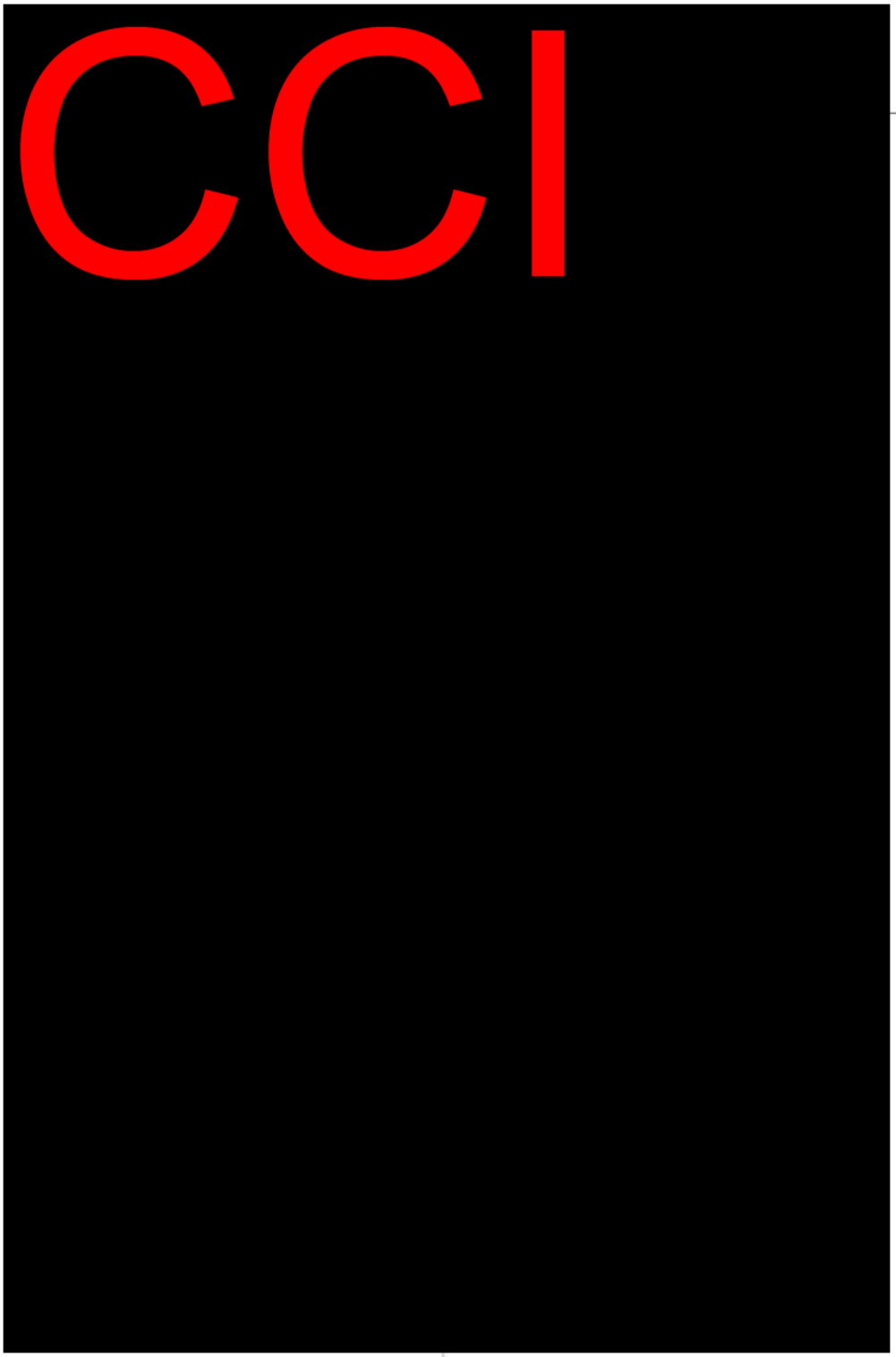

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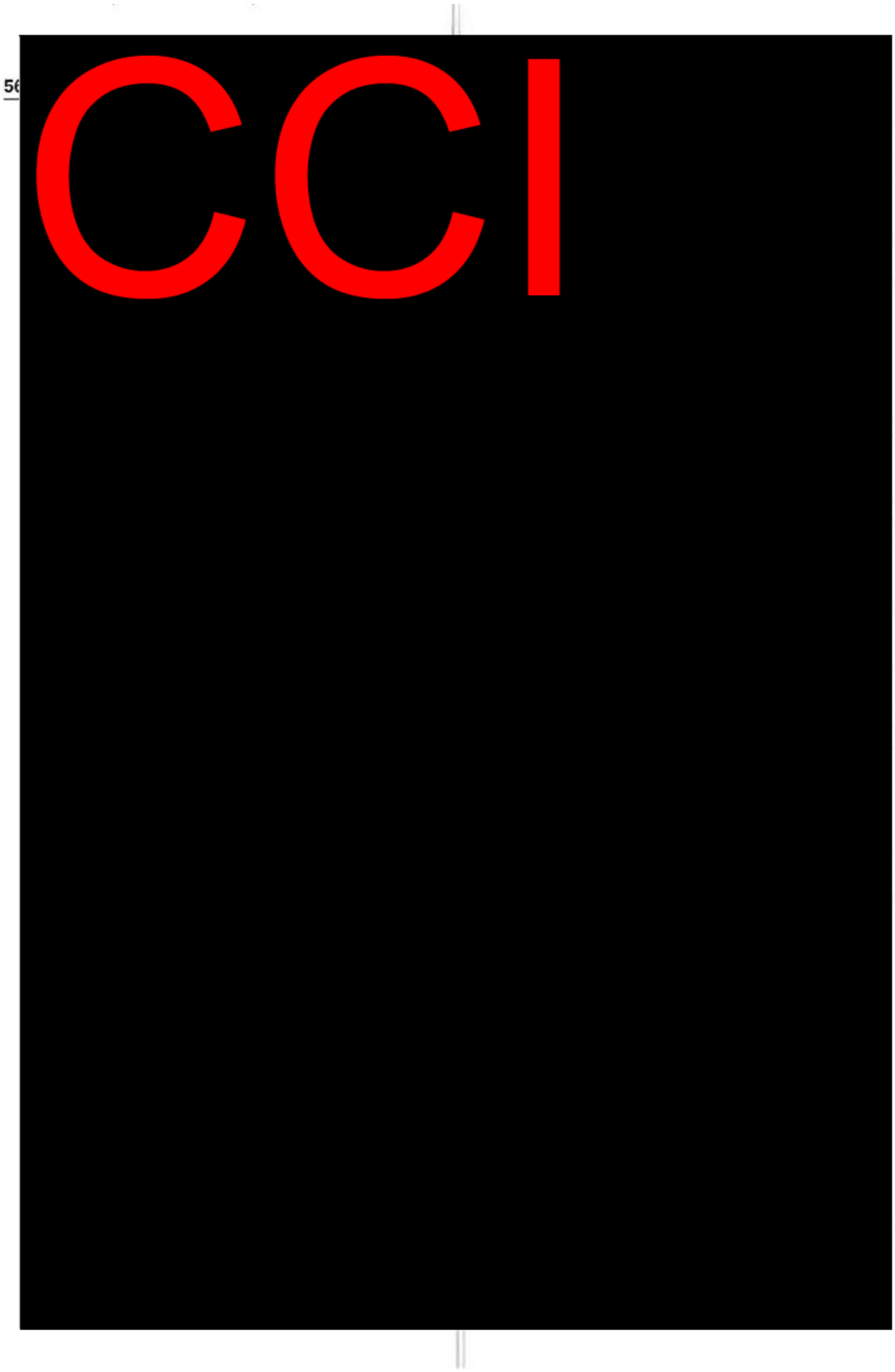
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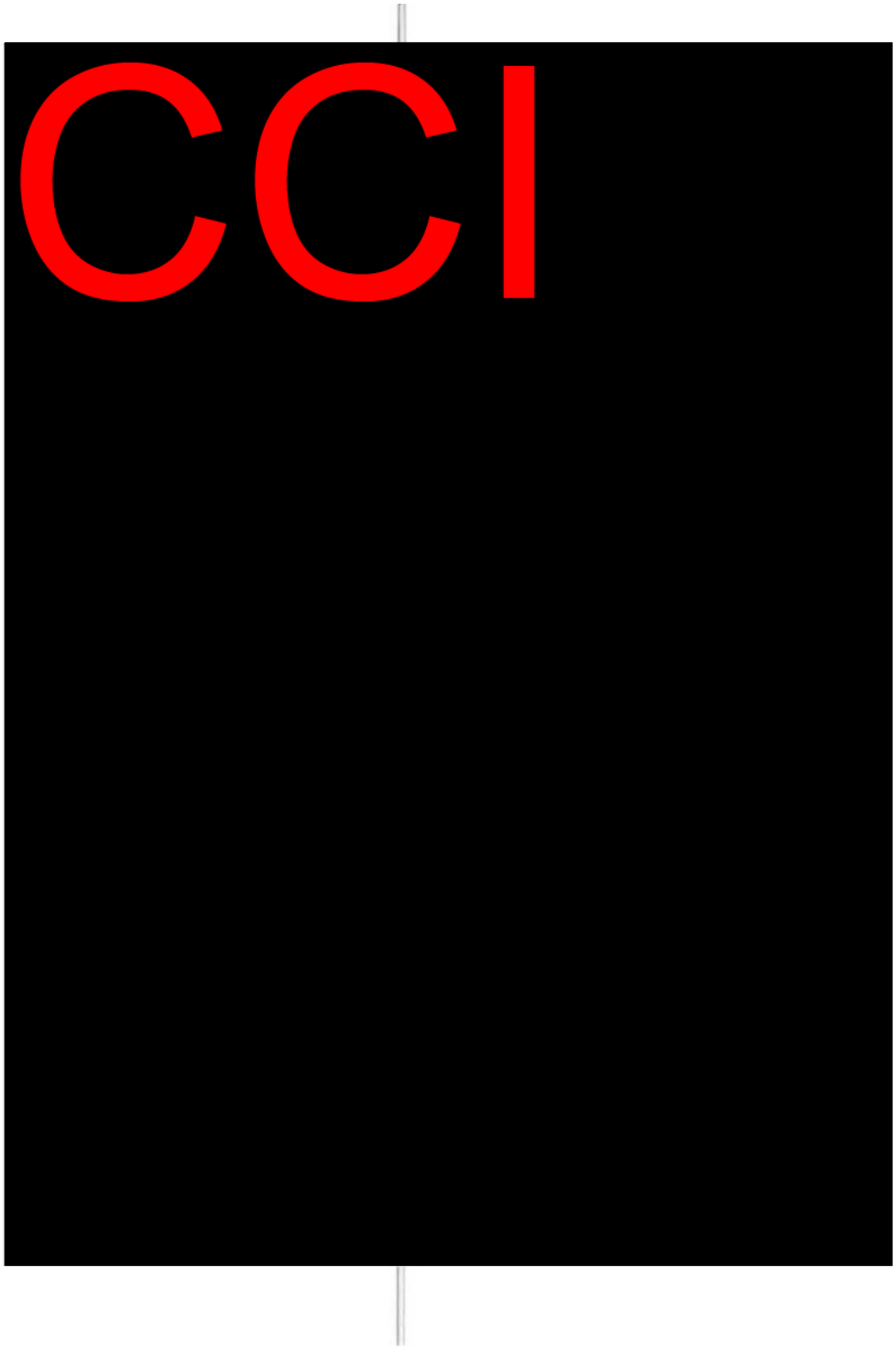
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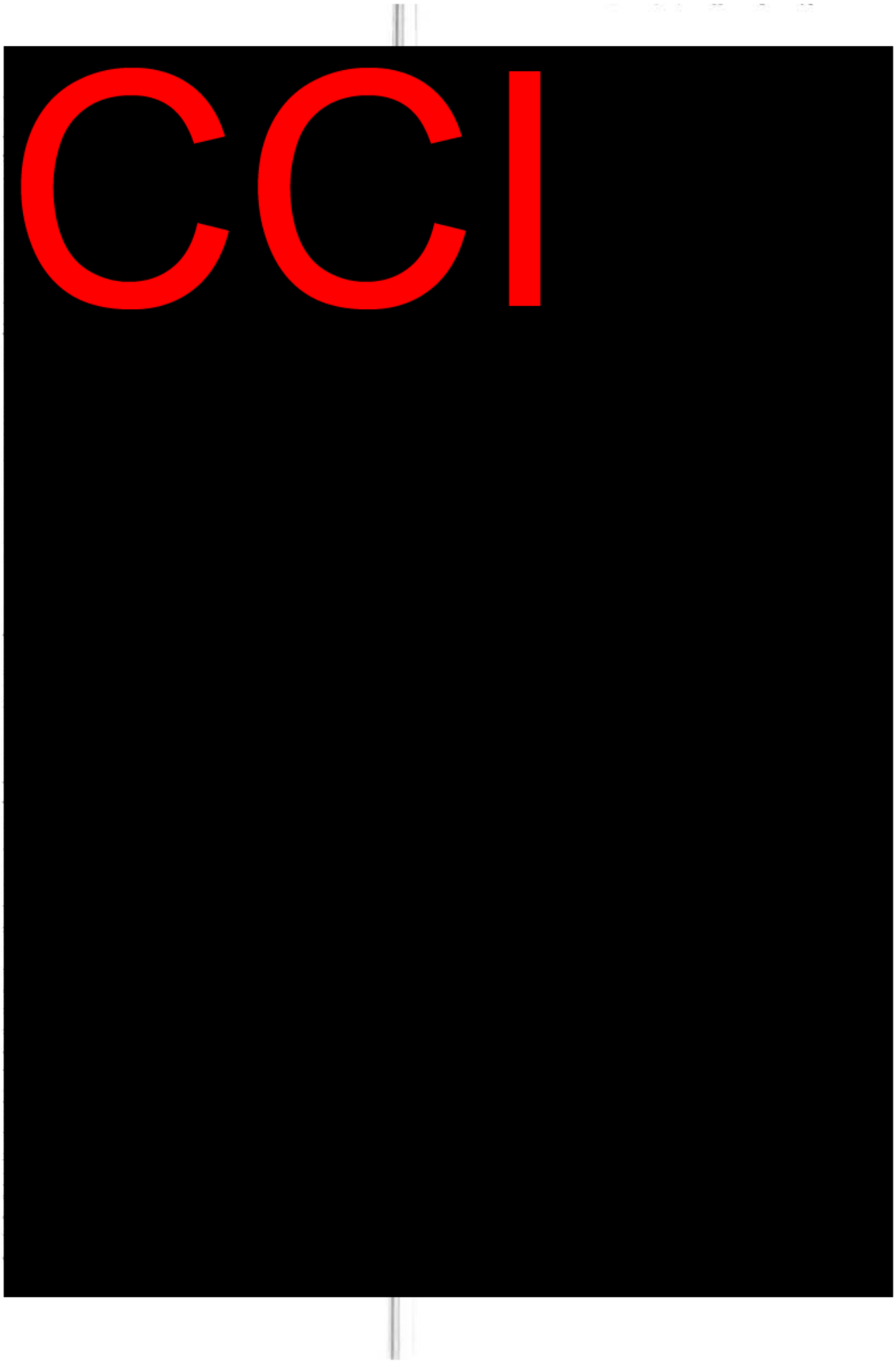
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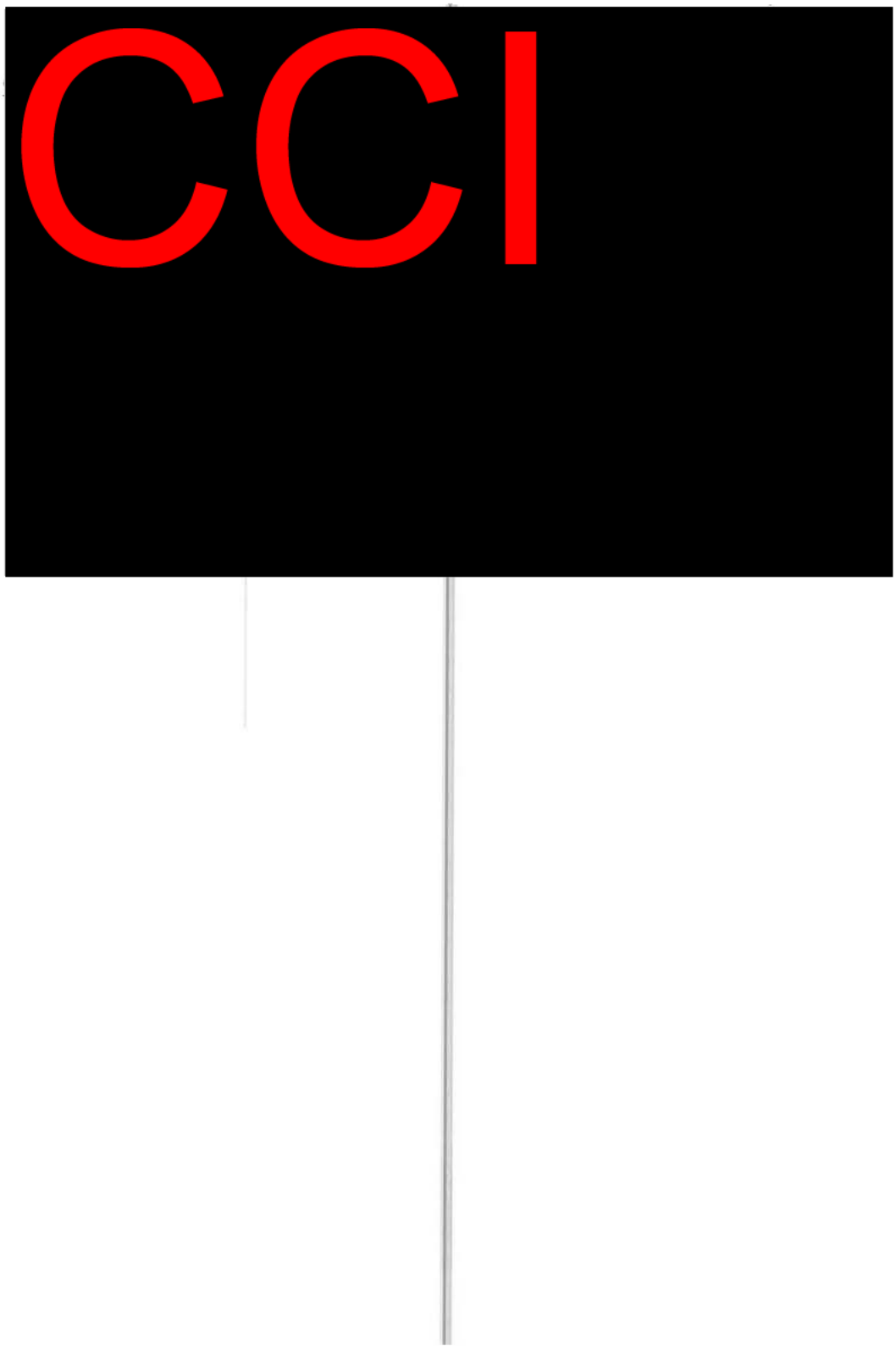
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Attachment 17. IrRECIST Assessment

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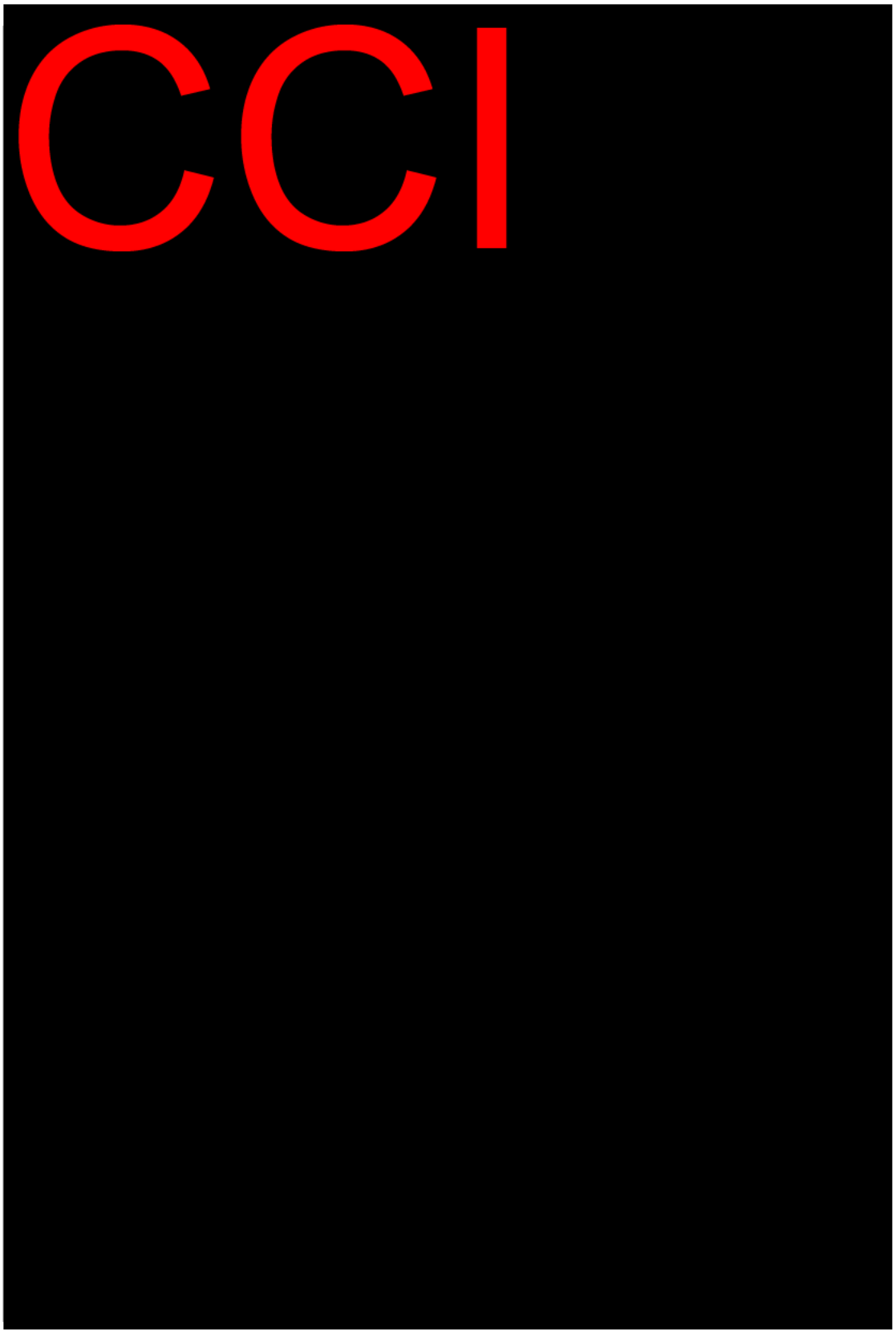
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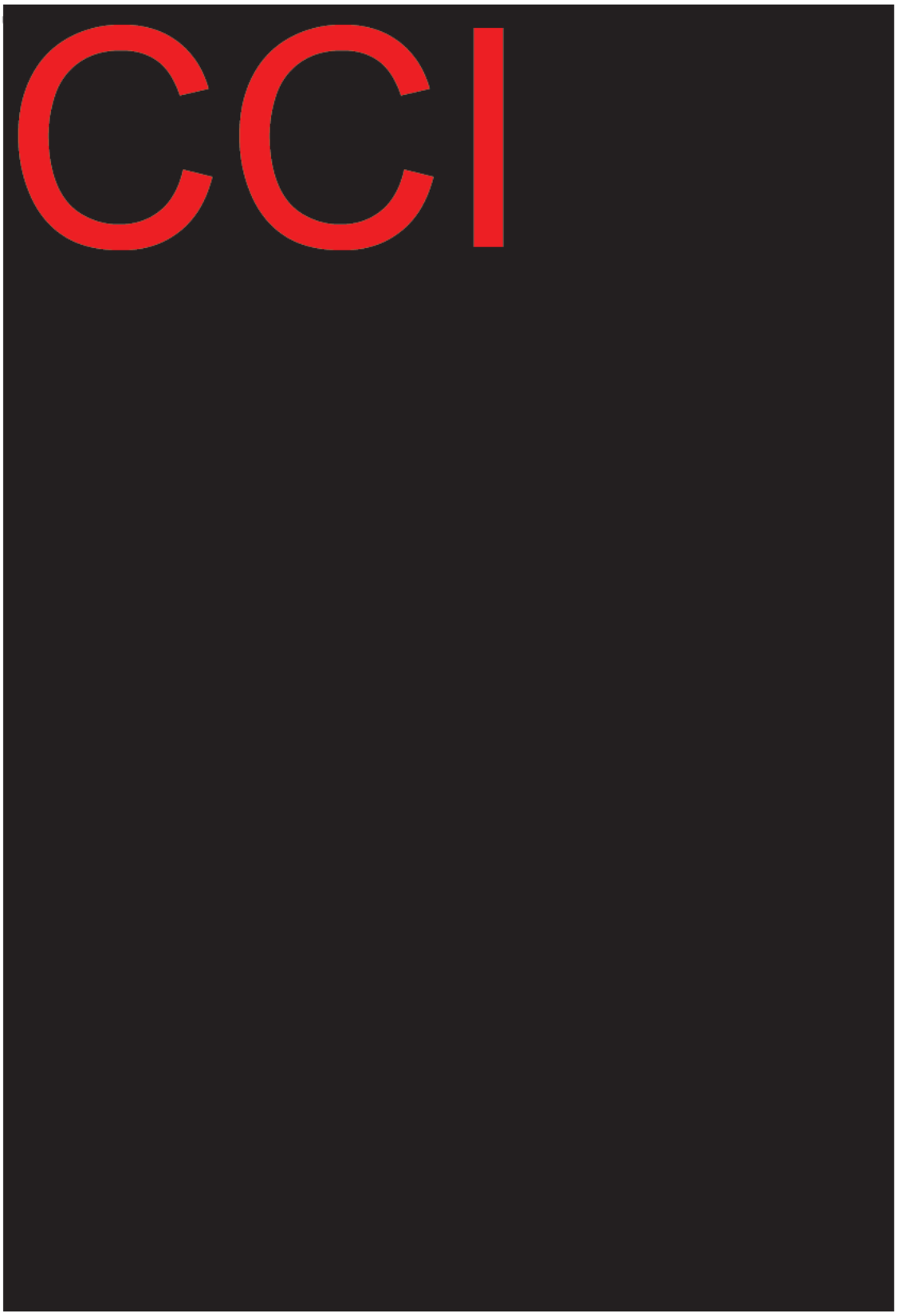
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Attachment 18. Protocol JBAS Sorafenib Adverse Events

The following drug-related adverse reactions and laboratory abnormalities (very common, ≥10%; common, 1 to <10%; uncommon, 0.1% to <1%) were reported from clinical trials of sorafenib (NEXAVAR; Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey, USA):

- Cardiovascular
    - Common: congestive heart failure,*† myocardial ischemia and/or infarction
    - Uncommon: hypertensive crisis*
    - Rare: QT prolongation*
- Dermatologic
    - Very common: erythema
    - Common: exfoliative dermatitis, acne, flushing
    - Uncommon: folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin
- Digestive
    - Very common: increased lipase, increased amylase
    - Common: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia
    - Uncommon: pancreatitis, GI reflux, gastritis, GI perforations,* cholecystitis, cholangitis
        - Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values
- General disorders
    - Very common: hemorrhage (including GI* and respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain)
    - Common: decreased appetite, influenzalike illness, pyrexia
    - Uncommon: infection
- Hematologic
    - Very common: leukopenia, lymphopenia
    - Common: anemia, neutropenia, thrombocytopenia
    - Uncommon: INR abnormal
- Hypersensitivity
    - Uncommon: hypersensitivity reactions (including skin reactions and urticaria)
- Metabolic and nutritional
    - Very common: hypophosphatemia
    - Common: transient increases in transaminases
    - Uncommon: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism
- Musculoskeletal

  - Common: arthralgia, myalgia
- Nervous system and psychiatric
  - Common: depression
  - Uncommon: tinnitus, reversible posterior leukoencephalopathy*
- Renal and genitourinary
  - Common: renal failure
- Reproductive
  - Common: erectile dysfunction
  - Uncommon: gynecomastia
- Respiratory
  - Common: hoarseness
  - Uncommon: rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis, and lung inflammation)
- In addition, the following medically significant adverse reactions were uncommon during clinical trials of sorafenib:
  - transient ischemic attack,
  - arrhythmia, and
  - thromboembolism

  For these adverse reactions, the causal relationship to sorafenib has not been established.

* Adverse reactions may have a life-threatening or fatal outcome.
† Reported in 1.9% of patients treated with sorafenib (N=2276).

The following adverse drug reactions have been identified during postapproval use of sorafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Dermatologic: Stevens-Johnson syndrome and toxic epidermal necrolysis
- Hypersensitivity: angioedema, anaphylactic reaction
- Hepatobiliary disorders: drug-induced hepatitis, including reports of hepatic failure and death

Source: Bayer HealthCare, 2013

Attachment 19. Protocol Amendment H9H-MC-JBAS(a) Summary (A Randomized Phase 2 Study of LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma)

Overview

Protocol H9H-MC-JBAS, A Randomized Phase 2 Study of LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

Amendment (a) revisions are summarized as follows:

- Updated Attachment 1 study schedule for patients in extension period with changes including:
  - Addition of a statement to specify that cardiovascular monitoring should be conducted only for patients receiving galunisertib
  - Correction of the frequency of cardiac assessments (echocardiography with Doppler, ECG, and ECG chemistry) from each cycle to every other cycle
  - Addition of a statement to clarify that for patients receiving sorafenib who are subjected to the ECG imaging procedure, ECG chemistry, or special chemistry, the standard treatment of care should be followed
  - Chest CT scan/MRI is still required. The information was incorrectly added to "tumor assessment, radiological" and this error has been corrected
  - Addition of a statement to specify that Hepatitis B serology can be performed at local labs during the extension period
  - Addition of a statement to clarify that analysis of serum markers should be performed as clinically indicated and can be performed at local labs during the extension period
  - Deletion of laboratory tests for assessment of TGF-β + PF4, aPTT/PT/INR levels.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

5.2.1 Rationale for Amendment (a)

The rationale for this amendment was to update the study schedule for patients on extension period. Specifications were added to clarify the cardiovascular monitoring for patients receiving galunisertib. Consistent with the study schedule, the frequency of cardiac assessments is corrected from each cycle to every other cycle. Other minor corrections and clarifications were made within the study schedule for patients on extension period.

Attachment 19 lists changes made in the protocol amendment.

10.3.1. Other Safety Measures

10.3.2.1. Electrocardiography

For each patient, 12-lead digital ECGs will be obtained as single ECGs according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee will be responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study-report purposes.

It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central

ECG laboratory, the investigator (or qualified designee) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

Other safety measures include assessments of physical examinations, preexisting conditions, transfusions and hospitalizations, and AEs. Patients will be assessed before each visit by using the CTCAE version 4.0.

For patients in the extension period, monitoring should be performed at predose on Day 1 of every other cycle for patients receiving galunisertib. The standard care of treatment should be followed for patients receiving sorafenib.

10.3.2.2. Echocardiographs with Doppler and Chest Computed Tomography Scans

Because of the cardiotoxicity monitoring in this study, echocardiographs with Doppler and chest CT scans are being performed (see Attachment 1, Attachment 14, and Attachment 15). Echocardiography with Doppler will be locally assessed at screening for enrollment and throughout the study according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. The individual must be identified at each site. A central reading will be performed for the data used in the study report.

Chest CT scan with contrast of thorax and abdomen to evaluate the large vessels of the heart will be locally assessed at screening for enrollment and every 6 months throughout the study and at the end of study visit (Visit 801) according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

Chest CT scan with contrast of thorax and abdomen for tumor assessment will be locally assessed at screening for enrollment and every 6 weeks starting Cycle 2 Day 14 until radiological disease progression according to the Study Schedule (Attachment 1) by a physician or a person who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography, ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and 805).

If there are no clinically significant cardiac findings at discontinuation (Visit 801), 1 more echocardiography, ECG, and ECG chemistry will be performed after 2 months (Visit 802). If a patient receives another treatment, Visit 802 cardiac assessments will not be performed.

For cardiac monitoring of patients in the extension period, chest CT scan or MRI will be locally assessed every 6 months for patients receiving galunisertib. Tumor and radiological assessments are recommended at regular intervals during the extension period. The rest of the monitoring

described in the previous 2 paragraphs ~~also applies to~~ will also be applicable for patients in the extension period. Therefore, for these cases, the patient does not discontinue from the study at the end of the 30-day safety follow-up period but after the cardiac findings have either resolved or, if not resolved after 6 months, after discussions between the Lilly CRP and investigator.

Study Schedule, Protocol H9H-MC-JBAS–Extension Period

Cycle (Visit)	Study Treatment (v501, v502, etc)[a]	Post Discontinuation Follow-Up Periods		Comments
		30-day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802)	Refer to Section 10 of the protocol for descriptions of the study periods
Procedures				
Physical exam	X	X		Performed once per cycle on Day 1 of each cycle in extension period
Vital signs (heart rate, blood pressure, weight)	X	X		Performed once per cycle predose on Day 1 of each cycle in extension period
CTCAE grading	X	X	X[c]	Performed once per cycle predose on Day 1 of each cycle in extension period
Concomitant medications	X	X	X	Performed once per cycle predose on Day 1 of each cycle in extension period
Performance status	X	X		Performed once per cycle predose on Day 1 of each cycle in extension period
Imaging procedures				
Echocardiography with Doppler[d]	X	X[e]	X[e]	For patients receiving galunisertib: Performed once per cycle predose on Day 1 of every other ~~each~~ cycle in the extension period.
Chest CT scan or chest MRI	X	X[f]		For patients receiving galunisertib: CT scan or MRI every 6 months (for cardiac assessment).
Tumor assessment, radiological		~~X[g]~~	~~X[g]~~	Recommended at regular intervals ~~Optional~~during the extension period. ~~Including chest CT scan or MRI every 6 weeks~~
ECG	X	X[e]	X[e]	For patients receiving galunisertib: Perform predose on Day 1 of ~~each~~ every other cycle in the extension period. For patients receiving sorafenib only, follow standard of care.

Cycle (Visit)	Study Treatment (v501, v502, etc.)[a]	Post Discontinuation Follow-Up Periods		Comments
		30-Day Safety Follow-Up (v801)	Long-Term Follow-Up[b] (v802)	Refer to Section 10 of the protocol for descriptions of the study periods
Laboratory tests				
Hepatitis B serology	X~~[h]~~[g]	X~~[h]~~[g]		HBsAg carriers only. Can be done at local labs during the extension period.
ECG chemistry	X	X[e]	X[e]	For patients receiving galunisertib: Perform predose on Day 1 of every other ~~each~~ cycle in the extension period. Can be done at local labs during the extension period. For patients receiving sorafenib only, follow standard of care.
Special chemistry	X	X		For patients receiving galunisertib: Perform predose on Day 1 of each cycle in the extension period. Can be done at local labs during the extension period. Includes troponin and BNP. For patients receiving sorafenib only, follow standard of care.
Hematology	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum markers	AFP only	X		~~Includes AFP, AFP L3, E-cadherin, PIVKA-II. Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period~~ As clinically indicated. Can be done at local labs during the extension period.
~~TGF-β+PF4~~		~~X~~		
~~aPTT/PT/ INR~~	~~X~~			~~Perform predose on Day 1 of each cycle in extension period. Can be done at local laboratories during the extension period~~

Abbreviations: ~~AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time;~~ BNP = brain natriuretic peptide; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; exam = examination; HBsAg = hepatitis B surface antigen; ~~INR = international normalized ratio;~~ MAP = multi-analyte panel; MRI = magnetic resonance imaging; ~~PF4 = platelet factor 4; PIVKA-II = prothrombin induced by vitamin K absence; PT = prothrombin time; TGF-β = transforming growth factor beta;~~ v = visit.

a A delay at the start of a cycle (Day 1) of no more than 3 days because of holidays, weekends, inclement weather, or other justifiable events will be permitted and not counted as a protocol violation.

b Follow-up consists of Visit 802 and all subsequent visits (60 days-±7 days). For the patients in the extension period, long-term follow-up will not be conducted unless there are cardiac toxicities (Section 10.3.2.2).

c If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

d Echocardiography with Doppler can be performed up to 3 days prior to Day 1.

e If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography with Doppler and ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and V805). If there are no cardiac findings at discontinuation (Visit 801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (Visit 802) unless a patient is receiving another treatment (see Section 10.3.2.2).

f If there are no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

g ~~Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.~~ HBsAg carriers should be closely monitored with assessment of hepatitis B serology during the study treatment and 30-day safety follow-up period.

~~h HBsAg carriers should be closely monitored with assessment of hepatitis B serology during the study treatment and 30-day safety follow-up period.~~

Leo Document ID = 89f22e5b-a6a2-418b-af9e-33a8e9d20831

Approver: PPD
Approval Date & Time: 18-Dec-2017 02:15:44 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 18-Dec-2017 18:33:13 GMT
Signature meaning: Approved