JBAK Statistical Analysis Plan Version 3

Phase 2 Study of LY2157299 in Patients with Hepatocellular Cancer

NCT01246986

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1. Statistical Analysis Plan: [H9H-MC-JBAK]: Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma

Confidential Information

TGF-β Kinase I Inhibitor (LY2157299) Hepatocellular Carcinoma

This is an open-label, multicenter, multicountry, randomized Phase 2 study of 2 doses of LY2157299 in Child-Pugh class A or B patients with hepatocellular carcinoma.

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[Protocol H9H-MC-JBAK]
[Phase 2]

Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

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3. Revision History

This is the first version of the Statistical Analysis Plan (SAP); it was approved prior to first patient visit.

This SAP includes the definitions of the analysis populations, the pharmacokinetics (PK), the pharmacodynamic (PD), efficacy and safety endpoints, the tables, figures and listings (TFLs) from the analyses and is based on the study protocol approved on 27th October 2010.

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

Pharmanet/i3 will produce all pre-planned standard TFLs in the study. The documentation and validation of programs written by Pharmanet/i3 for the production of TFLs will follow all applicable Lilly SOPs.

Additional exploratory analyses will be outlined and documented once the results for the Phase I study are available.

The interpretation of the study results will be the responsibility of the investigator with Lilly CRP/CRS, Pharmacokineticist and Statistician. The CRP/CRS and Statistician will be also responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly.

This is the second version and was written to align with Protocol Amendment (b) approved on 5th July 2012.

The keys changes of amendment(b) are:

- Study design was modified to potentially have 3 parts in this study. Part A will evaluate HCC patients with AFP ≥1.5 ULN in 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). Part B will evaluate HCC patients with AFP <1.5 ULN at LY2157299 of 300 mg/day to assess the efficacy of LY2157299 in all HCC patients. Part C (if implemented) will evaluate patients with advanced HCC with Child-Pugh B7 or B8 who have received no prior systemic treatment. This is warranted given the safety profile of LY2157299.
- Additional PK sampling was included in the study schedule to assess the clearance of LY2157299 prior to restarting the treatment. Footnote ‘e’ in the study schedule was updated accordingly.
- Section 5.1.5.1 was updated with results from first interim analysis and unplanned review of biomarker and safety data.
- Introduction was updated to provide a table with experimental treatments used as second line therapy in HCC patients.
- In the discontinuations section (Protocol Section 8.3), it was clarified that a patient may be discontinued if there is evidence of objective progressive disease (radiological assessments by RECIST 1.1 and/or the patient is clinically symptomatic.
  The important decision determining whether or not a patient can continue on study drug could be based on their clinical symptoms, even if the patient has progressive disease based on radiological evidence. The investigator may also take into consideration biomarker responses.

- Protocol Section 9.8 (Concomitant Therapy) was updated to clarify that palliative radiation therapy to non-target lesions is allowed.

Additional changes to this version of SAP:

- Derivation of time-to-event endpoint was updated to be measured from date of first dose as the study is no longer randomized after Amendment (b).
- The NCCN-FACT-Hepatobiliary Symptom Index 18 [NFHSI-18] (Sections 5.1.2 and 5.3.8.4) and its subscales was added as an improvement to FHSI-8. The NFHSI-18 scales are moderately and highly correlated to general quality of life as measured by FACT-G subscales and HRQoL as measured by FACT-Hep subscales.

This is the third version and was written to align with Protocol Amendment (c) approved on 2nd July 2013.

The keys changes of amendment(c) are:

- **Study Design:** This is an open-label, multicenter, multicountry, Phase 2 study of LY2157299 in patients with hepatocellular carcinoma. The study design consists of 3 parts. In Part A, patients with AFP ≥1.5 upper limit of normal (ULN) will be randomly assigned to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). In Part B, patients with AFP <1.5 ULN will receive LY2157299 300 mg/day. **In Part C, patients with no prior systemic treatment will receive LY2157299 (160 or 300 mg/day) in combination with sorafenib 400 mg BID**.
- Changes were made for the secondary endpoints, sec 4.2
- Addition in section 5.3.3 for safety and efficacy comparison between Parts A, B, and C
- Corresponding word changes in many other sections to incoprate Part C addition

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to characterize both the TTP distributions and the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) of study treatment in patients with HCC.

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

- 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
- To recommend which doses of LY2157299 as monotherapy and in combination with sorafenib to use in future trials recruiting HCC patients
- To characterize other time-to-event distributions, such as progression-free survival (PFS, based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and modified RECIST [mRECIST], for HCC) and overall survival (OS)
- To estimate antitumor efficacy using response rate (RR, based on RECIST 1.1 and mRECIST, for HCC)
- To assess patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life (Functional Assessment of Cancer Therapy Hepatobiliary [FACT-Hep])
- To explore E-cadherin, pSMAD, and β-integrin (and other markers associated with epithelial-to-mesenchymal transition (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 the utility of exploratory imaging techniques (for example, positron emission tomography [PET] scan, contrast echography) to assess treatment effect with LY2157299 as monotherapy and in combination with sorafenib when possible
- To explore fibrosis-related biomarkers, such as Fibrotest

5. A Priori Statistical Methods

5.1. Endpoint Definitions

5.1.1. Clinical Efficacy Endpoints

The primary efficacy endpoint for this study is time to tumor progression (TTP). Secondary efficacy endpoints include progression-free survival (PFS), overall survival (OS), duration of tumor response (DR), time to treatment failure (TTF), overall response rate (ORR) and clinical benefit rate.

A central review of all radiographic examinations will be conducted. Response will be determined by both RECIST 1.1 and mRECIST; although, the primary method will be RECIST 1.1. Best response is determined from the sequence of cycle responses assessed. For complete response (CR) or partial response (PR), best response must be confirmed. A second assessment should be performed ≥28 days but no longer than 42 days after the first documentation of response. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. All lesions must be assessed by the same method as at baseline to qualify for response.

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. From Amendment (b), patients that are clinically asymptomatic may continue on study treatment even if they have objective progression. These patients will then be discontinued from study treatment because of overall symptomatic deterioration, worsening of biomarker results, or other causes. The date of objective progression and date of overall symptomatic deterioration will be collected on CRF. The time to tumor progression, progression free survival, and response rate will be estimated up to the date of objective progressive disease.

Patients who come off therapy and do not have objective progressive disease should be followed every 2 months after discontinuation from study treatment until objective progressive disease is determined (using the same radiological scans as at baseline) or death. Patients who progress should then be followed for survival every 2 months, even if a patient starts a new anticancer therapy. The start date of any new anticancer therapy (occurring during the 30-day poststudy drug discontinuation period or during the long-term follow-up period) will be collected.

The definitions for efficacy endpoints are as follows:

- **Time to tumor progression (TTP)** is measured from the date of first dose to the first date of objective progression of disease. For each patient who is not known to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, or who has died without progression of disease, time to progression will be censored for that analysis at the date of the patient's last tumor assessment prior to that cut-off date.
- **Progression-free survival (PFS)** duration is measured from the date of first dose to the first date of objective progression of disease or death from any cause. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, PFS will be censored at the date of last prior contact. PFS duration will be calculated and analyzed twice: (1) including clinical

progressions of disease (i.e. not based on lesion measurements), and (2) excluding clinical progressions.

- **Overall survival (OS)** duration is measured from the date of first dose 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 duration will be censored for that analysis at the date of last prior contact. Patients that are still alive when the study finished will be censored at the end of the study.
- **Duration of tumor response (DR)** is measured from the date of the first objective status assessment of a CR or PR to the first date of objective progression of disease or death from any cause. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, duration of tumor response will be censored at the date of last prior contact.
- **Time to treatment failure (TTF)** is measured from the date of first dose until the date of discontinuation of study treatment due to AE, progression of disease, or death from any cause. For each patient who has discontinued study treatment for any other reason, time to treatment failure will be censored at the date of discontinuation of study treatment. If a patient is still on study treatment as of the data-inclusion cut-off date for the particular analysis, time to treatment failure will be censored for that patient at that cut-off date.
- **Overall response rate (ORR)** is the percentage of patients who achieved a best overall response of either complete response (CR) or partial response (PR). The overall response rate for each dose cohort will be estimated by dividing the total number of confirmed responders by the number of patients who received at least 1 dose of study drug.
- **Clinical benefit rate** is the percentage of patients who received benefit of a confirmed response, PR, or SD per RECIST 1.1 and mRECIST. The clinical benefit rate for each dose cohort will be estimated by dividing the total number of patients experiencing benefit by the number of patients who received at least 1 dose of study drug.

5.1.2. Health Outcomes Endpoints

The assessment of patient-reported outcomes, including disease-specific symptoms and health-related quality of life (HRQoL) will be assessed using the FACT-Hep questionnaire. The FACT-Hep consists of 45 items in five subscales: (1) physical well-being (PWB); (2) social and family well-being (SFWB); (3) emotional well-being (EWB); (4) functional well-being (FWB); and (5) the hepatobiliary cancer subscale (HCS) to assess health related quality of life in patients with liver cancers. The 27 item FACT-G total score include PWB, SFWB, EWB and FWB of FACT-Hep to assess the general HRQoL and the 18 item HepCS to assess disease specific issues (specifically on hepatobiliary).

FACT-Hep total, FACT-Hep subscales scores, trial-outcome index (TOI), NCCN-FACT-Hepatobiliary Symptom Index 18 [NFHSI-18]), NFHSI-18 subscale scores and individual symptoms from HCS subscale will be assessed.

Scoring the FACT-G:

Scoring for the FACT-Hep will follow the guidelines and algorithms developed by the FACIT (Functional Assessment of Chronic Illness Therapy) group (http://www.facit.org/).

Negatively stated items in the FACT-G are reversed by subtracting the response from "4" before being added to obtain the subscale totals.

For the following items, compute individual item score by subtracting each item response from "4".

- Physical well-being (PWB): items GP1 to GP7
- Emotional well-being (EWB): items GE1, GE3 to GE6
- Hepatobiliary cancer subscale (HCS): items C1, C2, C5, Hep1, Cns7, Cx6, HI7, Hep2 to Hep6, HN2, Hep8

A subscale score is the sum of individual item scores after reversing for the selected items above and it is calculated as follows:

Subscale score = [Sum of item scores] × [N of items in subscale] ÷ [N of items answered]

The subscale scores are prorated if there are missing items in the subscale. This is acceptable as long as 50% of the items in each subscale were answered (eg. a minimum of 4 out of 7 items, 4 out of 6 items etc). Number of items in each subscale are as follows: 7 items in PWB, SWB, FWB; 6 items in EWB; and 18 items in HCS. The range of each subscale score are as follows: PWB: 0 – 28; SWB: 0 – 28; EWB: 0 – 24; FWB: 0 – 28 and HCS: 0 – 72.

The total scores (TOI, FACT-G, FACT-Hep and NFHSI-18) are summation of the component subscales scores.

The FACT-G total score (score range: 0 – 108) is the sum of the un-weighted subscale scores of PWB, SWB, EWB and FWB. Response rate for the FACT-G has to be greater than 80% (at least 22 out of 27 items completed) for it to be acceptable indicator of patient's quality of life.

The FACT-Hep total score (score range: 0 – 180) is the sum of the un-weighted subscale scores of PWB, SWB, EWB, FWB and HCS.

The FACT-Hep trial-outcome index (TOI) (score range: 0 – 128) is the sum of the un-weighted subscale scores of PWB, FWB and HCS.

See SAP Attachment 1 for FACT-Hep Scoring Guidelines for the above scores.

The NFHSI-18 total scale score consider 18 symptoms (score range: 0-72) in FACT-Hep and is calculated by summing GP1, GP2, GP3, GP4, GP5, GP6, AN7, GE1, GE6, GF3, GF5, GF7, C2, C6, CNS7, HI7, Hep2, and Hep8. The subscale scores of NFHSI-18 consists of NFHSI-DRS-14 (disease related symptoms; score range: 0-56), NFHSI-FWB-3 (functional well-being; score range: 0-12) and NFHSI-TSE-1 (treatment side effects; score range 0-4). See SAP Attachment 2 for guidelines on scoring of NCCN/FACT Hepatobiliary Symptom Index-18 and the subscales.

The higher the scores the better the quality of life.

5.1.3. Pharmacodynamic Efficacy Endpoints

Elevated AFP is a marker of disease progression in HCC patients. Hence, a treatment effect can be measured by following the kinetics of AFP reduction during the treatment period and a sustained reduction of 50% over 3 months is a relevant change suggesting a treatment effect.

Other AFP response criteria will be studied including the following definition : AFP response is >20% decrease in AFP from baseline (samples collected closest to first dose) during 8 weeks of treatment.

Elevated TGF-β1 (possibly adjusted for PF4 level), though less validated, correlated with poor clinical outcome in HCC patients. Hence, a reduction in TGF-β1 levels is another marker of activity of a beneficial treatment effect.

The protein, E-cadherin, is associated with EMT and elevated levels of this marker is found in aggressively growing HCC. Hence, a change in kinetics of its level may reflect treatment effect.

Additional PD endpoints (for example, Fibrotest, T-cells counts, AFP L3, PIVKII) may be considered for analysis.

5.1.4. Safety Endpoints

Safety measures that will be used in the study include hematology, chemistry, urinalysis, vital signs, adverse events (AE), serious adverse events (SAE), treatment-emergent adverse events (TEAE), electrocardiogram (ECG), echocardiogram, dose adjustments and omissions, and blood transfusions. All safety summaries and analyses will be based upon the safety population as defined in Section 5.2. All adverse events will be mapped to MedDRA (Medical Dictionary for Regulatories Activities) LLT (Lowest Level Term) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

5.2. Analysis Sets

Efficacy and safety analyses will be based on all enrolled patients receiving at least one dose of LY2157299.

Pharmacokinetic (PK) analysis will be conducted on patients who received at least one dose of study drug and have had samples collected.

Pharmacodynamic (PD) analysis will be conducted on patients who have received at least one dose of the study drug and have had samples collected.

Pharmacogenomic analysis will be conducted on patients from whom a valid assay result has been obtained from whole blood and serum, and tumor tissue blocks from diagnostic or surgical tumor samples.

5.3. Statistical Methods

5.3.1. Design Considerations

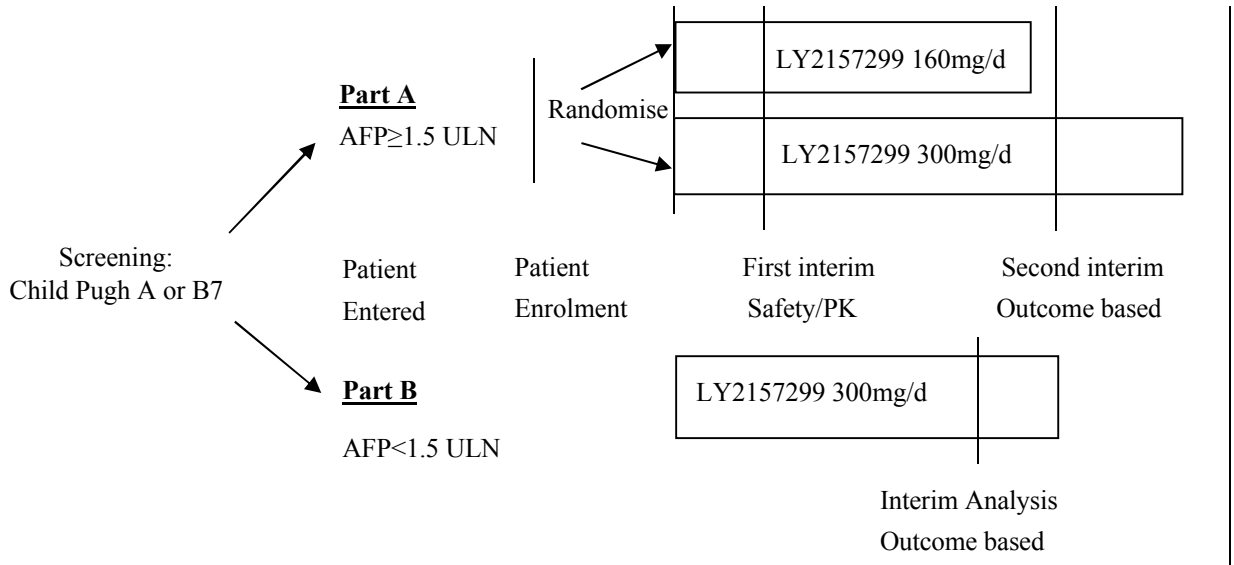
Study JBAK is a multicenter, randomized trial characterizing the TTP distribution of study treatment in Child-Pugh Class A or B HCC patients.

Starting with Amendment (c), there may be 3 parts to this study: Child-Pugh A and B7 patients are enrolled in Part A and Part B; Parts A and B are distinguished based on baseline AFP levels (Figure JBAK.5.1.). In Part C, patients with no prior systemic treatment will receive LY2157299 (160 or 300 mg/day) in combination with sorafenib 400 mg BID.

A maximum of 190 patients will be enrolled into the study: 109 into Part A, 40 into Part B, and approximately 40 into Part C. Given these changes, the primary objective of this study is to characterize both the TTP distributions and the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) of study treatment in patients with HCC.

In Part A, patients with AFP ≥1.5 ULN will be randomized to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). Eligible patients will be randomized through interactive voice response system (IVRS) after completing screening at Visit 0 into 1 of these cohorts (the 2 cohorts being balanced as far as possible through IVRS using minimization methods for AFP levels, etiology, and whether sorafenib naïve or not) and will receive LY2157299 for 14 days followed by 14 days of rest.

In Part B, patients with normal AFP (<1.5 ULN) will receive LY2157299 300 mg/day for 14 days followed by 14 days of rest. Patients who have a normal AFP level and who meet all criteria for enrollment will be assigned by the IVRS to receive the LY2157299 300-mg/day dose after completing the screening at Visit 0.



Abbreviations: AFP = alpha-fetoprotein; PK = pharmacokinetics; ULN = upper limit of normal.

Figure JBAK.5.1.Illustration of study design for Protocol H9H-MC-JBAK Part A and Part B

Part C will evaluate LY2157299 in combination with sorafenib in patients with advanced HCC and Child-Pugh A status who have not received previous systemic treatment. Patients who have not received prior systemic treatment and who meet all criteria for enrollment will be assigned by the IVRS to receive either the LY2157299 80 mg BID or the LY2157299 150-mg BID dose after completing the screening at Visit 0.Up to 40 patients may be enrolled.

Part C comprises a safety lead-in of 2 cohorts followed by an expansion phase with selected safe dose(s) (Figure JBAK.5.2.). Patients enrolled in Cohort 1 will be administered LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. Three patients will be enrolled on Cohort 1; if no dose-limiting toxicities (DLTs) (related to LY2157299 or combination regimen) are observed in Cycle 1, 3 patients will be treated on Cohort 2 at LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. If a DLT related to LY2157299 or combination regimen is observed in either cohort in the first 3 patients in Cycle 1, then that cohort will be expanded to include additional 3 patients. Six to 12 patients may be enrolled in the safety lead-in, depending on the observed DLTs. PK sampling will be conducted in Cycle 1 with the intent to assess drug-drug interactions between LY2157299 and sorafenib.

Depending on the results from the safety lead-in cohorts and analysis from Parts A and B, the expansion cohort will consist of 1 of the following:

- Single treatment group: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Single treatment group: LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Two treatment groups: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 versus LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28. Both cohorts being on a 28-day cycle.

Patients enrolled in the safety lead-in cohorts may continue treatment as per that cohort.

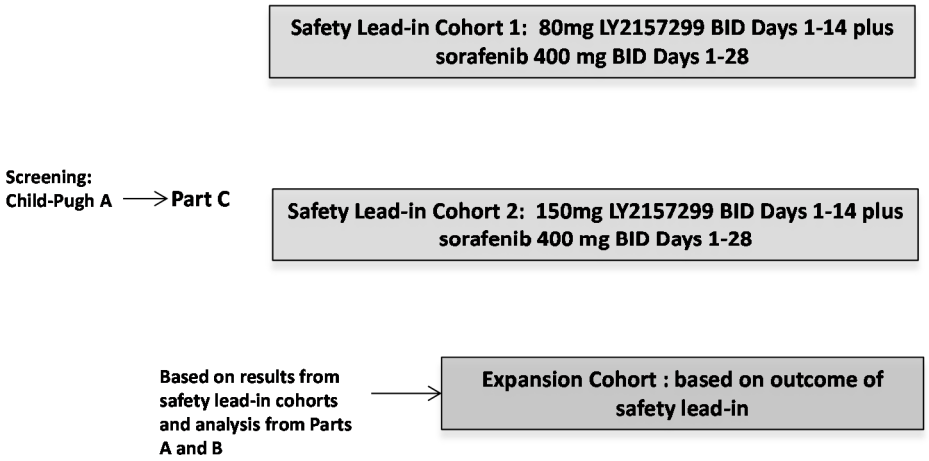


Figure JBAK.5.2. Illustration of study design for Protocol H9H-MC-JBAK Part C.

Dose escalation will be driven by safety using the 3+3 method. Both cohorts will have a minimum of 3 patients enrolled into it. If 1 patient in either dose level experiences a DLT within the first cycle of LY2157299 and sorafenib, then up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in 2 or more patients at either dose level in the first cycle, dose escalation will cease and either the previous dose level will be declared the MTD or, following discussions between the sponsor and investigators, additional patients may be treated at intermediate doses between the previous and current dose levels.

One cycle is defined as 28 days (a minimum of 26 days and a maximum of 31 days: the treatment period must be a minimum of 10 days and a maximum of 14 days; the "off-treatment" period can vary to ensure an overall cycle length of 26 to 31 days). In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14. (In Part C safety lead-in in Cycle 1, patients must have received 14 days of LY2157299 treatment). If patients are not evaluable for safety and/or PK in Cycle 1 of Part C safety lead-in, the patients will be replaced.

The planned treatment duration is 6 cycles, but patients may continue to receive study drug if they are still benefiting from treatment in the opinion of the investigator and Lilly physician.

In case of occurrence of severe toxicities in later cycles in patients being treated with either LY2157299 monotherapy or with LY2157299 in combination with sorafenib, the sponsor will review and choose a lower dose, if necessary.

This Phase 2 study will be considered complete once 85% of events for survival analysis in Part C have occurred. Patients still on treatment at the time that the study is considered complete, may enter the treatment extension period and continue to the study treatment.

5.3.2. Interim Analyses

There were 2 planned interim analyses in Amendment (a) (the cohorts planned in Amendment (a) will be designated as Part A from Amendment (b)) . The first interim analysis reviewed both safety and PK of LY2157299. Safety was assessed after 20 patients (10 patients/dose) had enrolled and completed 1 cycle of treatment. The PK interim analysis occurred after the PK sample on Day 15 had been collected from 20 patients (this was carried out after the safety review).

For enrollment to continue in either dose level, there had to be no evidence of cardiotoxicity in any patient at that dose level and no drug-related CTCAE Grade 3/4 toxicity that was not manageable. The PK of LY2157299 in HCC patients were compared to those of patients with glioblastoma observed in Study JBAH. Since only sparse sampling is being performed in this study, comparisons between the 2 populations were carried out by simulations (median and 20th and 80th percentiles) using the population PK model from Study JBAH.

The decision to continue was based on the following:

1. If neither dose was considered tolerable, then the study would be terminated.
2. If only 1 dose was considered tolerable, then enrollment would continue into this dose cohort, and the other dose cohort would close.
3. If the predicted 80th percentile of the distribution of AUC exceeded 10.96 (mg.h/L) for either dose, enrollment into this dose cohort may have been ceased.

Enrollment after the first interim analysis continued in both dose cohorts, and a second interim analysis was planned when an additional 30 patients had been enrolled in each arm (ie, 40 in each arm) and had been actively followed for 3 months or progressive disease or death had been observed. This was to be after the second planned radiological assessment (planned every 6 weeks) and after the collection of biomarker (specifically AFP) samples for all patients. Any patient who was lost to follow-up or started a new anticancer therapy before 3 months had elapsed without an event being observed was not eligible for inclusion in the interim analysis.

The decision for dropping 1 of the 2 dose cohorts was to be based on a composite endpoint, including the number of patients who were free from progression at 3 months, amount reduction in AFP and other TGF-β related biomarkers from baseline (adjusting for baseline levels if needed), and safety.

For examples:

1. If the observed mean percentage reduction from baseline in AFP concentrations in either cohort was more than 50%, enrollment into the dose cohort may continue.

2. If the difference in mean percentage change from baseline in AFP concentrations between the 2 doses is >20%, then the dose with the lowest reduction from baseline may be dropped after taking into consideration the observed results for E-cadherin and other TGF-β related biomarkers.

3. Either dose or both doses will be dropped if there is evidence of cardiotoxicity and/or drug-related CTCAE Grade 3/4 toxicity that is not manageable in any patient.

4. If the number of patients who are free from progression at 3 months in either dose is 21 or less, then the dose level may be discontinued.

    - This cut-off represents a risk of continuing when the true median TTP is not considered clinically meaningful over no intervention (that is, median TTP = 3 months) is 32% and of deciding not to continue when the true median TTP is considered meaningful (that is, median TTP = 4.5 months) is 11%. (Information for risks of an incorrect decision using other cutoff values will be provided in the SAP. However, this planned interim was not carried out and this information was not provided.)

Two effects of LY2157299 are of interest for changes in AFP levels – whether there is evidence of a reasonably sustained 50% or greater reduction from baseline (as this is considered indicative of clinical benefit) in either dose and whether there is a difference of 20% in the percent change from baseline between the 2 doses (for example, 50% reduction at 300 mg/day and 30% reduction at 160 mg/day). With 40 patients enrolled at each dose cohort and an assumed within-patient coefficient of variation of 44% (data on file), there is at least 95% probability that treatment effect of 50% within a dose group will be detected as significant at the 5% significance level. The more sensitive situation concerns the probability of detecting a difference of 20% in the percentage reduction in pre and postdose concentrations between the 2 dose groups in order to choose a dose at this stage. The power to detect a 20% difference in percent reduction between the 2 doses is approximately 80%, at the 20% 2-sided significance level.

Analysis of the mean fold change from baseline of biomarker concentrations levels will be estimated from a mixed-effects model with sampling time, dose and their interaction as fixed effects, baseline levels (either as a continuous variable or categorical) as a covariate and patient as a random effect. The choice of variance-covariance structure will depend on the data. Biomarker concentrations will be log transformed prior to analysis. Specific details of these analyses will be provided in the TFL shells and requirements.

If at the second interim analysis, when a total of 40 patients had been enrolled at each dose and followed as described, results of the comparison between the doses were still inconclusive, the decision to either continue enrollment into both doses or to choose 1 dose was to be made after discussions between the investigator, Lilly, and study statistician.

However, the planned second interim analysis described in Amendment (a) was not carried out. The decision to carry out an additional data review is described in Protocol section 5.1.5.1. Based on this review, the decision was to close Cohort 1 and continue enrollment until 70 patients have been enrolled in Cohort 2. At the time of the decision, 74 patients had been treated.

As part of Amendment (b), the second interim analysis for Part A is now planned after the 70th patient has enrolled into Cohort 2 and started Cycle 1. The purpose of this analysis is to help inform the decision to prepare for further development of the compound in patients with HCC

with elevated AFP levels. This analysis was completed in December 2012 (Faivre et al. 2013). Safety, efficacy (TTP, ORR, clinical benefit rate) and PK will be assessed at the second interim analysis. Pharmacodynamic markers and health outcome data will also be reviewed at this second interim to gain preliminary insight to patient benefit in this indication for inclusion into the end of Phase 2 briefing document.

The purpose of the interim analyses in Part B and Part C is to prepare for further development of the compound and to inform the decision as to whether all second-line HCC patients, irrespective of baseline AFP levels, and all first-line Child-Pugh A or B7 patients may benefit from treatment with LY2157299. Safety, efficacy and PK will be assessed at these interim analyses. Pharmacodynamic markers data will also be reviewed at subsequent interim analyses. The timing of the interim analyses for Parts B and C is based on assuming Parts B and C are designed as a Simon's 2-stage design with the same characteristics as used in the original protocol: where the assumption of a poor treatment is if the proportion free from disease progression is 50% at 3 months (assumes median TTP = 3 months) and a good treatment is if the proportion free from disease progression at 3 months is 63% (assumes median TTP = 4.5 months). The operating characteristics of this design are as follows: The null hypothesis is that the true response rate is 50%. In the first stage, 18 patients will be accrued and actively followed for at least 3 months or until they have discontinued. If there are 8 or fewer patients free from disease progression in these 18 patients, this may be indicative that patients with normal AFP levels are not benefiting from the treatment. The additional 22 patients will be accrued for a total of 40. The null hypothesis will be 'rejected' at the end of Parts B and C if 22 or more patients out of 40 patients in each part are observed to be free from disease progression at 3 months. This design yields a type I error rate of 15% and power of 78% when the true response rate is 63%. From Amendment (c), the above calculations now only apply to the third interim analysis (for Part B, completed June 2013). Given the change in strategy for Part C, only safety reviews are planned while the study is ongoing. An additional analysis may be carried out if needed to help with clinical planning of the compound for treating first-line patients.

The final analysis for Parts A and B will be conducted after the study objectives for these two parts have been met. For example, the final analysis for Part A will be carried out when there are a sufficient number of events of overall survival (for example, approximately 75% OS events); the final analysis for Part B will also be carried out after a sufficient number of deaths have occurred in Part B in order to have a reasonable estimate of overall survival in this patient group (AFP<1.5 ULN). The final analysis for Parts A and B can be conducted at different times and interim reports will be written. The analysis for Part C will be the final analysis for the study.

5.3.3. General Considerations

All patients who have received at least 1 dose of study drug will be evaluated for safety, efficacy, toxicity, and pharmacodynamic endpoints. The pharmacodynamic responses will 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.

After Amendment (b), patients are allowed to continue on study treatment at the investigator's discretion, even when objective progression is determined by radiological measurements, if they do not have overall symptomatic deterioration as well. This change should not affect the primary objective (estimation of TTP), PFS, or response rate. However, bias may be introduced in the assessment of OS, since patients prior to Amendment (b) will have discontinued based on objective progression alone. Therefore, patients discontinued from objective progression prior to the amendment (b) will be considered separately from those that discontinued due to objective progression or overall symptomatic deterioration after the amendment in the assessment of OS.

Patients from all sites will be pooled for all analyses. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.10, unless otherwise stated. Patients with Child-Pugh Class A and B7 will be considered as 1 group of patients, given the similarity of Class B7 patients to Class A patients. If all patients in Part A and Part B are second-line, Part C patients will be analyzed as a separate group. If there are some first-line patients in Part A or Part B, different subgroups may be considered.

Efficacy:

For efficacy endpoints, no formal hypothesis testing based on a priori power calculations is planned; rather differences in various endpoints (eg, hazard ratios for TTP, OS) between appropriate treatment groups will be estimated. Since Part C patients are different in 2 ways from patients in Parts A and B (first-line versus second-line and treated with LY2157299 in combination with sorafenib compared to LY2157299 monotherapy, respectively), the only estimate of differences between Parts A and/or B with Part C will be between Part C and the sorafenib-naive patients from Parts A and B. The interpretation of any estimate will be considered in light of the size of this subgroup.

Safety:

Summary statistics, plots, and listings for all safety data collected will be provided in aggregate and by dose in Part A and Part C, and in aggregate for Part B separately. Comparisons between doses and parts will be summarized for Part A and Part B, and may be compared to Part C. Comparisons between other subgroups of interest may be required.

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.

The following data handling conventions will be used in the analysis.

Term	Definitions or Rule

Study day	If assessment is on or after date of first treatment dose then
	(date of assessment) – (date of first study treatment dose) + 1
	If assessment precedes first treatment dose then
	(date of assessment) – (date of first study treatment dose)
	There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose.

Cycle day	If assessment is on or after date of first treatment dose then
	(date of assessment) – (date of first study treatment dose in cycle) + 1
	If assessment precedes first treatment dose then
	(date of assessment) – (date of first study treatment dose in cycle)
	There is no cycle day 0. Cycle day 1 is the date of first dose in the cycle and cycle day -1 is the day before the first dose.

Baseline	For change from baseline analysis, baseline value is defined as the last reported measure on or before the first dose date. For change from baseline within a cycle, the measure prior to the first dose if that cycle is baseline.

Entered	Patients who have signed the informed consent document directly.
Randomized	Patients who have been assigned to study treatment and have not received any study treatment (LY2157299).
Screen failures	Patients who have signed informed consent, do not meet eligibility criteria and are not randomized.
Enrolled, Patients on therapy	Patients who have been assigned to study treatment and have received at least 1 dose of study treatment (LY2157299).

5.3.4. Handling of Missing Data

For time-to-event endpoints, the method for handling missing data will be censoring. Patients that withdrew from the study without response will be censored for response at the date of the last tumor assessment.

5.3.5. Patient Disposition

All patient discontinuation from study treatment and study will be documented, and the extent of each patient's participation in the study will be reported. Reason for their discontinuation from both study treatment and study will be listed and summarized by pre-determined categories. The planned treatment duration is 6 cycles, but patients may continue to receive study drug if they are still benefiting from treatment in the opinion of the investigator and Lilly physician. If known, unique reason for discontinuation will also be listed. If reason for discontinuation is due to AE or death, the associated AE or cause of death will be reported.

A listing of patients with identified protocol violations, including patients who did not meet inclusion/exclusion criteria, did not sign inform consent document at visit 0 and who discontinued due protocol violations, will be provided. See SAP attachment 3 for a list of potential protocol violations.

All enrolled patients will be accounted for in the summary of disposition. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

5.3.6. Patient Demographics and Baseline Disease Characteristics

5.3.6.1. Demographics and Baseline Disease Characteristics

Patient demographics and baseline disease characteristics will be listed and summarized by Part A, B, and C with descriptive statistics for all enrolled patients. We will compare baseline characteristics for 300 mg patients enrolled in Part A after dropping of the 160mg group with those before dropping to satisfy a concern that these may be worse in terms of prognosis.

Patient demographics will include a summary of sex, race, age, height and weight.

Baseline disease characteristics will include a summary of Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), CLIP staging, and etiology. After Amendments (b), both Child-Pugh Class A patients, Child-Pugh Class B7 patients, Child-Pugh A are eligible and will be enrolled into the study.

Special instructions regarding presentation of race: patient may select more than one of the values for Race in the electronic case report form (eCRF). Derive Race to 'Multiple' if more than one race is selected. Otherwise, race equals the single race selected. For example, if a patient selects both 'White' and 'Asian' then RACE = 'Multiple'. However, if a patient select only 'Asian' then RACE = 'Asian'.

A listing will be provided to show baseline habits of tobacco, alcohol, and caffeine/Xanthine use for enrolled patients.

5.3.6.2. Historical Illnesses and Pre-existing Conditions

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using preferred term from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed.

Pre-existing conditions are existing clinically relevant events that started prior to signing the inform consent document. These conditions will be graded using NCI CTCAE v4.0x terms and will be part of the adverse event listing.

5.3.6.3. Prior and Post Discontinuation Therapies

All prior therapies performed for HCC, including systemic, surgical, radiotherapy, locoregional, will be listed separately. The listing for prior systemic therapies will detail the reason for the regimen, treatment received, treatment start and stop date, response outcome, date of progression. Combination systemic therapies will be linked through same regimen number. The listing of prior surgical procedures will include surgery intent, the procedure and location. For prior radiotherapy listing, dosing information and irradiated location will be included. The type of procedure used and date of procedure will be reported in the listing of locoregional treatments. Combination of prior systemic, surgical, radiotherapy and/or locoregional will be linked through overlapping treatment period.

Any post therapies following discontinuation will also be listed.

5.3.7. Concomitant Medications

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be listed for enrolled patients. If concomitant medication use is due to AE, the associated AE will be listed. A summary of the concomitant medication will also be provided.

5.3.8. Efficacy Analyses

5.3.8.1. Clinical Efficacy Analyses

Time to tumor progression (TTP) is the primary clinical endpoint for this study. A listing of TTP, including date of first dose, date of progression, date of death, censoring and TTP duration will be listed. The time to progression distribution will be characterized using the Kaplan-Meier method. Kaplan-Meier curves of TTP will be presented. Median TTP, quartiles and TTP rate after specific time points (for example, after 12 months and 24 months on treatment) will be estimated from the survival curves. All these parameter estimates will be reported together with their 90% confidence intervals. A comparison between the observed TTP distributions of each dose cohort will be performed using the log rank test and the p-value reported. The hazard ratio between the observed TTP distributions of different cohorts/parts (or different subgroups of interest) will be estimated. The interpretation of any estimate will be considered in light of the size of this subgroup. The list of possible comparsions are:

1) In part A: 160 vs 300 mg (160 reference)

2) Between Part A and Part B 300 mg groups (Part A reference)

3) Between Part A, Part B and Part C (sorafenib naïve or not)

Sensitivity analyses using alternative distributions of survival times, such as Weibull (with and without estimating a shape parameter) will be explored and median TTP with its 90% CIs will be reported.

Secondary time-to-event parameters will follow the same analyses described above.

Additional exploratory analyses on clinical endpoints such as TTP or OS will be carried out. Prognostic factors, such as baseline AFP levels, etiology, and whether sorafenib naïve or not, may be added to the time-to-event models to explain the variability in duration of progression. Analyses using subgroup identification methods, such as classification and regression tree (CART) (classification and regression tool) may also be carried out.

The best overall response rate and clinical benefit rate together with their 90% exact confidence intervals will be reported for each dose cohort in Part A, Part B and Part C. These rates will be compared between dose cohorts using Chi-squared tests. Odds ratios, 90% confidence intervals and p-values will be reported. Cohorts comparison should follow the above list for types of comparsions for TTP and OS.

5.3.8.2. Pharmacodynamic Analyses

Pharmacodynamic (PD) markers (for example, AFP, AFP L3, PIVKII, E-cadherin, TGF-β1 (possibly adjusted for PF4 level)) will be analyzed using a mixed-effects model with patient as a random effect and dose, sampling time, and baseline values as fixed effects. Depending on the data, an appropriate variance-covariance structure will be added to the model. Serum concentrations will be log transformed prior to analysis.

Comparisons between subgroups in baseline AFP (AFP: ≤ 400ng/mL or >400ng/mL [the threshold value of 200 ng/mL will also be used]), etiology (viral hepatitis, alcohol, other), and use of sorafenib may be carried out by either including these terms as fixed effects in the above models or as separate analyses. Interactions terms will be included if appropriate. The decision to perform this analysis will be made based on whether there is any evidence that the variability of data between the different subgroups and the actual number of patients enrolled in each subgroup.

Geometric means by dose and time together with 95% confidence intervals will be provided for this analysis. Ratio of means and 95% confidence intervals between doses for each subgroup of interest and between subgroups of interest within each dose will be estimated from the models.

Plot of means over time will be provided for each biomarker in the dosing cohorts. Bar plots with ratio of means and 95% confidence intervals may be provided for the subgroup analyses.

In addition, each marker will be summarized descriptively by subgroup of interest, dose and time.

Percent of maximum change from baseline in AFP level will also be summarized: >0%, 0-25% reduction, 25-50% reduction, >50% reduction. Waterfall plots of maximum reduction and line plots of raw data and percent change from baseline over time will also be provided.

Previously reported AFP response criteria will be evaluated.

The association between changes in PD markers and clinical endpoints will be explored to determine their value as predictive biomarkers of drug effect on clinical outcome. Biomarkers with categorical data will be listed with baseline values, first post dose value in the hypothesized direction of change and time to this post baseline value. Biomarkers with continuous data will be listed with baseline values, first maximum change from baseline based on their hypothesized direction of change and time to this first maximum change. The patient's TTP will also be included in the listing to relate biomarker responses to therapy with improved TTP. A descriptive summary of patients with specific level of maximum change from baseline and time to this maximum change may be provided.

For biomarkers with categorical data, frequency and percentages will be used to summarize the data.

5.3.8.3. Pharmacokinetic/ Pharmacodynamic 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.

The PK parameter of interest will be evaluated with dose concentration and fix effects (such as weight or age) in the model. Interindividual variation and residual variation will also be reported.

The plasma concentration will be summarized descriptively and presented graphically in JBAK study report.

In addition, data from patients in this study may be combined with data from JBAH study, for PK population analysis.

In Part C, Cycle 1 assesment of possible sorafenib exposure change during monotherapy and combination will be made.

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 on exposure-response using TTP and/ or other clinical endpoints may be explored if data warrant.

Lilly Pharmacokineticist will be responsible for this analysis. Details on the analysis can be found in the Pharmacokinetic plan.

5.3.8.4. Health Outcome Analyses

The following will be carried out for each part separately.

Questionnaire compliance rates will be ascertained at each assessment: baseline (prestudy), day 1 of every cycle starting from cycle 2, and discontinuation (Visit 801).

For those patients who completed at least one questionnaire, summary descriptive statistics of FACT-Hep subscales scores (PWB, SWB, EWB, FWB, HCS), NCCN-FACT subscales scores based on FACT-Hep (NFHSI-DRS-14, NFHSI-FWB-3, NFHSI-TSE-1), total scores (FACT-G, FACT-Hep, TOI, NFHSI-18) and individual symptoms from the HCS subscales will be provided at each time point by dosing cohort and pooled. This summary will include number of patients, number of patients with completed questionnaire, mean, standard deviation, median, minimum, and maximum scores.

J.L Steel (2005) has estimated minimally important differences (MIDs) in FACT-Hep based on 158 patients diagnosed with hepatobiliary carcinoma (85% of patients with HCC) to help interpret individual and group differences on HRQoL measures. The MIDs are given as follows: (1) FACT-Hep subscales: 2 – 3; (2) FACT-G: 6 – 7; (3) FACT-Hep: 8 – 9; (4) HCS: 5 – 6; (5) TOI: 7 – 8; and (6) FHSI-8: 2 – 3. These MIDs will be used to assess and interpret change from baseline scores.

For those patients who completed a baseline and one post-baseline questionnaire, change from baseline on subscale and total scores will be assessed.Repeated measures ANOVA will be performed on each cohort to test changes over time from baseline (pre-study) to patient discontinuation at visit 801. P-values indicating significant differences will be provided. Same analysis will be performed on pooled data from both cohorts. Waterfall plots of change from baseline of individual patients will be provided. Plots of mean subscale scores, total scores, TOI and NFHSI-18 over time will be provided.

Time to worsening of symptoms, using the MIDs as a reference, will also be evaluated for PWB, FWB, HCS, TOI and NFHSI-18. For example, a decrement in score of 2 or 3 in PWB would consider a worsening of symptoms. Data from each dosing cohort and pooled will be analyzed

using Kaplan-Meier plots with censoring at the last assessment for patients with no worsening. Median time to worsening with 95% confidence interval will be provided.

5.3.9. Safety Analyses

5.3.9.1. Study Drug Exposure

The number of cycles completed per patient and dose intensity will be summarized using descriptive statistics (mean, median, minimum, and maximum).

Dose intensity for LY2157299 is derived according to the following formula:

- Planned cumulative dose (mg):

  PLC_i = number of cycles * assigned dose per day * 14

  where 14 is the planned number of dosing days per cycle.

- Prescribed cumulative dose (mg):

  PRC_i = sum of presecribed dose multipled by the number of dosing days in that cycle over all cycles.

  The actual dosing is collected on days 1, 12, 13, and 14 of cycle 1 and day 1 of cycle 2, which aligns with the PK sampling day. Any dose modifications collected during the treatment period will be considered in the calculation of prescribed cumulative dose. Additional and/or detailed considerations for deriving of prescribed cumulative dose will be included in the TFL requirements. For interim data cut, the number of cycles up to the last completed cycle for patients in active treatment will be considered for this calculation; for patients that has discontinued from treatment, the number of cycles up to the last cycle will be considered.

- Dose intensity in percent:

  $$PDC_i = (PRC_i / PLC_i) * 100\%$$

For each patient, dose intensity for LY2157299 will be listed based on cumulative doses received during study. Note prescribed dose is the same assigned dose if there is no dose modification. Listings of dose assignment and dose information on LY2157299 will also be provided.

Cycle delays, dose reductions, and dose omissions of LY2157299, including reasons, will also be listed. If the reason for dose modification is due to AE, the associated AE will be provided. The number and percentage of patients with any dose modifications will be summarized for the entire treatment period as well as for each cycle.

5.3.9.2. Adverse Events

The adverse events will be reported in CTCAE terms using CTCAE Version 4.0x. Any listings or summaries using MedDRA will use preferred terms in the most current version of MedDRA at the time of reporting. The version of MedDRA used in any reports will be documented.

Treatment-emergent adverse events (TEAEs) are defined as follows:

- Any AE, regardless of causation, that were not present prior to first dose and emerges on or after the day of the first dose of study treatment
- Or any PEC (emerged prior to informed consent) or any AE (emerged after signed informed consent) that were still present prior to first dose but has increased in severity (CTC grade) following the start of treatment, regardless of causation.

A listing of all adverse events by patient,including pre-existing conditions, will be presented. This listing will include patient number, adverse event (actual term, CTCAE term, and preferred term), event start and end dates, CTCAE grade, relationship to study drug/procedure, seriousness, and outcome. A listing of SAE will be produced using the same format.

Adverse events will be summarized by frequency counts and percentages as follows:

- Patients with at least one AE
- Patients with at least one TEAE
- Patients with at least one grade 3 or 4 AE
- Patients with at least one SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died on therapy
- Patients who died within 30 days of last dose of study drug

For each category above, frequency counts and percentages will also be provided for patients who had events possibly related to study drug.

Adverse events in CTCAE terms will be also be summarized by CTCAE grade within the SOC. This summary will be provided for all adverse events with CTCAE grade, regardless of causation, and repeated for possibly drug related AE with CTCAE grade.

TEAEs will be summarized by CTCAE term in decreasing frequency within the SOC, regardless of causation, and repeated for TEAEs that are deemed by investigator to be possibly study drug related. Serious adverse events will summarized in the same format.

A listing of patient discontinuation due to AE or death will also be provided.

Chi-squared test may also be performed to compare AE incidences between the 2 doses and study parts adjusting as necessary for baseline AFP levels or other important variables.Any significant differences (p-value <0.05 or p-value< 0.01) will be indicated in the summaries.

5.3.9.3. Cardiac Safety

Cardiac safety data from this study will be provided to France regulatory authorities on a periodic basis (every 6 months from first patient visit) and will be assessed through echocardiography, ECG, chest CT scan, ECG chemistry and cardiac related adverse events.

Echocardiography, ECG and ECG chemistry will be assessed at screening for enrollment, predose at every other cycle starting from Cycle 2 (C2, C4, C6), at Visit 801 and follow-up. 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, 805, and 807).

Chest CT scan will be assessed at screening for enrollment, every 6 months from first assessment and at discontinuation (Visit 801). Alternatively, chest and/or abdomen MRI are performed. If there were no clinically significant findings at the last assessment conducted within the last 30 days and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

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 803). If a patient receives another treatment, Visit 803 cardiac assessments will not be performed.

A central reading will be performed for the data used in the final study report.

ECG data will be listed as qualitative and quantitative data separately. Qualitative ECG data includes information on rhythm, conduction, normality, morphology, ST segment, T wave and U wave. Quantitative ECG data listing would include PR, QRS, QTcb, and QT intervals. Occurrence of cardiac related AE data such as myocardial ischema, myocardial injury and myocardial infarction will also be included in this listing.

Plots of change from baseline in QTcF versus PK concentrations will be provided. Summary statistics of for QTcB and QTcF will be provided. Number of patients with maximum change from baseline in QTcF > 30 msec and > 60 msec and raw QTcF > 450 msec, > 470 msec and > 500 msec will be provided.

A listing of all ECG chemistry for Lipase, Thyroid Stimulating Hormone (TSH), Tri-iodothyronine (T3) and Thyroxine (T4) will be provided. Cardiac related adverse events (SOC='cardiac disorders') including their CTCAE grade will be listed.

Echocardiography measurement data will be listed separately. One listing will include variables such as LV internal dimension, LA volume, LA dimension, LV ejection fraction and LV mass. The other listing will include PA systolic pressure, pulmonary flow velocity acceleration time, mitral deceleration time, mitral E/A ratio, E/Em, RA dilation and RV dilation. Plot of LV ejection fraction over time will be provided. Echocardiography assessments with regurgitation,

wall motion, peridcardial effusion data will be listed, Patient listings of changes in echocardiographic measurements from baseline to post-dose visits will also be provided separately for the variables above. In addition, overall ECG assessments recorded from GLS and on CRF (including clinical significance) will be listed. Summary on the frequency of maximum change from baseline for RA dilation, RV dilation, left ventricular wall motion, pericardial effusion and valvular regurgitations will be provided.

5.3.9.4. Laboratory Parameters

A listing of all laboratory data will be provided (using SI units [International System of Units], when available) by treatment, patient and cycle. Normal reference ranges and percent of the result outside of range (result divided by lower limit if result is less than lower limit; result divided by higher limit if result is greater than higher limit) or change from baseline will also be included.

Relevant hematology and chemistry will be summarized according to CTCAE v4.0x grading. A listing of all hematology, chemistry (serum, special, ECG), AFP, E-cadherin, TGF-β+PF4, aPPT/PT/INR, Fibrotest and urine C-terminal telopeptides of Type 1 collagen will be provided by patient, cycle and cycle day.

5.3.9.5. Deaths

All deaths in this study, including the cause of death, will be listed by phase, treatment, patient and at the cycle when it occurred.

5.3.9.6. Hospitalizations and Blood Transfusions

A listing of patients who were hospitalized due to AE will be provided.

Patients that received blood transfusions, including the blood products received (that is packed red blood cells, platelets, fresh frozen plasma, or whole blood) will also be listed.

5.3.9.7. Vital Signs

Vital signs will be listed by patient, cycle and cycle day. This listing will include height, weight, respiratory rate, temperature, blood pressure and post-baseline ECOG performance status.

5.3.9.8. Electrocardiograms

Electrocardiogram (ECG) results will be listed for each patient by cycle, day within cycle, visit 801 and follow-up visits. This listing will include assessment of normality and clinical significance.

5.3.9.9. Echocardiograms

Echocardiograms (ECHO) results will be listed by treatment, patient and cycle and will include test date and left ventricular ejection fraction results.

5.3.9.10. Other Data

CT lot numbers of LY2157299 will be listed by treatment, patient and cycle.

5.3.10. Exploratory Analyses

Exploratory analyses/data mining will be carried out on imaging data, Fibrotest data, gene expression data, multi-analyte panel (MAP) of proteomics data and tumor-tissue data as appropriate, investigating links between these data and clinical and PD efficacy endpoints. Other TGF-β-signaling pathway biomarkers will also be included in this analysis.

After Amendment (a), both Child-Pugh Class A patients and Child-Pugh Class B7 patients are eligible and are being treated as 1 group given the similarity between these groups of patients, but additional analyes will look at the contribution of both classes to the clinical endpoints. In addition, as of Amendment (a), patients with liver transplant on maintenance immunosuppressive therapy are eligible, and possible differences in safety and efficacy endpoints between patients with and without liver transplant will be investigated.

After Amendment (c), first-line Child Pugh A patients are included in the study. Similar analyses to those conducted for patients in Parts A and B will be carried out for patients in Part C.

5.3.11. Clinical Registry Disclosure

The efficacy and safety analyses on the primary and secondary outcomes for CTR disclosure will be consistent with other document disclosure, for example CSR, manuscript and so forth. These results will be published on www.clinicaltrials.gov.

Analyses provided for the CTR requirements include an AE summary dataset and will be presented as follows:

- Both Serious Adverse Events and 'Other' Adverse Events will be summarized by treatment group and MedDRA preferred term.
- An adverse event is considered 'Serious' regardless of whether it is a treatment-emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious.
- For each Serious AE and 'Other' AE, for each event term and treatment group, the following are provided:
    - Number of patients at risk of an event
    - Number of participants who experiences each event term
    - Number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

6. References

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7. SAP Attachments

SAP Attachment 1. FACT-Hep Scoring Guidelines (Version 4)

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Hep).
5. The higher the score the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

HEPATOBILIARY	C1	4	-	_____	=_____
CANCER	C2	4	-	_____	=_____
SUBSCALE	C3	0	+	_____	=_____
(HCS)	C4	0	+	_____	=_____
	C5	4	-	_____	=_____
Score range: 0-72	C6	0	+	_____	=_____
	Hep1	4	-	_____	=_____
	Cns7	4	-	_____	=_____
	Cx6	4	-	_____	=_____
	HI7	4	-	_____	=_____
	An7	0	+	_____	=_____
	Hep2	4	-	_____	=_____
	Hep3	4	-	_____	=_____
	Hep4	4	-	_____	=_____
	Hep5	4	-	_____	=_____

Hep6	4	-	_____	=_____
HN2	4	-	_____	=_____
Hep8	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 18: _____
Divide by number of items answered: _____=**HC Subscale score**

To derive a FACT-Hep Trial Outcome Index (TOI):
***Score range*: 1-128**

_____+ _____+_____=_____=**FACT-Hep TOI**
(PWB score) (FWB score) (HCS score)

To derive a FACT-G total score:
***Score range*: 1-108**

_____+ _____+_____+_____=_____=**FACT-G Total score**
(PWB score) (SWB score) (EWB score) (FWB score)

To derive a FACT-Hep total score:
***Score range*: 1-180**

_____+ _____+_____+_____+_____=**FACT-Hep Total score**
(PWB score) (SWB score) (EWB score) (FWB score) (HCS score)

SAP Attachment 2. NCCN/FACT Hepatobiliary Symptom Index-18 (FHSI-18) Scoring Guidelines (Version 4)

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Scale	Item Code	Reverse item?		Item response	Item Score
FHSI-18	GP1	4	-	_____	=_____
Total	GP4	4	-	_____	=_____
	C2	4	-	_____	=_____
Score range: 0-72	HI7	4	-	_____	=_____
	CNS7	4	-	_____	=_____
	Hep2	4	-	_____	=_____
	GP6	4	-	_____	=_____
	Hep8	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GE1	4	-	_____	=_____
	GP5	4	-	_____	=_____
	AN7	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 18: _____

Divide by number of items answered: _____=**FHSI-18 score**

Subscale	Item Code	Reverse item?		Item response	Item Score
FHSI-DRS-P	GP1	4	-	_____	=_____
(Disease Related	GP4	4	-	_____	=_____
Symptoms-Physical)	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
Score range: 0-48	CNS7	4	-	_____	=_____
	Hep2	4	-	_____	=_____
	GP6	4	-	_____	=_____
	Hep8	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 12: _____

Divide by number of items answered: _____=**FHSI-DRS-P score**

FHSI-DRS-E	GE6	4	-	_____	=_____
(Disease Related	GE1	4	-	_____	=_____
Symptoms-Emotional)					

Score range: 0-8

Sum individual item scores: _____

Multiply by 2: _____

Divide by number of items answered: _____=**FHSI-DRS-E score**

FHSI-TSE	GP5	4	-	_____	=_____
(Treatment					
Side Effects)					

*Score range:*0-4 ***Sum individual item scores*: _____=FHSI-TSE score**

FHSI-F/WB	An7	0	+	_____	=_____
(Function/	GF3	0	+	_____	=_____
Well-Being)	GF7	**0**	+	_____	**=**_____

Score range: 0-12

***Sum individual item scores*: _____**

Multiply by 3: _____

***Divide by number of items answered*: _____=FHSI-F/WB score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

SAP Attachment 3. List of Protocol Violations for H9H-MC-JBAK

Below is a list of potential protocol violations for this study. However, not all protocol violations listed here will be determined through programming. Additional source for the identifying the remaining protocol violations will be through investigator logs or note to file.

General:

- Any protocol inclusion/exclusion criteria violations:
  - Protocol Sections 8.1 and 8.2.
  - If patient with "entry criteria not met" is marked at Visit 0 but patient moves on to Visit 1.

- Treatment compliance (see Protocol Section 9.9):
  - Patients who are significantly noncompliant <80% or >120% of expected study drug taken in a visit interval.
  - Patients who are consistently out of the compliance range may be discontinued.

- Failure to receive annual approval of the investigator for the conduct of the study (monitor to check).

Study specific:

- Prohibited concomitant therapy (See Protocol Section 9.8):
  - other anti-cancer therapy (chemotherapy, target therapy, radiotherapy, except palliative radiation to non-target lesions);
  - immunotherapy;
  - hormonal cancer therapy;
  - experimental/investigational medication;
  - Rapamycin analogues;
  - Increased immunosppressive therapy (Patients on maintenance immunosuppressive therapy after liver transplant are eligible;
  - At the discretion of the investigator, hormone-refractory prostate cancer patients who are stable on GnRH agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, and aromatase inhibitor) may have that treatment continued while they are enrolled in this study.

- Visit outside visit intervals specified in protocol:
  - If treatment is held for ≥ 24 weeks due to toxicity and the patient is not discontinued from the study.

- If the patient requires two dose de-escalations during the course of the study and is then re-escalated to the higher dose level.

- Study drug not omitted in the case of the following AEs which are considered at least possibly related to study treatment:
  - ANC <0.5 109/L for longer than 7 days, or ANC <1.0 109/L with a single temperature of >101°F/38.3°C or a sustained temperature of >100.4°F/38°C for more than 1 hour or platelet count <25 109/L.
  - CTCAE Grade 3 or 4 nonhematologic toxicity.
  - Study drug to be omitted from time of AE onset until adequate resolution (in the case of hematological toxicity, the definition of resolution is according to the investigator's opinion).

- Failure to perform PK collections.
  - Note: only collections "not done" are considered significant protocol violations.

- Failure to perform safety assessments.

- Failure to perform safety procedures or missing safety measurements per requirements in Study Schedule (Attachment JBAK.1 in Protocol).
  - Hematology/chemistry;
  - Chest CT/MRI 6 monthly;
  - ECGs;
  - ECHOs.
  - Note: only collections "not done" are considered significant protocol violations.

- Failure to perform efficacy procedures or missing efficacy measurements.
  - Tumor measurements:
    - Radiological Tumor Assessments (both baseline, post-baseline and post-baseline discontinuation from LY2157299 if applicable).
    - Palpable/visible (as applicable).
    - Note: only collections "not done" are considered significant protocol violations.

- Other protocol violations that result in study discontinuation as recorded on the CRF discontinuations page.

- Discontinuation criteria met but patient not removed from study (see Protocol Section 8.3.1)
  - If moderate or severe heart valve toxicities are observed, documented by echocardiography with Doppler and patient is not removed from study.

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