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Title Page

Protocol Title: An Open-Label Study of Regorafenib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma (HCC) after PD-1/PD-L1 Immune Checkpoint Inhibitors
Protocol Number: 21469

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Short Title: Pilot study of regorafenib plus pembrolizumab in advanced HCC patients who have been previously treated with PD-1/PD-L1 Immune Checkpoint Inhibitors

Sponsor Name: Non-US: Bayer AG

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

Table of Contents

Table of Figures

Version History

This Statistical Analysis Plan (SAP) for study 21469 is based on the protocol version 1.0 dated 20 AUG 2020 [1], the global amendment 1 to the protocol dated 08 JUN 2021 and the SAP version1.0

SAP Version	Date	Change	Rationale
1.0	23 NOV 2020	Not Applicable	Original version
2.0	12 JUN 2022	Adaptations for analysis of primary completion	Recruitment prematurely stopped, affecting analysis of primary completion

1. Introduction

This clinical study aims to evaluate the efficacy and safety of regorafenib in combination with pembrolizumab for the treatment of advanced Hepatocellular Carcinoma (HCC) in adult participants who have been previously treated with PD-1/PD-L1 immune checkpoint inhibitor in monotherapy or combinations regimens.

Treatment of advanced HCC remains an area of high unmet need in second line (2L).

Until 2020, only two oral multi-kinase inhibitors (MKIs), Sorafenib and Levantinib, were the approved first line (1L) systemic treatments for advanced HCC. Recently however, the Food and Drug Administration approved the combination of Atezolizumab, a PD-L1 checkpoint inhibitor, and Bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor, as a frontline treatment for patients with unresectable HCC and additional phase 2 and 3 clinical trials with immune checkpoint inhibitors in monotherapy and combination regimens also targeting the 1L setting are ongoing.

For 2L the best regimen is not well established, and all the current options were approved for the patients who were previously treated with MKI. Therefore, an ongoing high-unmet medical need remains for patients with unresectable HCC who progressed or did not tolerate these novel immunotherapy agents.

Regorafenib is a MKI and is the first systemic treatment shown to provide a survival benefit in HCC patients progressing on Sorafenib treatment [2] . Regorafenib is approved for 2L HCC treatment and has shown a comparable level of clinical benefit in the 2L setting as observed with Sorafenib as first-line therapy. Pembrolizumab, an anti-PD1 antibody, is approved for the treatment of patients with HCC previously treated with Sorafenib [3] . Targeting both the antiangiogenic and immune checkpoint pathways may provide synergistic anti-tumor activity.

This SAP further describes the interim and final analysis of the study outlined in the study protocol. Table, figure and listing specifications are contained in a separate document. The analysis of pharmacokinetic (PK) and biomarker data will not be described here but will be done in separate reports.

1.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the objective anti-tumor activity of Regorafenib in combination with Pembrolizumab as 2L treatment for advanced HCC	• Overall response rate (ORR) per RECIST 1.1 by central assessment
Secondary	
• To evaluate other measures of anti-tumor activity of Regorafenib in combination with Pembrolizumab as 2L treatment for advanced HCC	• Duration of response (DOR) per RECIST 1.1 by central assessment • ORR per RECIST 1.1 by investigator assessment • DOR per RECIST 1.1 by investigator assessment
• To evaluate safety and tolerability of Regorafenib in combination with Pembrolizumab	• Number of participants with adverse events (AEs) • Number of participants with serious AEs (SAEs) • Number of participants with safety-relevant changes in clinical parameters • Number of participants with dose modification (dose interruption, dose reduction, dose discontinuation)
Tertiary/Exploratory	
• To establish further exploratory indicators of efficacy of regorafenib in combination with pembrolizumab	• Disease control rate (DCR) per RECIST 1.1 by central assessment and investigator assessment • Progression free survival (PFS) as per RECIST 1.1 by central assessment and investigator assessment • Overall survival (OS) • ORR per HCC mRECIST and iRECIST by investigator assessment. • DOR per HCC mRECIST and iRECIST by investigator assessment;
• To evaluate the PK of regorafenib when concomitantly administered with pembrolizumab • To evaluate PK and immunogenicity of pembrolizumab when concomitantly administered with regorafenib	• Exposure of regorafenib and pembrolizumab, and incidence of anti-drug antibody for pembrolizumab
• To identify biomarkers in baseline tumor materials and/or blood that may associate with response	• Correlation of biomarkers before treatment with other study endpoints • Change from baseline in levels of

• To explore pharmacodynamic effects of regorafenib and pembrolizumab combination • To evaluate the PK/pharmacodynamic relationship for correlative biomarkers in blood such as peripheral lymphocytes, circulating proteins or nucleic acids (DNA or RNA), and/or tissues as well as measures of safety and/or efficacy • To further investigate the study intervention and similar drugs (i.e., mode-of-action-related effects and/or safety) and to further investigate pathomechanisms deemed relevant to cancer and associated health problems	biomarkers in blood or tumor • Retrospective exploratory analysis of the relationship between regorafenib exposure and biomarker, safety and/or efficacy measures • Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

1.2 Study Design

This is an open-label, uncontrolled Phase 2 trial for patients with advanced HCC consisting of an initial pilot phase and an expansion phase:

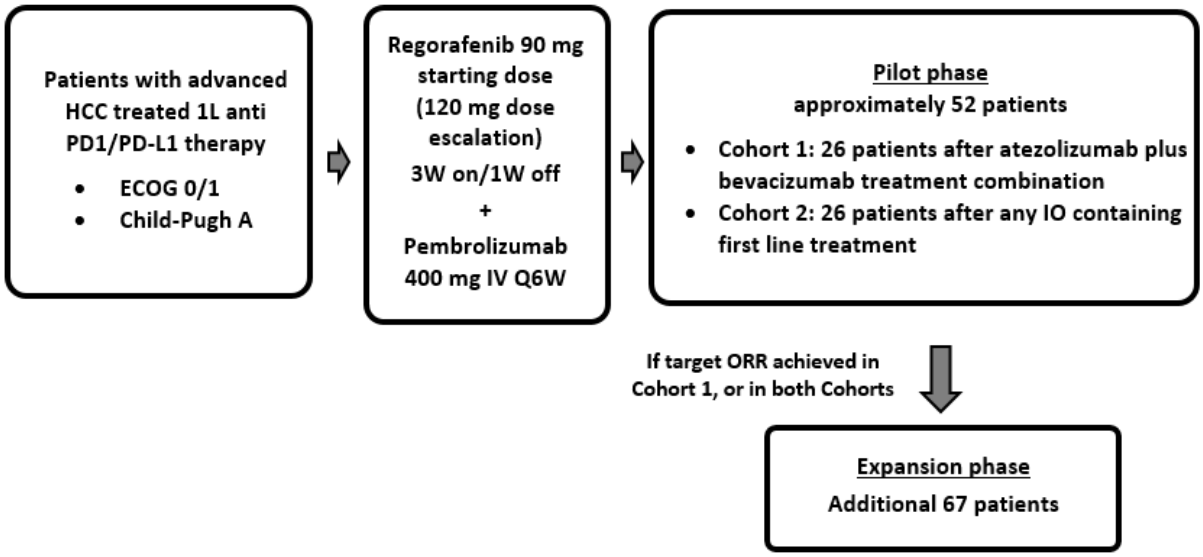
a) **Pilot phase:** Approximately 52 participants will be enrolled to receive Regorafenib in combination with Pembrolizumab
   - Cohort 1: 26 participants after Atezolizumab plus Bevacizumab treatment combination
   - Cohort 2: 26 participants after any immune oncology (IO) containing 1L treatment (excluding Atezolizumab plus Bevacizumab) in monotherapy or combination regimens

b) **Expansion phase:** If acceptable ORR is achieved in the pilot phase in cohort 1 or in the population of both cohorts, the study can be extended with approximately 67 new additional participants from the population which achieved the expected ORR (see Section 3).

An interim analysis for Cohort 1 of the pilot phase was performed, and due to the results recruitment was stopped. Therefore, it was decided to proceed with the analysis of primary completion.

The study design is also described in Figure 1–1.

Figure 1–1: Study design



Screening

The start of the screening phase is defined by signing of the ICF. Participants will be screened for eligibility up to 28 days immediately prior to W1D1.

Intervention Period

All participants will be treated with Regorafenib at a starting dose of 90 mg QD orally for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off) and 400 mg Pembrolizumab intravenous (IV) Q6W. If the starting dose of 90 mg Regorafenib daily is well tolerated, the dose should be escalated to the established maximum tolerated dose for this treatment combination: 120 mg, starting after the first 4-week cycle of Regorafenib. Rules for dose reductions and interruptions are described in the protocol.

During the study, participants will undergo evaluations for safety, efficacy, PK, and tissue and blood/plasma for biomarker will be collected.

Participants will continue to receive study intervention until disease progression as defined by RECIST 1.1, unacceptable toxicity, consent withdrawal, withdrawal from the study at the discretion of the investigator or his/her designated associate(s), or until any other withdrawal criteria are met. Treatment beyond radiological progression is possible if the participant is still benefiting from treatment.

Participants who complete 18 infusions of Pembrolizumab need to discontinue treatment with Pembrolizumab. Regorafenib treatment can be continued beyond 2 years until discontinuation criteria are met. Treatment with individual drugs (Regorafenib or Pembrolizumab) may continue on schedule even if the other drug is interrupted or permanently discontinued due to toxicity.

Active Follow-up

A mandatory safety follow-up visit will take place 30 days (window of +7 days) after the last administration of the last study intervention (Regorafenib and/or Pembrolizumab).

If applicable, an additional safety follow-up must occur 90 days (window of +7 days) after the last Pembrolizumab administration.

Participants who discontinue study intervention due to radiologically confirmed progressive disease (PD) will complete the mandatory safety follow-up visits.

Participants who discontinue from the study for any reason other than PD (or death, withdrawal of consent, or lost to follow-up) will be followed for progression during the active follow-up period. During the active follow-up period, computed tomography / magnetic resonance imaging evaluations will be performed at efficacy follow-up visits. In addition, study intervention-related toxicity/AE, information about survival status, and subsequent anti-cancer therapy will be followed up until completion of the active follow-up.

Active follow-up will be terminated by radiological PD, or the start of a new anti-cancer treatment, or death, or withdrawal of consent for further participation, or lost to follow-up.

Long-term follow-up

All surviving participants will enter the long-term follow-up period after discontinuing from the active follow-up period except for participants who explicitly withdraw consent or are lost to follow-up.

Participants will be followed for OS and subsequent anti-cancer therapy at 3-month intervals (±14 days) until the end of the study, withdrawal of consent, lost to follow-up, or death, whichever comes first. Participants may be contacted at additional times throughout the course of the study in order to collect survival data to ensure that long-term follow-up data is current.

2. Statistical Hypotheses

There will be no statistical hypothesis testing done in the pilot phase of the study.

The primary hypotheses to be tested in the expansion phase of the study is

$$H_0: ORR_{Combination} \leq 20\% \text{ vs. } H_1: ORR_{Combination} > 20\%$$

The primary hypothesis will be tested by an exact binomial test. The significance level will be a 1-sided alpha of 2.5%.

3. Sample Size Determination

It was expected that approximately 170 participants will be screened to achieve the 119 evaluable participants for both study phases combined.

Pilot phase: A total of approximately 52 participants will be enrolled to receive Regorafenib in combination with Pembrolizumab divided in two cohorts: 26 of them after Atezolizumab plus Bevacizumab treatment combination (cohort 1); and 26 after any IO containing 1L treatment (cohort 2) in monotherapy or in combination, excluding Atezolizumab plus Bevacizumab treatment.

Expansion phase: If the target ORR is achieved in the pilot phase, the study can enroll approximately 67 new additional participants. These additional participants can be from cohort 1 (i.e., patients progressing on atezolizumab plus bevacizumab combination) or the combined population from cohort 1 plus cohort 2 (i.e., patients progressing on any immune checkpoint inhibitor), depending on which cohorts meet the response rate criteria for expansion.

2 scenarios should be considered depending on the pilot phase results.

- **Scenario 1**: if in the pilot phase at least 8 responders out of the 26 treated in cohort 1 are observed
- **Scenario 2**: if in the pilot phase at least 8 responders in each cohort are observed.

Due to the recruitment stop only 95 patients have been treated (43 out of 67 planned participants for expansion phase were treated) Therefore, the sample size is not sufficient to fulfill the statistical quality criteria planned for each of the two scenarios above (1-sided alpha of 0.025, conditional power of 0.95 to rule out an ORR of ≤ 20%). The results will be provided therefore in an exploratory manner.

4. Analysis Sets

The following analysis sets are defined:

Population	Description
Enrolled	All participants who sign the informed consent form (ICF)
Full Analysis Set	All participants who take at least 1 dose of study intervention will be included in the efficacy and safety evaluation.

All analyses will be performed on the Full Analysis Set.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

5. Statistical Analyses

5.1 General Considerations

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

All analyses will be conducted at one-sided type-I error level of 2.5% or two-sided type-I error level of 5% respectively. A one-sided exact binomial test will be conducted in the expansion phase to analyze the primary endpoint. 95% Confidence intervals will be presented for selected variables.

The analysis will be done by cohort. The cohorts will be determined by the first line treatment (1L): Cohort 1: (1L: Atezolizumab + Bevacizumab) and Cohort 2: (1L: Any other IO containing treatment)

The analysis will be based on the Global Standard tables version 4.1, default and optional, dated 17 NOV 2020 [4], [5], the Oncology Standard tables, version 3.6, dated 29 MAR 2018 [6] and the Standard Catalog of Tables/Listings Reporting Data Related to COVID-19 Pandemic, version 2.0, dated 09 MAR 2021 [7]. The listings are based on the Global Standard listings version 4.0, dated 08 JUL 2020 [8].

Dropouts

All participants who discontinue the study after enrollment for any reason except death before the protocol defined end are considered dropouts. Participants withdrawn from study treatment will not be replaced. Data of dropouts will be used up to the point of study discontinuation.

Handling of missing data

All missing or partial data will be presented in the participant data listing as they are recorded on the Case Report Form (CRF).
No imputation for missing values will be done, except for dates necessary for the calculation of time to event (TTE)-variables.

If a date is incomplete (e.g., only year and month of date of tumor assessment or date of death is available), then day 15 of the month will be used for the calculation of, for example, OS and PFS.

If the actual scan date of the radiological progression is missing and radiological or clinical progression has been documented based on criteria specified in the protocol, the scheduled scan date will be used to calculate the time to progression.

Missing or unevaluable tumor assessments, including scheduled assessments that were not done and incomplete assessments that did not result in an unambiguous tumor response evaluation according to RECIST 1.1, will not be used in the calculation of derived efficacy variables related to tumor assessments unless a new lesion occurred or the lesions that were evaluated already showed PD. No imputation will be performed for missing lesion assessments and tumor response evaluation.

Repeated Measurements

If multiple measurements for a planned timepoint before study intervention administration are available, the last value (i.e., of the measurement closest to the study intervention administration) will be used for the calculation of descriptive statistics.

If multiple measurements for a planned timepoint after study intervention administration are available, the first value (i.e., of the planned measurement) will be used for the calculation of descriptive statistics.

Baseline

Unless specified otherwise, baseline is the last pre-dose measurement performed prior to the first administration of the first study intervention.

Data rules

All time to event (TTE) variables will be calculated using the formula

$$TTE = end\ date - start\ date$$

For participants with no post-baseline data or deaths on the day of first study treatment, TTE will be set to 1.

For all other variables, duration in days will be calculated using the formula

$$duration = (end\ date - start\ date) + 1$$

When data are collected in days, duration in months will be calculated as [number of days / 30.44].

Regions

The following regions are defined in this study:

- Asia (India, Japan, South Korea)
- Western Europe and Israel (France, Germany, Israel, Italy, Spain)
- North America (United States of America)

5.2 Participant Dispositions

The number of participants enrolled and included in each of the analysis populations will be tabulated overall, by region, country and center. A summary table will also be presented for the number of participants enrolled and the number and percentage of participants in each of the defined populations. The reasons for participants excluded from each of the participants populations will also be tabulated.

The number and percentage of participants who started screening, as well as the number of participants who prematurely discontinued screening will be summarized. Screening failures will be listed with primary reason.

The number and percentage of participants who started and discontinued treatment, active follow-up and long-term follow-up will be given as well as the reason for discontinuation.

Protocol deviations will be summarized by country and trial unit.

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of Endpoint(s)

The primary endpoint of this study is ORR per RECIST 1.1 by central assessment and will be analyzed after all participants meet the criteria for primary completion.

Primary completion is reached when the last participant

- has completed at least two post-baseline scans; or
- has been followed for approximately 14 weeks from the first study treatment dose; or
- has discontinued before due to progression or any other reason.

The database will then be locked for analysis.

ORR is defined as the proportion of participants with best overall response of confirmed complete response (CR) or partial response (PR). Participants for whom best overall tumor response is not CR or PR, as well as participants without any post-baseline tumor assessment will be considered non-responders.

5.3.2 Main Analytical Approach

The primary endpoint will be analyzed using a one-sided exact binomial test to investigate the hypothesis stated in Section 2. The historic response rate is assumed to be 20%.

The result of the exact binomial test will be presented in a table, giving the response rate, the number of responders observed, the test-statistic and the p-value.

Further analysis of the primary endpoint includes frequency tables (with the ORR table also including all “Best overall response” categories) as well as corresponding 95% two-sided Clopper-Pearson confidence intervals.

A listing of best overall response by central and investigator assessment for all participants will be provided.

5.3.3 Sensitivity Analyses

Not applicable.

5.3.4 Supplementary Analyses

Not applicable.

5.4 Secondary Endpoint(s) Analysis

5.4.1 Key/Confirmatory Secondary Endpoint(s)

Secondary efficacy endpoints in this study are:

- DOR per RECIST 1.1 by central assessment and by investigator assessment
- ORR per RECIST 1.1 by investigator assessment

Secondary safety endpoints in this study are:

- Number of participants with AEs
- Number of participants with SAEs
- Number of participants with safety-relevant changes in clinical parameters
- Number of participants with dose modification (dose interruption, dose reduction, dose discontinuation)

5.4.1.1 Definition of Endpoint(s)

For the calculation of DOR and PFS according to all RECIST versions the administration of palliative therapy to a symptomatic solitary lesion or to the brain will be considered as clinical progression.

DOR based on RECIST 1.1

DOR (for PR and CR) is defined as the time (in days and months) from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death occurs before progression is documented). DOR will be defined for confirmed responders only, i.e., participants with a CR or PR. The actual dates the tumor scans were performed will be used for this calculation.

DOR for participants without radiological progression, without administration of palliative radiation counting as progression, or without death will be censored at their last day of tumor evaluation. If the documentation of progression occurs after 2 consecutive missed or non-evaluable radiological assessments DOR will be censored at the date of the last evaluable scan before the 2 missing radiological assessments. If participant receives subsequent anti-cancer treatment, he will be censored on the last tumor assessment prior to the subsequent anti-cancer treatment.
Scans collected after the first PD will not be assessed for response by RECIST1.1.

ORR based on RECIST 1.1

For the definition of ORR refer to Section 5.3.1.

Secondary safety endpoints

An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

An AE is considered as treatment-emergent (TEAE) if it arises or worsens after start of first study intervention administration until 30 days after administration of any study intervention.

According to the protocol (See section 8.3.1 of the final study protocol) AE and SAE will be collected from the signing of the ICF until 30 days after last dose of study intervention. In addition, SAEs will be collected for 90 days after the last dose of Pembrolizumab, unless a new anti-cancer therapy has been initiated.

AE of special interest (AESI) in this study include:

- Pembrolizumab overdose (any dose of 1000 mg or greater), that is not associated with clinical symptoms or abnormal laboratory results.
- Hepatic events of clinical interest defined as:
    - Alanine aminotransferase (ALT):
        - ALT ≥5 × upper limit of normal (ULN) if baseline ALT <2 x ULN
        - ALT >3 × baseline level if baseline ALT ≥2 x ULN
        - Any ALT >500U/L
    - Any t-bilirubin >3.0 mg/dL
    - Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
        - New onset of clinically detectable ascites requiring intervention for >3 days
        - Hepatic encephalopathy

All AEs, whether considered drug-related or not, will be reported on the CRF with diagnosis, start/stop dates, dates of any grade change, action taken, whether treatment was discontinued, any corrective measures taken, and outcome. For all events, the relationship to treatment and the severity of the event will be determined by the Investigator. AEs will be classified the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and coded using the National Cancer Institute (NCI) Common Terminology Criteria Adverse Event (CTCAE), version 5.0.

For further definitions of the terms AE, SAE, seriousness, intensity, causal relationship with treatment, causal relationship to protocol-required procedures, action taken, and outcome refer to the respective section of the protocol.

5.4.1.2 Main Analytical Approach

DOR based on RECIST 1.1

DOR will be summarized descriptively using summary statistics, Kaplan Meier methodology and plots, as well as median estimates based on Greenwood's formula, including 95% two-sided confidence interval.

ORR based on RECIST 1.1

ORR will be analyzed using frequency tables, point estimates as well as 95% two-sided Clopper-Pearson confidence intervals.

A listing of best overall response by investigator assessment for all participants will be provided.

Safety analysis

AEs will be classified using the NCI CTCAE grading system, version 5.0, and the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology. A listing of Pre-treatment AEs will be provided. Descriptive summary tables will be presented for the following:

- TEAEs by worst CTCAE grade
- TEAEs with grades 3, 4 or 5
- TEAEs related to any study interventions
- TEAESI
- TEAEs resulting in the discontinuation (of any study intervention; of Regorafenib; of Pembrolizumab; and of both study interventions)
- TEAEs resulting in dose reduction of Regorafenib
- TEAEs resulting in dose interruption (of any study intervention; of Regorafenib; of Pembrolizumab; and of both study interventions)

TEAEs by worst CTCAE grade will also be analyzed for the following subgroups:

- Sex (male vs. female)
- Age (<65 years vs. ≥65 years)
- Region (Asia vs. Western Europe and Israel vs. North America)
- BCLC stage (BCLC stage B vs. BCLC stage C)

A subgroup will only be analyzed if there are more than 5 participants included.

SAEs will be classified using the most recent version of the NCI CTCAE grading system, version 5.0, and the most recent version of the MedDRA terminology.

The following descriptive summary tables will be presented:

- Treatment-emergent SAEs
- Treatment-emergent SAEs with grades 3, 4 or 5
- Treatment-emergent SAEs related to any study interventions
- SAEs related to any study intervention after 30 days post permanent treatment discontinuation

The incidence of deaths in the study will be summarized by cause of death. All deaths within start of treatment and 30 days of last dose of study medication and between 30 days post permanent treatment discontinuation and 90 days after last infusion of Pembrolizumab will be listed by participant with last dose, start and stop date of study medication, date of death, and

cause of death. All deaths before treatment and beyond 30 days after last dose of study intervention will be displayed in separate listings.

5.4.1.3 Sensitivity Analyses

Not applicable.

5.4.1.4 Supplementary Analyses

Not applicable.

5.4.2 Supportive Secondary Endpoint(s)

Not applicable.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

Exploratory efficacy endpoints of this study are:

- DCR per RECIST 1.1 by central assessment and investigator assessment
- PFS as per RECIST 1.1 by central assessment and investigator assessment
- OS
- ORR per HCC mRECIST and iRECIST by investigator assessment.
- DOR per HCC mRECIST and iRECIST by investigator assessment.

Exploratory PK and other biomarker endpoints of this study will not be detailed in this SAP; separate reports will be provided for these endpoints.

5.5.1 Definition of Endpoint(s)

DCR based on RECIST 1.1

DCR is defined as the proportion of participants with best overall response of CR, PR or SD. Participants for whom best overall tumor response is not CR, PR or SD, as well as participants without any post-baseline tumor assessment will not be considered.

PFS based on RECIST 1.1

PFS is defined as the time (in days and months) from start of treatment to date of progression or death due to any cause. Besides radiological progression, administration of palliative radiation therapy to a symptomatic solitary lesion or to the brain will be considered clinical progression. Participants without progression or death at the time of analysis will be censored at the date of last evaluable radiological tumor assessment without evidence of progression. PFS for participants without radiological progression or without administration of palliative radiation counting as progression or without death will be censored at their last day of tumor evaluation. PFS for participants who discontinued the study before any post-baseline tumor assessment and without death will be censored at day 1.
If the documentation of progression occurs after 2 consecutive missed or non-evaluable radiological assessments, PFS will be censored at the date of the last evaluable scan before the 2 missing radiological assessments.
Participant who receive subsequent anti-cancer treatment will be censored at the last date of tumor assessment before the subsequent anti-cancer treatment.

OS

OS is defined as the time (in days and months) from start of treatment to death due to any cause. Participants alive at the time of analysis will be censored at the last known alive date (LKAD) or the cut-off date whichever comes first.

For participants lost to follow-up and without contact after start of study drug administration the OS will be censored at Day 1.

The LKAD is derived from the main data sources. The last available date across all selected data panels listed below will be picked as the LKAD by participant. Information from selected data, i.e., visit dates, exposure information, demographics, laboratory measurements, tumor assessment dates, survival status date will be used to determine survival status. Within all the dates from the selected data panels, the latest available date will be identified as the LKAD for each participant.

ORR per HCC mRECIST

For the definition of ORR refer to Section 5.3.1.

iORR per iRECIST

iORR is defined as the proportion of participants with best overall response of confirmed iCR or iPR. Participants for whom best overall tumor response is not iCR or iPR, as well as participants without any post-baseline tumor assessment will be considered non-responders.

DOR per HCC mRECIST

For the definition of DOR refer to Section 5.4.1.1.

iDOR per iRECIST

iDOR is defined as the time (in days and months) from the date of the first response iCR /iPR (whichever is first recorded) to the date of death or disease progression (iUPD, later confirmed as iCPD), whichever comes first. iDOR is only defined for participants who have best overall response of iCR or iPR. If a participant has iPR (#1) followed by an iUPD (#1) which is not confirmed, then an iPR (#2) followed by an iUPD (#2) which is confirmed at the next assessment, then the iDOR is from iPR (#1) up to iUPD2. This rule will be described more detailed in the TLF specifications. The actual dates the tumor scans were performed will be used for this calculation.

iDOR for participants without radiological progression, without administration of palliative radiation counting as progression, or without death will be censored at their last day of tumor evaluation. If the documentation of progression occurs after 2 consecutive missed or non-evaluable radiological assessments iDOR will be censored at the date of the last evaluable scan before the 2 missing radiological assessments. Participants who receive subsequent anti-cancer treatment will be censored at the last date of tumor assessment before the subsequent anti-cancer treatment.

5.5.2 Main Analytical Approach

Exploratory efficacy endpoints

All exploratory efficacy endpoints will be analyzed by means of descriptive statistics using frequency tables for response endpoints and summary statistics for continuous endpoints. TTE variables will be summarized descriptively using summary statistics, Kaplan Meier methodology and plots, as well as median estimates based on Greenwood's formula, including 95% two-sided confidence interval.

PFS rates and OS rates will be given for the time points 6, 12, 18 and 24 months, if at least one participant has reached this time point.

PD-L1 expression

PD-L1 expression data will be analyzed under separate cover.

5.6 Other Safety Analyses

5.6.1 Extent of Exposure

The treatment duration, the number of applications and the dosages of the study interventions, as well as the dose modifications will be summarized using descriptive statistics and frequency tables. Additionally, a swimmer plot for the time on study treatment will be provided.

The dose of Pembrolizumab will be calculated using the formula:

$$dose[mg] = \frac{actual\ dose\ per\ administration[mg] \times volume\ actually\ administered[ml]}{volume\ prior\ to\ infusion[ml]}$$

The actual dose per day for both study interventions will be calculated using the formula:

$$total\ daily\ dose[mg] = \frac{total\ amount\ of\ dose[mg]}{days\ on\ treatment}$$

5.6.2 Adverse Events

AEs are described in Section 5.4.

5.6.3 Additional Safety Assessments

Clinical laboratory

Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) will be presented for clinical laboratory tests (hematology, clinical biochemistry and urinalysis) and their changes from baseline (including baseline value).

Laboratory abnormalities for available results of laboratory tests based on the categorization provided by CTCAE v. 5.0 will be presented.

Frequency and incidence rates will be provided. Frequency tables will also be provided for changes in severity from baseline to worst value post-baseline. The following summaries will be generated separately for hematology and biochemistry:

- Incidence of abnormal hematological and biochemical laboratory values during treatment period based on the categorization provided by CTCAE 5.0
- Worst change from baseline of abnormal hematological and biochemical laboratory values during treatment period using the categorization provided by CTCAE 5.0.

The last non-missing value before or (without timing of information) on the first day of study drug will be retained as "baseline" data.
Unscheduled laboratory data will not be included in the summary tables but listed in Section 16 of the clinical study report.

Electrocardiogram (ECG)

The number and percent of participants with new clinically significant abnormalities on ECGs per the investigator's assessment at post-baseline time points will be summarized.

Unscheduled ECG data will be listed only.

Eastern Cooperative Oncology Group (ECOG) status

The ECOG performance status will be summarized by descriptive statistics tables over time, including change from baseline.

Vital signs

Vital signs will be tabulated and summarized by visit and changes from baseline using descriptive statistics, as appropriate.

Unscheduled vital signs data will be listed only.

Pregnancies

Pregnancy tests will be summarized by visit. A listing of pregnancy tests and pregnancies will be provided.

5.7 Other Analyses

5.7.1 Other Variables and/or Parameters

Time to best overall response

Time to best overall response is defined as the time (in days and months) from start of treatment until the date of the tumor assessment in which the best overall response (CR, PR, SD, or PD) was found. Participants with no post-baseline assessments will be censored on day 1.
The analysis will be done based on RECIST by central and investigator assessment.

Time to best overall response will be listed. A swimmer plot for best overall response will be provided.

Time to response

Time to response is defined as the time (in days and months) from start of treatment until date of the first tumor assessment in which a response (CR or PR) was found. Time to response will be only defined for participants with CR and PR. The analysis will be done based on RECIST 1.1 by central and investigator assessment.

Time to response will be summarized using descriptive statistics.

Percentage reduction from baseline in target lesion

Percentage reduction from baseline will be calculated using the formula

$$Reduction\ from\ baseline[\%] = \frac{tumor\ size\ at\ baseline[cm] - tumor\ size[cm]}{tumor\ size\ at\ baseline[cm]} \times 100$$

Percentage reduction from baseline in target lesion will be analyzed separately using central and investigator assessment. A spider plot will be provided.

Maximum percentage reduction from baseline in target lesion

Best percentage reduction from baseline in target lesion is defined as the maximum of the percentage reduction from baseline in target lesion from all tumor assessments. The analysis will be conducted separately using central and investigator assessment.

Best percentage reduction from baseline will be listed. A waterfall plot will be provided.
In the waterfall plot showing the best percentage reduction for central assessment adjudicated values and values without adjudication flag will be regarded. Values with adjudication flag=N will be disregarded.

5.7.2 Subgroup Analyses

Not applicable.

5.8 Interim Analyses

An interim analysis was planned to determine the participant population (participants after treatment with atezolizumab in combination with bevacizumab, or after any 1L treatment) for the expansion phase of the study. Due to recruitment stop it was decided to continue with the analysis of primary completion.

5.8.1 Data Monitoring Committee or Other Review Board

Not applicable.

6. Supporting Documentation

6.1 Appendix 1: List of Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria Adverse Event
DCR	Disease control rate
DNA	Desoxyribose Nucleic Acid
DOR	Duration of response
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
ICF	Informed consent form
IO	Immune oncology
IV	Intravenous
LKAD	Last Known Alive Date
MedDRA	Medical Dictionary for Regulatory Activities
MKI	Multi-kinase inhibitors
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
Q6W	Every 6 weeks
QD	Once per day (quaque die)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribose Nucleic Acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
TEAE	Treatment-emergent adverse event
TTE	Time to event
ULN	Upper Limit Normal

6.2 Appendix 2: Changes to Protocol-planned Analyses

Not applicable.

6.3 Appendix 3: Baseline Population Characteristics

The following baseline values and demographic characteristics are documented in the study:

- Date of birth (year, age) if allowed according to local law
- Gender
- Race, if legally allowed
- Ethnicity, if legally allowed
- Weight
- Height
- Childbearing status (if applicable)
- Alcohol consumption
- Smoking status
- Caffeine consumption

All baseline and demographic values will be listed and summarized by descriptive tables (frequency tables or summary statistics).

Medical history

Medical history findings will be collected as available to the investigator if:

- they start before signing of informed consent; and

- they are considered relevant for the participant's study eligibility.

The data will be coded using the most recent version of MedDRA. Summary statistics (frequency and percentage) will be provided by system organ class and high-level term.

Medications

The dictionary used for coding medications is the WHO Drug dictionary. Prior medication is defined as all medication started before treatment start. Concomitant medication is all medication taken after treatment start and before end of treatment. Post-treatment medication is all medication taken after end of treatment. Systemic anti-cancer therapies will be displayed by frequency of participants for each drug, (prior and during follow-up). Diagnostic and therapeutic procedures will be tabulated by frequency of participants by procedure (prior, concurrent and during follow-up), other concomitant medications will be presented by frequency of participants for each drug category.

Baseline cancer characteristics

Baseline cancer characteristics including cancer type, location of the primary tumor, histology, tumor stage at study entry, date of diagnosis of first metastasis, presence of metastases (e.g., liver, lung, brain or bone), tumor mutational burden, microsatellite instability status, and PD-L1 expression (if available), time since progression, prior cancer therapies and procedures will be collected and summarized in descriptive tables.

6.4 Appendix 4: COVID-19 Related Findings

All COVID-19 related findings will be presented as a separate listing and in applicable tables (e.g., protocol deviations) as separate findings.

7. References

[1] Clinical Study Protocol No. 734506 / 21469, Version 1.0, dated 20 AUG 2020
[2] Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet. 2017 Jan 7; 389(10064):56-66
[3] Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial [published correction appears in Lancet Oncol. 2018 Sep;19(9):e440], Lancet Oncol. 2018 Jul;19(7):940-52.
[4] Global Standard Tables catalog - DEFAULT Version 4.1, dated 17 NOVJUL 2020
[5] Global Standard Tables catalog - OPTIONAL, Version 4.0, dated 08 JUL 2019
[6] Oncology Standard Tables, Version 3.6, dated 29 MAR 2018
[7] Standard Catalog of Tables/Listings Reporting Data Related to COVID-19 Pandemic, Version 2.0, dated 09 MAR 2021
[8] Global Standard Listings, Version 4.0, dated 08 JUL 2020