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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
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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

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The approval of the Statistical Analysis Plan is documented in a separate signature document.

Table of Contents

Title Page **1**

Table of Contents **2**

Version History **3**

1. Introduction **3**
1.1 Objectives and Endpoints 4
1.2 Study Design 4

2. Statistical Hypotheses **4**

3. Sample Size Determination **4**

4. Analysis Sets **4**

5. Statistical Analyses **4**
5.1 General Considerations 4
5.2 Participant Dispositions 4
5.3 Primary Endpoint(s) Analysis 4
5.3.1 Definition of Endpoint(s) 4
5.3.2 Main Analytical Approach 5
5.3.3 Sensitivity Analyses 5
5.3.4 Supplementary Analyses 5
5.4 Secondary Endpoint(s) Analysis 5
5.4.1 Key/Confirmatory Secondary Endpoint(s) 5
5.4.2 Supportive Secondary Endpoint(s) 6
5.5 Tertiary/Exploratory Endpoint(s) Analysis 6
5.5.1 Definition of Endpoint(s) 6
5.5.2 Main Analytical Approach 6
5.6 Other Safety Analyses 6
5.6.1 Extent of Exposure 6
5.6.2 Adverse Events 7
5.6.3 Additional Safety Assessments 7
5.7 Other Analyses 7
5.7.1 Other Variables and/or Parameters 7
5.7.2 Subgroup Analyses 7
5.8 Interim Analyses 7
5.8.1 Data Monitoring Committee or Other Review Board 7

6. Supporting Documentation **7**
6.1 Appendix 1: List of Abbreviations 7
6.2 Appendix 2: Changes to Protocol-planned Analyses 8
6.3 Appendix 3: Baseline Population Characteristics 8
6.4 Appendix 4: COVID-19 Related Findings 8

7. References **8**

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 version 1.0 and 2.0

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
3.0	31 OCT 2023	Adaptations for final analysis	

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. In May 2020, 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 final analysis of the study outlined in the study protocol. Table, figure and listing specifications are contained in a separate document.

1.1 Objectives and Endpoints

Refer to main SAP v2.0, dated 12 JUN 2022

1.2 Study Design

Refer to main SAP v2.0, dated 12 JUN 2022

2. Statistical Hypotheses

Refer to main SAP v2.0, dated 12 JUN 2022.

3. Sample Size Determination

Refer to main SAP v2.0, dated 12 JUN 2022.

4. Analysis Sets

Refer to main SAP v2.0, dated 12 JUN 2022.

5. Statistical Analyses

5.1 General Considerations

Refer to main SAP v2.0, dated 12JUN 2022.

5.2 Participant Dispositions

The number of participants enrolled and included in each of the analysis populations will be tabulated. The reasons for participants excluded from each of the participants populations will also be tabulated.

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 was first analyzed after all participants met the criteria for primary completion.

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

Refer to main SAP v2.0, dated 12JUN 2022.

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)

Refer to main SAP v2.0, dated 12JUN 2022.

5.4.1.1 Definition of Endpoint(s)

Refer to main SAP v2.0, dated 12JUN 2022.

5.4.1.2 Main Analytical Approach

DOR based on RECIST 1.1

DOR will be listed.

ORR based on RECIST 1.1

Refer to main SAP v2.0, dated 12JUN 2022.

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 (all and occurring in at least 5% of participants)
- 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 interruption (of any study intervention; of Regorafenib; of Pembrolizumab; and of both study interventions)

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 related to any study interventions

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

Refer to main SAP v2.0, dated 12JUN 2022.

5.5.1 Definition of Endpoint(s)

Refer to main SAP v2.0, dated 12JUN 2022.

5.5.2 Main Analytical Approach

Exploratory efficacy endpoints

Overall survival (OS) and progression free survival (PFS) 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 intervals.

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.

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

Refer to main SAP v2.0, dated 12JUN 2022.

5.7 Other Analyses

5.7.1 Other Variables and/or Parameters

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

Not applicable.

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
CR	Complete response
CTCAE	Common Terminology Criteria Adverse Event
DOR	Duration of response
HCC	Hepatocellular carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MKI	Multi-kinase inhibitors
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TTE	Time to event

6.2 Appendix 2: Changes to Protocol-planned Analyses

Not applicable.

6.3 Appendix 3: Baseline Population Characteristics

Refer to main SAP v2.0 dated 12 JUN 2022.

6.4 Appendix 4: COVID-19 Related Findings

Refer to main SAP v2.0 dated 12 JUN 2022.

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.

For further references refer to main SAP v2.0, dated 12 JUN 2022.