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Title Page

Protocol Title: A Multi-indication, Single-treatment Arm, Open-label Phase 2 Study of Regorafenib and Nivolumab in Combination in Patients with Recurrent or Metastatic Solid Tumors
Protocol Number: 21136 Original Protocol

Compound Number: BAY 73-4506

Short Title: Multi-indication study of regorafenib plus nivolumab for recurrent or metastatic solid tumors

Sponsor Name: Non-US: Bayer AG
US territory: Bayer HealthCare Pharmaceuticals Inc.

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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.

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Version History

This statistical analysis plan (SAP) version 3.0 dated 12 MAR 2024 describes the analyses and data presentations for final clinical study report addendum when all participants have discontinued the trial. This SAP is based on the SAP version 2.0 dated 25 JAN 2023 and on 21136 integrated protocol amendment 1 dated 27 JAN 2021.

SAP Version	*Date*	*Change*	*Rationale*
1.0	*08 JAN 2021*	*Not Applicable*	*Original version*
2.0	*25 JAN 2023*	*Not Applicable*	*Addendum to SAP 1.0 dated 08 JAN 2021 for primary completion analysis*
3.0	*12 MAR 2024*	*Adaptations for final analysis*	

1. Introduction

Study 21136 is a multi-indication, single-treatment arm, open-label Phase 2 study of regorafenib in combination with nivolumab in patients with recurrent or metastatic solid tumors.

This study contains six cohorts:

- Head and Neck Squamous Cell Carcinoma (HNSCC) Immune Oncology (IO) naïve,
- Head and Neck Squamous Cell Carcinoma (HNSCC) Immune Oncology (IO) treated,
- Esophageal Squamous Cell Carcinoma (ESCC),
- Pancreatic ductal adenocarcinoma (PDAC),
- Biliary Tract Carcinoma (BTC),
- Glioblastoma Multiforme / Anaplastic Astrocytoma (GBM/AA).

The SAP describes the final analyses and data presentations at the time all participants had discontinued the trial.

Table, figure and listing specifications are contained in a separate document.

1.1 Objectives and Endpoints

Refer to main SAP v2.0, dated 25 JAN 2023.

1.2 Study Design

Refer to main SAP v2.0, dated 25 JAN 2023.

2. Statistical Hypotheses

Refer to main SAP v2.0, dated 25 JAN 2023.

3. Sample Size Determination

Refer to main SAP v2.0, dated 25 JAN 2023.

4. Analysis Sets

Refer to main SAP v2.0, dated 25 JAN 2023.

5. Statistical Analyses

5.1 General Considerations

Refer to main SAP v2.0, dated 25 JAN 2023.

5.2 Participant Dispositions

The number of participants enrolled and included in each of the analysis populations will be tabulated overall, by 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 (i.e. FAS, SAF…).

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.

Demographic, baseline characteristics, prior medications and medical history analyses will not be presented in the CSR addendum.

Protocol deviations analyses are defined under Section 6.4.

Concomitant medications, follow-up medications analyses are defined under Section 6.6.

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of Endpoint(s)

The primary endpoint of this study is ORR.

Refer to main SAP v2.0, dated 25 JAN 2023.

5.3.2 Main Analytical Approach

ORR will be displayed using frequency counts and percentages as well as 80% two-sided Clopper-Pearson confidence intervals, by cohort.

Summary statistics will be displayed for all best response categories: CR, PR, stable disease (SD), progression disease (PD) by radiographic imaging and PD by clinical judgment. Frequency counts and percentages with 80% two-sided Clopper-Pearson CI will be displayed.

Following analyses will be created per cohort:

-Swimmer plot of overall response and waterfall diagram of best overall response with maximum percentage reduction in target lesion from baseline up to the time of the first progression per RECIST 1.1 for solid tumors cohorts and per RANO for GBM/AA cohort.

-Change in sum of target lesions from baseline per RECIST1.1 over time by individual participants for solid tumor cohorts (except GBM/AA cohort) presented by a spider plot.

-Change in the sum of products of perpendicular diameters of target lesions from baseline over time per RANO by individual participants for GBM/AA cohort presented by a spider plot.

5.3.3 Sensitivity Analyses

No sensitivity analysis is planned.

5.3.4 Supplementary Analyses

No supplementary analysis is planned.

5.4 Secondary Endpoint(s) Analysis

5.4.1 Key/Confirmatory Secondary Endpoint(s)

Refer to main SAP v2.0, dated 25 JAN 2023.

5.4.1.1 Definition of Endpoint(s)

Refer to main SAP v2.0, dated 25 JAN 2023.

5.4.1.2 Main Analytical Approach

DOR (duration of response), DCR (disease control rate), PFS (progression free survival) and OS (overall survival) will be presented, following same analyses as those at primary completion.

AEs will be presented following same analyses as those at primary completion.

5.4.1.3 Sensitivity Analyses

No sensitivity analysis is planned.

5.4.1.4 Supplementary Analyses

No supplementary analysis is planned.

5.4.2 Supportive Secondary Endpoint(s)

Not applicable.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

5.5.1 Tertiary Endpoint(s)

Tertiary or exploratory efficacy endpoints will not be presented.

5.5.1.1 Definition of Endpoint(s)

Not applicable

5.5.1.2 Main Analytical Approach

Not applicable

5.6 (Other) Safety Analyses

5.6.1 Extent of Exposure

Analyses of treatment duration, dose modifications will be conducted as described in main SAP v2.0, dated 25 JAN 2023.

5.6.2 Adverse Events

AEs are described in Section 5.4.

Deaths:

Analyses of deaths will be conducted as described in main SAP v2.0, dated 25 JAN 2023.

Immune-Mediated Adverse Events (IMAE) and Immune-modulating medication:

Analyses of IMAE and Immune-modulating concomitant medications will be conducted as described in main SAP v2.0, dated 25 JAN 2023.

5.6.3 Additional Safety Assessments

Clinical laboratory data:

Clinical laboratory will be presented per main SAP v2.0, dated 25 JAN 2023

ECG:

12-lead ECG will not be presented.

Vital signs and ECOG PS:

Analyses of vital signs , ECOG PS will be conducted as described in main SAP v2.0, dated 25 JAN 2023.

Pregnancies:

Pregnancy tests will not be presented.

5.7 Other Analyses

5.7.1 Other Variables and/or Parameters

Following analyses will be created per cohort to support efficacy analyses:

- Time to follow-up: the duration of follow-up defined as time from start of study-drug intake to last contact or death at the database cut-off date. Time will be summarized using descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum).

5.7.2 Subgroup Analyses

Subgroup analyses will not be performed.

5.8 Interim Analyses

Refer to main SAP v2.0, dated 25 JAN 2023.

5.8.1 Data Monitoring Committee or Other Review Board

Not applicable

6. Supporting Documentation

6.1 Appendix 1: List of Abbreviations

Abbreviation	Definition
AA	Anaplastic astrocytoma
AE	Adverse event
BTC	Biliary tract carcinoma
CI	Confidence interval
CR	Complete response
DCR	Disease control rate
DOR	Duration of response
ESCC	Esophageal squamous cell carcinoma
FAS	Full analysis set
GBM	Glioblastoma multiforme
HNSCC	Head and Neck Squamous Cell Carcinoma
IMAE	Immune-mediated adverse event
ORR	Overall response rate
OS	Overall survival
PD	Progression disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression free survival
PR	Partial response
RANO	Response assessment in neuro-oncology
RECIST	Response evaluation criteria in solid tumors
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease

6.2 Appendix 2: Changes to Protocol-planned Analyses

Not applicable.

6.3 Appendix 3: Baseline characteristics and demographics

Baseline characteristics and demographics will not be presented in this report.

6.4 Appendix 4: Protocol deviations

Refer to main SAP v2.0, dated 25 JAN 2023

6.5 Appendix 5: Medical history

Medical history will not be presented in this report.

6.6 Appendix 6: Prior/concomitant/follow-up medications (including dictionary)

Medications will be summarized on the FAS population per cohort per main SAP v2.0, dated 25 JAN 2023.

7. References

Not applicable.