Protocol No.: SRF617-201

A Phase 2 Trial of SRF617 in Combination with AB928 (Etrumadenant) and AB122 (Zimberelimab) in Patients with Metastatic Castration-Resistant Prostate Cancer

Statistical Analysis Plan

Version: v2.0

Date: 19 June 2023

SIGNATURE PAGE

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Date

Surface Oncology, Inc.

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MODIFICATION HISTORY

Version	Version Date	Author	Changes from Previous Version
Final 1.0	29SEP2022	[redacted]	NA
Final 2.0	19JUN2023	[redacted]	Combined related TEAE to TEAE related to any drug; Kept summary of "Primary Composite Response Rate", but removed other efficacy analyses; Removed the analysis sets that are not used in final analysis.

ABBREVIATIONS

ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
BP	Blood Pressure
bpm	Beats per minute
CFB	Change from Baseline
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DCR	Disease control rate
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of Treatment
iv	Intravenously
MedDRA	Medical Dictionary for Regulatory Activities
mCRPC	Metastatic Castration-Resistant Prostate Cancer
mg	milligram
mL	milliliter
mmHg	millimeter of mercury
NCI	National Cancer Institute
NE	Not Evaluable
ng	nanogram
ORR	Objective Response Rate
PAP	Prostatic Acid Phosphatase
PCWG	Prostate Cancer Working Group
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PDMP	Protocol Deviations Management Plan
PFS	Progression Free Survival
PK	Pharmacokinetics
PN	Preferred Name
p.o.	*per os*, by mouth
PR	Partial Response
PSA	Prostate-Specific Antigen
PSA_{30}	At least 30% decline in PSA
PSA_{50}	At least 50% decline in PSA
PT	Preferred Term
q2w	Once every 2 weeks
q4w	Once every 4 weeks
q.d.	*quaque die*, once a day
QTc	Heart rate-corrected QT interval
QTcF	QT Interval corrected with Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety Review Committee
SSE	Symptomatic Skeletal Event
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures

1 INTRODUCTION

The objective of this document is to detail the statistical methodology to be used in the statistical analyses of clinical protocol SRF617-201 "A Phase 2 Trial of SRF617 in Combination With AB928 (Etrumadenant) and AB122 (Zimberelimab) in Patients With Metastatic Castration-Resistant Prostate Cancer" Amendment 1.1 dated on 30JUL2021) and Patient Case Report Forms (CRFs version 3.0 dated on 19MAY2022)

Pharmacokinetics and pharmacodynamics analyses, with the exception of data summaries, and reporting are not included in this analysis plan.

1.1 Discrepancies Between the SAP and the Protocol

Surface (sponsor) terminated the study when 15 subjects received treatment. The abbreviated analysis will focus on safety assessments.

Pharmacokinetics Analysis Set, Blood Biomarker Analysis Set, Tumor Biopsy Analysis Set, and Immunogenicity Analysis Set, and corresponding analyses are removed from this SAP.

2 STUDY DESIGN

This is a Phase 2, open-label, safety and preliminary efficacy trial in patients with mCRPC who have progressed on or after prior ARSI therapy. The study will employ a 2-stage design with an integrated safety lead-in for the triplet combination of SRF617, etrumadenant, and zimberelimab.

Stage 1 will enroll *approximately* 17 patients, including the Safety Lead-in that will initially treat 6 patients. After the first 6 patients have been enrolled, enrollment will be paused until these patients have received 1 cycle of the triplet combination and the Safety Review Committee has reviewed the aggregate safety data. Once the SRC deems it safe to proceed, an additional 11 patients will be enrolled.

Based on an evaluation of safety and response data, the trial will proceed to the Stage 2 expansion if ≥ 1 radiographic complete response (CR)/partial response (PR) or prostate-specific antigen (PSA) responses (defined as a ≥ 50% decline [PSA_{50}]) according to the Prostate Cancer Working Group 3 (PCWG3) criteria are observed in 17 evaluable patients. An additional 23 patients will be enrolled in Stage 2 for further evaluation of the safety and efficacy of the combination. At the end of Stage 2, at least 8 responses (radiographic responses or PSA response) are needed to claim preliminary efficacy of the study treatment.

Tumor biopsies are optional; they will be performed to explore potential biomarkers of response to the combination in patients who consent to the procedure, who have non-bone metastases amenable to biopsy, and for whom the procedure is deemed safe.

Patients will continue to receive study drug for up to 2 years or until documented disease progression or unacceptable toxicity. Patients may remain on study drug longer than 2 years with agreement from the trial Investigator and Sponsor.

In November 2022, the Sponsor announced that development of SRF617 would be discontinued. Patients enrolled and/or consented for treatment on SRF617-201 were permitted to continue treatment per study protocol, but additional patients were not enrolled. Importantly the decision to discontinue development of SRF617 was a business decision; there were no safety concerns. As of 19JUN2023, 15 subjects received treatment.

2.1 Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
• To evaluate the preliminary efficacy of SRF617 administered in combination with etrumadenant and zimberelimab as determined by objective response and PSA decline • To evaluate the safety and tolerability of the combination	• The proportion of patients with a response, defined as PSA_{50} response (≥50% decline) and/or radiographic objective response of CR or PR per PCWG3 criteria • Incidence and severity of AEs
Secondary Objectives	**Secondary Endpoints**
• To evaluate additional preliminary efficacy parameters of the combination including objective response rate (ORR), PSA response, clinical benefit, duration of response, and radiologic progression-free survival (PFS) • To evaluate the PK of SRF617 when administered in combination with etrumadenant and zimberelimab • To characterize additional safety parameters including development of antidrug antibodies (ADAs) and symptomatic skeletal events (SSEs)	• ORR per PCWG3 criteria, ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, duration of response, disease control rate, PSA_{50} response, PSA decline ≥ 30% (PSA_{30}) response, time to PSA progression, radiographic PFS, and landmark PFS rate at 6 and 12 months • Serum concentrations of SRF617 • Percentage of patients with ADAs to SRF617 • Incidence of SSEs
Exploratory Objectives	**Exploratory Endpoints**
• Explore potential biomarkers of response and/or safety of the combination • Explore the effects of the triplet on peripheral blood immune cell subsets and circulating serum cytokines and chemokines • Explore the biological effects of the triplet on tumor cells and immune cell populations in the tumor microenvironment • Explore germline DNA polymorphic variations in relation to the PK, pharmacodynamics, safety, and/or preliminary efficacy • Explore correlations between prostate cancer biomarkers in tumors with biomarkers in serum in patients who undergo tumor biopsy • Explore correlations between prostate cancer biomarkers in tumors with clinical response parameters in patients who undergo tumor biopsy	• Changes in selected blood and tumor tissue biomarkers • Germline DNA polymorphic sequence variations in relation to the PK, pharmacodynamics, safety, and/or preliminary efficacy of SRF617 • Serum prostatic acid phosphatase (PAP) levels • PAP expression levels in tumors in patients who undergo tumor biopsy • Programmed death-ligand 1 (PD-L1) and CD39 expression levels in tumors in patients who undergo tumor biopsy

2.2 Study Treatment

Treatment cycles are 28 days in duration.

Study Drug	Dosing Route and Schedule	Initial Dose	1st Reduction	2nd Reduction
SRF617	iv q2w on Days 1 and 15 of each cycle	1400 mg	700 mg	350 mg
Etrumadenant	orally at a daily dose	150 mg	100 mg	75 mg
Zimberelimab	iv q4w on Day 1 of each cycle	480 mg	NA	NA

2.3 Sample Size Considerations

This trial will enroll approximately 40 patients. A patient is enrolled in the trial after they have provided informed consent and met all trial eligibility criteria.

A 2-stage design will be implemented. Stage 1 will include a 6-patient Safety Lead-in followed by enrollment of an additional 11 patients for a total of 17 patients. At least 1 radiographic CR/PR or 2 PSA_{50} responses by PCWG3 criteria out of 17 evaluable patients must be observed in order to consider opening Stage 2, which will enroll an additional 23 patients for further evaluation of the safety and efficacy of the triplet. The trial will have met its primary endpoint if at least 8 patients in total achieve a response.

The sample size for this triplet combination therapy dose expansion is based on a null hypothesis of a 10% composite response rate (PSA_{50} or CR/PR) with PD-1 blockade alone versus the alternate hypothesis that the composite response rate is 30%, with a calculated alpha of 0.040 and power of 0.93.

3 ANALYSIS SETS

3.1 Enrolled Analysis Set

The enrolled analysis set includes all patients who provided informed consent and met all study eligibility criteria as recorded in the eCRF. Patients who are later found to be incorrectly enrolled are also included this analysis set, but they may be excluded from some or all other analysis sets according to an agreement to be reached and documented in the Final Data Review Decisions document before database lock.

3.2 Safety Lead-in Evaluable Analysis Set

The Safety Lead-in Evaluable Analysis Set is defined as the first 6 patients enrolled in Stage 1 who completed at least 50% of the prescribed combination therapy doses during the first cycle of therapy (D1–28) or who received less than 50% of the prescribed combination therapy doses due to any Grade ≥ 3 related AE (including relationship to SRF617, Etrumadenant and/or Zimberelimab as Definite, Probable, and/or Possible) during the first cycle of therapy (D1–28).

This analysis set will be used to assess the preliminary safety of the combination therapy in the Safety Lead-in Period.

3.3 Safety Analysis Set

The Safety Analysis Set is defined as all patients who received any amount of SRF617. This analysis set will be the primary analysis set for all safety endpoints, excluding safety lead-in evaluation.

3.4 Response-Evaluable Analysis Set

The Response-Evaluable Analysis Set is defined as all enrolled patients who received SRF617 and had at least 1 post-Baseline response assessment (including PSA assessment and/or tumor assessment) or who discontinued the treatment phase because of radiographic or symptomatic disease progression (including death caused by disease progression) within 6 weeks (+ 2-week window) of the first dose of SRF617. This analysis set will be the primary analysis set for the primary efficacy endpoint and other efficacy endpoints.

4 GENERAL CONSIDERATIONS

4.1 Programming Environment

Unless otherwise specified, all analyses will be conducted using SAS® version 9.4 or later.

4.2 General Statistical Methods

The statistical analyses will be presented for the different analysis sets being defined in Section 3.

Descriptive Summaries:

In general, numerical variables will be summarized using descriptive statistics, displaying the number of patients in the analysis set, the number of patients with data, sample mean, sample standard deviation (calculated as the square root of an unbiased variance estimate), sample median, minimum (min) and maximum (max).

Categorical variables will be summarized by using frequency counts and percentages. In addition, the number of patients with missing values will be displayed. Unless otherwise specified, the denominators used for calculating sample proportions will be the number of patients in the specified statistical analysis set (or a subset of the statistical analysis set under use).

Presentation Conventions:

Means and medians will be presented by 1 additional decimal place and standard deviation will be presented by 2 additional decimal places than the original data. Minimum and maximum values will be presented using the same number of decimal places as the original data. If not otherwise stated, percentages will be presented to 1 decimal place. However, when the percentage (or estimated proportion) is 100% exactly, no decimal place will be shown, whereas a presented 100.0% implies that the percentage is in the half-open interval [99.95%, 100%). The number of decimal places may be adjusted, e.g., if the above default choices may lead to misinterpretation of the presented data.

In general, rounding will only occur when presenting data but not when analyzing data. By default, presented data will be rounded to the nearest required presentation precision, with a half-up tie-breaking rule. However, when presenting confidence intervals, the lower interval limit will always be rounded down and the upper interval limit will always be rounded up in order preserve the claimed (exact or asymptotic) confidence level. When either limit is outside of the parameter space (e.g., below 0 or above 1 for proportions), the interval will be truncated at the boundary of the parameter space.

If the number of patients in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown. However, structural zeros (e.g., when the count is deemed to be 0 before obtaining actual data), missing data or inapplicable/unevaluable summaries will be presented as −, NA or NE.

In listings, data will be sorted by site and patient, and when appropriate by visit or other identifiers for sequence or type of observation.

4.3 Subgroups

Subgroup analyses will not be performed.

4.4 Multiple Comparison/Multiplicity

No multiplicity adjustment is planned.

5 DEFINITIONS & DATA HANDLING CONVENTIONS

5.1 Study Day, Duration, and Study Periods

Day 1 will be the date corresponding to the first administration of SRF617. Study Day will be computed as the given date minus the date of Day 1 +1 (i.e., Study Day = Date – Date of Day 1 + 1) for dates on or after date of Day 1. For study assessment or treatment prior to Day 1, Study Day = Assessment Date – Date of Day 1.

Unless otherwise specified, day is the primary time unit for derived time and durations. Derived time units include week=7 days, month=30.436875 days, and (Gregorian) year=365.2425 days=12 months. Thus, 1 month and 4 weeks are considered different.

Unless otherwise specified, duration of time is defined from the starting day through the ending day, inclusive of both boundary days.

Study periods are defined as follows:

- screening period: beginning on the day of informed consent, or Study Day -30, whichever is latest, and ending on Day -1.
- treatment period: beginning on Study Day 1 and ending on the date of EoT visit. In case that the EoT visit is missed for any reason, the treatment period will end on the 7th day since the last dose of any study drug.
- safety follow-up period: beginning on the first day after the treatment period and ending on the last day of the Safety Follow-up visit (or study discontinuation, whichever occurs first). Safety Follow-up visit is scheduled to be approximately 30 days after the last dose of SRF617, 30 days after the last dose of etrumadenant, or 90 days (+ 7 days) after the last dose of zimberelimab (30 days after the last dose of zimberelimab if the patient initiates a new anticancer therapy), whichever is latest.

Unless otherwise specified, events in the screening period are considered as pre-treatment, and events in the treatment period or safety follow-up period are considered as on-treatment.

5.2 Analysis Visit Windows

Patient visits will be presented according to the nominal visit as obtained upon the eCRF. All values will be included in the patient data listings.

5.3 Data Derivation

Baseline and Change from Baseline

The baseline value is defined to be the last non-missing assessment prior to the first dose of SRF617. For assessments performed on Cycle 1 Day 1, if the time of the day is missing but scheduled time point is recorded as preinfusion or pre-dose, the assessment may be considered the baseline assessment for the respective study procedures. Unless otherwise specified, change from baseline (CFB) calculations for a treatment window assessment will be the applicable treatment window assessment minus the baseline assessment. If either the treatment window assessment value or the baseline value is/are missing, then CFB will be set to missing for descriptive analysis purposes, unless otherwise specified.

5.4 Missing Data

5.4.1 Partial or Missing Dates and Time

The missing component(s) of incomplete dates (e.g., start and/or stop dates of AE, concomitant medication) will be assumed as the most conservative value possible. In general, unless the available parts of the partial date preclude an AE to be treatment-emergent, the AE will be considered treatment-emergent; similarly, unless the available parts of the partial date preclude a medication to be concomitant, the medication will be considered as a concomitant medication.

For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations, etc. If day is missing for an end date, the last day of the month will be imputed. If the start date has a missing month value, the first month of the year will be imputed for study day computations, etc. If month is missing for an end date, the last month of the year will be imputed. For determination of treatment-emergent status, the start date will be imputed as the date of the first dose of study drug, unless there is clear evidence (through comparison of partial dates/times) to suggest otherwise.

Date imputation will only be used for computational purposes such as treatment-emergent status, etc. Actual data values, as they appear in the original eCRFs, will be presented in the patient data listings. Non-monotone partial dates (e.g., day and month are non-missing but year is missing) need to be queried and resolved before DBL.

5.4.2 Other Missing Values

Every effort will be made to obtain required data at each scheduled evaluation from all patients who have been enrolled. In general, missing data will not be imputed and the data will be analyzed as they are recorded.

6 STUDY POPULATION, CONDUCT AND PATIENT DISPOSITION

6.1 Analysis Sets

The number and percentage of patients in each analysis set as defined in Section 3 will be descriptively summarized using the enrolled analysis set. Corresponding data listing will be provided using the enrolled analysis set.

6.2 Patient Disposition

The number and percentage of patients in the following categories will be descriptively summarized using the safety analysis set.

- SRF617 treatment ongoing
- SRF617 treatment discontinuation
- Reason for SRF617 treatment discontinuation
  - Death
  - Adverse Events
  - Progressive Disease
    - RECIST Progression, only
    - Clinical Progression, only
    - PSA Progression, only
    - Any combinations of the above
    - Other Progression
  - Non-compliance with study protocol
  - Physician Decision
  - Study terminated by sponsor
  - Withdrawal by subject
  - Lost to follow-up
  - Other
- Etrumadenant treatment ongoing
- Etrumadenant treatment discontinuation
- Reason for Etrumadenant treatment discontinuation
  - Death
  - Adverse Events
  - Progressive Disease
    - RECIST Progression, only
    - Clinical Progression, only
    - PSA Progression, only
    - Any combinations of the above
    - Other Progression
  - Non-compliance with study protocol
  - Physician Decision
  - Study terminated by sponsor
  - Withdrawal by subject
  - Lost to follow-up
  - Other

- Zimberelimab treatment ongoing
- Zimberelimab treatment discontinuation
- Reason for Zimberelimab treatment discontinuation

  - Death
  - Adverse Events
  - Progressive Disease
    - RECIST Progression, only
    - Clinical Progression, only

    - PSA Progression, only
    - Any combinations of the above
    - Other Progression
  - Non-compliance with study protocol
  - Physician Decision
  - Study terminated by sponsor
  - Withdrawal by subject
  - Lost to follow-up
  - Other

- Study ongoing
- Study discontinuation
- Reason for study discontinuation
  - Death
  - Adverse Events
  - Progressive Disease
  - Non-compliance with study protocol
  - Physician Decision
  - Study terminated by sponsor
  - Withdrawal by subject
  - Lost to follow-up
  - Completed Safety Follow up visit
  - Other

Disposition of patients will be provided in a data listing using the safety analysis set.

6.3 Protocol Deviations

Protocol Deviation Management Plan (PDMP) version: 3.0 dated on 03Mar2023 defined the study specific procedures and responsibilities for managing Protocol Deviations (PDvs). The document listed the definition of Bioclinica Deviation Description and Deviation Area, as well the Deviation Category (major vs minor). Subject level protocol deviations will be documented in the Clinical Trial Management System (CTMS). Protocol Deviation Review meeting will review protocol listing for quality control.

Major deviations (Important Protocol Deviation, IPD) from the clinical protocol may include (if assessed as), but are not limited to:

- ICF/Subject Information
- Ineligible Subject Enrolled
- IMP Dose Error
- IMP Other Error
- Prohibited Medication
- SAE or AESI Reporting Failure

All protocol deviations (both major and minor) will be provided in a data listing for all treated patients.

7 DEMOGRAPHICS AND BASLEINE CHARACTERISTICS

7.1 Demographics

The following demographic characteristics will be descriptively summarized using the safety analysis set:

- Sex at birth
- Age (years, as reported in Demographics EDC)
- Age (>= median vs. < median; and >= 70 years vs. < 70 years)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Unknown, Other, Not Reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown)
- ECOG performance status (0, 1)
- ALP at baseline (>= median vs.< median)
- LDH at baseline (>= median vs.< median)

Demographic characteristics will also be provided in a data listing using the safety analysis set.

7.2 Cancer History

The following primary and metastatic cancer history characteristics will be summarized using the safety analysis set:

- TNM stage at initial diagnosis
  - Pathological T category (T1, T2, T3a, T3b, T4, Unknown)
  - Regional lymph node N category (NX, N0, N1, Unknown)
  - Distant metastasis M category (cM0, cM1a, cM1b, cM1c, pM1a, pM1b, pM1c, Unknown)
- Castrate-Resistant Status (Chemical, Surgical)
- Gleason score at Diagnosis (6, 7, ≥8)
- Type of Progression at Trial Entry
  - PSA only
    - Nadir PSA on last therapy (ng/ml)
  - Radiographic progression
    - Bone only
    - Bone with Nodal Disease
    - Nodal disease only
    - Visceral
- Distribution of metastatic disease
  - Metastatic Site Type
    - Pelvic nodal
    - Extra-pelvic nodal
    - Bone
    - Visceral
  - Volume
    - High (number of lesions ≥ 4)
    - Low (0 ≤ number of lesions ≤ 3)
- PSA at baseline (>= median vs.< median)
- Time since prostate cancer diagnosis (months), defined as time from the date of prostate cancer diagnosis to the date of first SRF617 dose

- Time since metastatic disease diagnosis (weeks), defined as time from the date of metastatic disease diagnosis to the date of first SRF617 dose
- Time since castrate resistance (weeks), defined as time from the date the disease became castrate resistant to the date of first SRF617 dose
- Mutation/genetic alteration analysis
  - Yes
  - No
- MSI status and MMR status
  - MSI-H (microsatellite instability-high)
  - MSI-L (microsatellite instability-low)
  - MSS (microsatellite stable)
  - dMMR (mismatch repair deficient)
    - Due to MLH1
    - Due to MSH2
    - Due to MSH6
    - Due to PMS2
  - pMMR (mismatch repair proficient)
- DNA Damage Repair (DDR) Alterations
  - ARD1A
  - ATM
  - BARD1
  - BRCA1
  - BRCA2
  - BRIP1
  - CDK12
  - CHEK2
  - FANCA
  - <insert all of Genes in the eCRF>
  - Other
- TMB
  - ≤10
  - >10
  - Unknown
- PD-L1 expression
  - Negative
  - Positive
    - n, mean, standard deviation, median, min, max
    - <1%, >=1%
  - Unknown

Primary cancer history characteristics and tumor genomic alterations/protein expression will also be provided in a data listing using the safety analysis set.

7.3 Prior Systemic Cancer Therapies

The following prior systemic anti-cancer therapy characteristics will be summarized descriptively using the safety analysis set:

- Prior systemic anticancer therapies
  - Yes

  - No
- Lines of therapy
  - 0
  - 1
  - 2
  - ≥3
  - n, mean, standard deviation, median, min, max
- Type of systemic therapy
  - Chemotherapy
    - Taxane therapy: Yes, No
  - Immunotherapy
  - Hormonal therapy:
    - Novel ASRI - androgen receptor antagonist
    - Novel ASRI - CYP17 inhibitor
    - GnRH analog or antagonist
    - Older general androgen receptor antagonist
    - Other
  - Targeted therapy
  - Other
- Setting of therapy
  - Neoadjuvant
  - Adjuvant
  - Advanced/Metastatic
  - Palliative
  - Other
- Disease state for which the latest therapy was given
  - Biochemical (PSA only) non-metastatic castrate sensitive
  - Biochemical (PSA only) non-metastatic castrate resistant
  - Metastatic castrate sensitive
  - Metastatic castrate resistant
- Primary reason for stopping last line treatment
  - Treatment completed
  - Progressive Disease
  - Toxicity
  - Adverse Event
  - Other
- PSA response across all prior systemic therapies
  - Sensitive
  - Resistant

Prior systemic cancer therapy information will also be provided in a data listing using the safety analysis set.

7.4 Prior Radiation Therapies

The following prior radiation therapy characteristics will be summarized descriptively using the safety analysis set. Number and percentage with

- Any prior radiation therapy

- Total duration of prior radiation therapy (weeks): A subject may receive multiple courses of radiation therapies. The total duration is the sum of the duration of each course of radiation therapy.
- Type of radiation: Brachytherapy, EBRT, IGRT, IMRT, Implanted radioisotopes, Proton-beam, Radium-223 chloride/alpharadin, Strontium-89, Samarium-153, Other radionuclide, Other: A subject may receive multiple types of radiation therapy.

7.5 Medical History

The medical history will be coded using MedDRA 24.1.

The number and percentage of patients with conditions coded to each primary system organ class (SOC) and preferred term (PT) will be summarized using the safety analysis set. If a patient has more than one medical condition within an SOC or PT, the patient will be counted only once for the respective SOC or PT.

Data listings of all medical history records will be provided using safety analysis set.

8 PROTOCOL-REQUIRED DRUG EXPOSURE AND COMPLIANCE

Safety analysis set will be used to summarize exposure and compliance.

8.1 Study Drug Exposure

The dosing data for SRF617, Etrumadenant, and Zimberelimab will be summarized descriptively (n, mean, standard deviation, median, min, max) using the safety analysis set:

- Total number of cycles started is defined as the maximum number of treatment cycles that a patient receives each drug
- Cumulative dose (mg), including cycle 1, 2, 3, 4, and overall:
  - SRF617 (mg) is the sum of the 'Actual dose administered' that the patient receives across cycles as recorded in the **Administration** eCRF
  - Zimberelimab (mg) is the sum of the 'Actual dose administered' that the patient receives across cycles as recorded in the **Administration** eCRF
  - Etrumadenant (mg) is the sum of the 'Actual dose administered' that the patient receives across cycles as recorded in the **Administration** eCRF plus Sum of (Assigned Dose × (Number of Capsules Taken per day/Number of Capsules per Assigned Dose) ×(End Date - Start Date+1) in the **Etrumadenant Diary Information** eCRF
- Total planned dose (mg), including cycle 1, 2, 3, 4, and overall:
  - SRF617 (mg) is the sum of the 'Dose Level' that the patient receives across cycles as recorded in the **Administration** eCRF
  - Zimberelimab (mg) is the sum of the 'Dose Level' that the patient receives across cycles as recorded in the **Administration** eCRF
  - Etrumadenant (mg) is the sum of the 'Dose Level' that the patient receives across cycles as recorded in the **Administration** eCRF plus Sum of (Assigned Dose × (End Date - Start Date+1) in the **Etrumadenant Diary Information** eCRF
- Compliance is 100*(Total cumulative dose/ Total planned dose), including cycle 1, 2, 3, 4, and overall
- Actual dose intensity (mg/cycle): cumulative dose / number of cycles initiated

- Planned dose intensity (mg/cycle):
  - SRF617: The planned dose intensity is 1400 × 2 = 2800 mg/cycle.
  - Etrumadenant: The planned dose intensity is 150 × 28 = 4200 mg/cycle.
  - Zimberelimab: The planned dose intensity is 480 mg/cycle.
- Relative dose intensity (%): 100 × (actual dose intensity / planned dose intensity)
- Number of doses missing:
  - SRF617 is the total number not administered in the **Administration** eCRF
  - Zimberelimab is the total number not administered in the **Administration** eCRF
- Number of patients with at least one dose missing for Etrumadenant
- Number of infusions interrupted, for SRF617 and Zimberelimab only

The number and percentage of patients with dose missing (not administrated), infusion interrupted, reasons for dose missing (COVID-19 Related, Other), reasons for infusion interrupted (Infusion Reaction, Adverse Event other than Infusion Reaction, Other) will be presented. The number and percentage of patients with Relative dose intensity (<50%, ≥50% – <80%, ≥80% – <120%, and ≥120%) and Compliance (<50%, ≥50% – <80%, ≥80% – <120%, and ≥120%) will be presented.

All dosing data and the above derived dosing parameters will also be presented in a data listing using the safety analysis set.

9 PRIOR AND CONCOMITANT THERAPIES

Safety analysis set will be used to summarize prior and concomitant therapies.

9.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHODrug-Global-B3 September 2021 with Anatomical Therapeutic Chemical Classification System (ATC) and preferred names (PN). Prior medications include non-study drug medications that are ended before Day 1. Concomitant medications include non-study drug medications that are used on/after Day 1.

The number and percentage of patients with prior medication or concomitant medications will be summarized by ATC level 2 category and preferred name (PN). If a patient received more than 1 drug within an ATC class or PN, the patient will be counted only once for this ATC class of PN. Prior and concomitant medications information will also be provided in a data listing.

9.2 Prior and Concomitant Procedures

Prior and concomitant procedure information will be provided in a data listing.

10 EFFICACY ANALYSIS

The assessment of tumor response is based on PCWG3 criteria as well as RECIST v1.1 being evaluated by Investigators. The summary will be presented using response-evaluable analysis set.

Assessment of response will be evaluated by computed tomography or magnetic resonance imaging of chest/abdomen/pelvis and bone scan every 12 weeks. PSA assessment will be performed every cycle. Patients should continue past PSA progression until clear radiologic progression or clinical progression (eg, symptomatic or physical deterioration in the absence of radiographic progression that meets PCWG3 criteria). The overall PCWG3 criteria and RECIST v1.1 Response visit responses include Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Non-CR/Non-PD, Not Evaluable (NE), Not Assessed (NA),

10.1 Definitions of Efficacy-related Variables

10.1.1 Best Overall Response

The best overall response (BOR) will be derived from all of visit overall responses per patients, including CR, PR, SD, PD, NE. Initial assessment of CR or PR per PCWG3 criteria or RECIST v1.1 needs to be confirmed by a second scan performed at least 4 weeks later. Unconfirmed CR or PR will be categorized as SD. Non-CR/Non-PD will be considered as SD and NA will be considered as NE during derivation. The patients in response-evaluable analysis set without any visit overall response will be categorized as NE. RECIST 1.1 BOR and PCWG3 BOR will be derived separately. Disease assessments after the start of new anticancer therapy will be excluded from efficacy derivation.

10.1.2 PSA_{50} Response

PSA_{50} response (PSA_{50}) is defined as a confirmed PSA decrease from Baseline of 50% or more based on 2 consecutive assessments measured 3 to 4 weeks apart. PSA_{50} response rate is the proportion of patients with PSA_{50}.

10.1.3 Primary Composite Response Rate

The primary composite response rate (PCRR) is defined as the proportion of patients achieving PSA50 and/or radiographic objective response of confirmed CR/PR measured using PCWG3 criteria.

10.1.4 Efficacy Endpoints Excluded from Analysis

- Objective response rate (ORR),
- Duration of primary composite response,
- Duration of response,
- Disease control rate,
- radiographic progression-free survival,
- time to radiographic progression,
- PSA30 response, and
- Time to PSA progression

will not be summarized.

10.2 Analysis of Efficacy Variables

10.2.1 Primary Composite Response Rate

The point estimate (calculated as a sample proportion), and 80%- and 95%-exact (Clopper-Pearson) two-sided binomial confidence intervals for the Primary Composite Response Rate will be presented, together with the number and percentage of subjects with each type of Composite Response.

One-sided *p* value of Primary Composite Response Rate vs 10% will be calculated with exact test.

11 SAFETY ANALYSES

The Safety Lead-in Analysis will be based on the safety lead-in evaluable analysis set. All other safety analyses will be performed using safety analysis set.

11.1 Adverse Events

Adverse events (AE) will be coded using MedDRA 24.1 and graded according to the NCI-CTCAE version 5.0.

Summaries of AEs will be based on treatment-emergent AEs (TEAEs). A TEAE is an AE that emerges or worsens in the period from the first dose of study drug to 30 days after the last dose of SRF617, 30 days after the last dose of etrumadenant, or 90 days after the last dose of zimberelimab (30 days after the last dose of zimberelimab if the patient starts another anticancer therapy), whichever is latest. TEAE summaries will be presented by primary System Organ Class (SOC) and Preferred Term (PT). Although AEs may be reported more than once for a PT or a SOC in a patient, each patient will only be counted once within the SOC or PT.

An overview of Treatment Emergent Adverse Events (TEAEs), including number and percent of patients who had any TEAE, TEAEs related to any drug, serious TEAEs, serious TEAEs related to any drug, TEAEs leading to any drug withdrawal, TEAEs leading to any drug interruption, TEAEs leading to any drug dose reduction, adverse events of special interest (AESIs), TEAEs ≥ grade 3 in severity, TEAEs related to any drug with grade ≥3, symptomatic skeletal events, and TEAEs leading to death will be presented.

If the severity grade is missing, the severity of the event will be graded as severe (Grade 3). A TEAE will be categorized as ‘related’ to study drug if the relationship of ‘Possible’, ‘Probable’, ‘Definite’ is selected. If the relationship to study drug is missing, the event will be considered as related in the analysis.

The number and percentage of patients with TEAEs will be given by primary SOC and by PT within each SOC for the following:

- TEAEs
- TEAEs related to any drug
- TEAEs with grade 3 or higher
- TEAEs related to any drug with grade 3 or higher
- Serious TEAEs
- Serious TEAEs related to any drug
- TEAEs of Special interest

- TEAEs leading to any drug withdrawal
- TEAEs leading to any drug interruption
- TEAEs leading to any drug dose reduction
- Symptomatic skeletal event
- TEAEs leading to death

AESIs are defined as thromboembolic events, e.g., DVT, pulmonary embolism, stroke, and myocardial infarction.

Patient listings will be provided for all adverse events, serious TEAEs, TEAEs of special interest, Symptomatic skeletal event, infusion reaction TEAEs, TEAEs leading to treatment withdrawal, TEAEs leading to treatment interruption, and TEAEs leading to dose reduction, TEAEs leading to death.

11.2 Deaths

Death information will also be provided in a listing.

11.3 Vital Signs and Body Measurements

Vital signs and body measurements (including height, weight, temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) change from baseline, and percentage change from baseline (CFB) values will be summarized descriptively over time as described in Section 4.2.

Vital signs information will also be provided in a data listing.

11.4 Clinical Laboratory

For lab values in the form of <x, ≤x, below lower quantification limit, etc., the value will be imputed as x/2 or half of the lower quantification limit for the purpose of numerical descriptive summary. For lab values in the form of >x, ≥x, above upper quantification limit, etc., the value will be imputed as x or upper quantification limit for the purpose of numerical descriptive summary. When such imputation occurs, footnotes will be presented to clarify the imputation rule. The original lab values will be presented in data listings.

11.4.1 Hematology, coagulation, clinical chemistry, thyroid function tests, testosterone, PAP and PSA

The Laboratory test value, change from baseline, and percentage change from baseline for continuous parameters over hematology tests, chemistry tests, coagulation tests, thyroid function tests, testosterone, PAP and PSA will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum) by visit.

Shift of hematology tests, coagulation tests, and chemistry tests from baseline CTCAE grade to the worst postbaseline CTCAE grade will be presented. If a parameter includes both hypo- and hyper- CTCAE grade derivation, hypo- and hyper- will be tabulated separately. If the baseline is not CTCAE gradable (e.g., AST increase), the baseline measurement will be categorized as low/normal/high according to reference ranges. The programmatic grading will be modified from the CTCAE by using numerical lab results only, ignoring any other grading conditions in the CTCAE, e.g., clinical symptoms or signs.

Additionally, the liver function tests (AST, ALT, ALP, and Total Bilirubin (TBL)) will be summarized in the following categories:

- Aspartate Aminotransferase (AST)
  - >3 x ULN
  - >5 x ULN
  - >10 x ULN
  - >20 x ULN
- Alanine Aminotransferase (ALT)
  - >3 x ULN
  - >5 x ULN
  - >10 x ULN
  - >20 x ULN
- AST or ALT
  - >3 x ULN
  - >5 x ULN
  - >10 x ULN
  - >20 x ULN
- Total Bilirubin (TBL)
  - >1.5 x ULN
  - >2 x ULN
- Alkaline Phosphatase (ALP)
  - >1.5 x ULN
  - >2 x ULN
- (AST or ALT) and TBL
  - AST or ALT > 3 x ULN and TBL > 1.5 x ULN
  - AST or ALT > 3 x ULN and TBL > 2 x ULN
- (AST or ALT) and ALP and TBL
  - AST or ALT > 3 x ULN and ALP < 2 x ULN and TBL > 2 x ULN

Laboratory hematology, chemistry, coagulation, thyroid function tests will be provided in data listings by patient.

11.4.2 Urinalysis

A data listing of all urinalysis tests will be provided.

11.4.3 Serology

HIV tests and hepatitis (anti-HCV antibody, HCV RNA, HBV DNA and HBV surface antigen) will be screened in the study and a data listing of all virology screening results will be provided.

11.5 ECG

QTcF Interval (msec) will be collected. QTcF Interval value at baseline will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum)

All ECG data (scheduled or unscheduled) will be displayed in a data listing.

11.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

All ECOG scores will be provided in a data listing.

12 OTHER ANALYSES

12.1 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic analyses

These analyses are not covered by this SAP and will be reported separately.

12.2 Pharmacodynamic Analyses

These analyses are not covered by this SAP and will be reported separately.

12.3 Immunogenicity Analyses

These analyses are not covered by this SAP and will be reported separately.

13 INTERIM ANALYSES

Because of early termination of the study without proceeding to Stage 2, the analysis at the end of Stage 1 will be considered as the final analysis.

14 STATISTICAL ANALYSES FOR SAFETY MONITORING

The safety monitoring in this study is not supported by any statistical analyses.

15 REFERENCES

1. ICH Harmonised Tripartite Guideline E9, Statistical Principles for Clinical Trials, 1998
2. ICH Harmonised Tripartite Guideline E3, Structure and Content of Clinical Study Reports. 1995
3. ICH Harmonised Tripartite Guideline E6(R2), Guideline for Good Clinical Practice, 1996
4. ICH guideline E2F, Note for guidance on development safety update reports, EMA/CHMP/ICH/309348/2008, September 2010
5. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.
6. Paules, M., Casey, M., Williams, G., Swann, R. S., Murphy, P. S., Salazar, V. M. Therasse, P. (2011). Recommendations for capture, validation and summarisation of data from studies using RECIST. Eur J Cancer, 47, 697-701.