NCT #: NCT05177770

TRIAL PROTOCOL
SRF617-201

Protocol Title:	A Phase 2 Trial of SRF617 in Combination With AB928 (Etrumadenant) and AB122 (Zimberelimab) in Patients With Metastatic Castration-Resistant Prostate Cancer
Protocol Number:	SRF617-201
Phase:	2
Date of Protocol:	Version 1.1 30 July 2021
Original:	Version 1.0 25 May 2021
IND:	144,623
Sponsor:	Surface Oncology, Inc. 50 Hampshire Street, Floor 8 Cambridge, MA 02139

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this trial protocol. I will conduct the trial according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Printed Name: _____

Signature: _____

Date (dd/mm/yyyy): _____

SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this trial:

[redacted]

30-Jul-21 | 18:00 EDT

[redacted]

Date

Surface Oncology, Inc.

CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Trial Title:

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

Protocol Number: SRF617-201

Phase: 2

Study Drugs: SRF617 in combination with etrumadenant (AB928) and zimberelimab (AB122)

Trial Population:

This open-label Simon 2-stage trial will enroll approximately 40 patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed on or after prior androgen receptor signaling inhibitor (ARSI) therapy. All patients will receive SRF617 in combination with etrumadenant and zimberelimab.

Duration:

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. All patients will have a Safety Follow-up visit after the last dose of study drug (SRF617, etrumadenant, and/or zimberelimab).

Trial Centers:

Enrollment is anticipated at approximately 15 sites in the United States and Canada.

Trial Design:

This Phase 2, open-label, safety and preliminary efficacy trial in patients with mCRPC will employ a Simon 2-stage design with an integrated safety lead-in for the triplet combination of SRF617, etrumadenant, and zimberelimab. Cycles are 28 days in duration. 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 (SRC) 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 2 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. 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.

Safety Review Committee

The SRC will be composed of a medical representative from the Sponsor, a Medical/Safety Monitor from the Contract Research Organization supporting the trial (if applicable), and all

Principal Investigators (or their specified delegates) at each of the enrolling sites. The SRC will meet regularly throughout the trial to review all available safety, pharmacokinetics (PK), and preliminary efficacy data. The SRC may recommend investigating intermediate doses or alternative schedules for administration of SRF617 to optimize combination dose determination. The SRC may recommend halting or stopping the trial at any time based on a comprehensive review of all clinical data.

Stage 1 Safety Lead-in

Once the first 6 patients in Stage 1 have received 1 cycle of the triplet combination, the SRC will review the aggregate safety data. To be considered evaluable for the Safety Lead-in, patients must have completed at least 50% of the prescribed doses of all 3 drugs during the review period (Day 1-28 = Cycle 1) and must not have discontinued treatment during Cycle 1 for reasons other than drug-related adverse events (AEs). For example, patients who discontinued study treatment during Cycle 1 for progressive disease or for patient or physician preference but without experiencing a Grade ≥ 3 related toxicity would not be considered fully evaluable for the Safety Lead-in and would be replaced. A 'related' toxicity is defined as those toxicities assessed by the Investigator to be possibly, probably, or definitely related to any study drug.

This analysis set will be used to assess the preliminary safety of the triplet therapy.

The following safety stopping rule will also be applied during the Safety Lead-in: If 2 or more of these 6 patients experience a Grade ≥ 3 related AE (with the exception of toxicities listed in the table below), any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (>14 days in initiating Cycle 2 due to toxicity), the trial will be halted for SRC review.

Stopping Rule Exceptions

The following Grade ≥ 3 toxicities considered at least possibly related to study treatment would **not** be considered to meet criteria for a safety stopping rule:	
Nausea	Any Grade ≥ 3 event responding to supportive treatment within 3 days
Vomiting	
Diarrhea	
Fatigue	Grade ≥ 3 lasting < 7 days
Asymptomatic amylase/lipase elevations	Grade ≥ 3 lasting any duration if asymptomatic/ no clinical signs of pancreatitis
Thyroid function abnormalities (eg, hypo- or hyperthyroidism)	Grade ≥ 3 lasting any duration if can be controlled with treatment such as thyroid supplementation or beta blockade
Rash	Grade ≥ 3 recovering to Grade 1 with treatment (ie, steroids) within 7 days
Alopecia	Grade ≤ 2 lasting any duration
Non-hematologic laboratory abnormalities	Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, electrolytes, uric acid, etc.

Adverse Event Monitoring

All patients will be monitored continuously for toxicity while on study drug. AE severity will be assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events

(NCI-CTCAE) version 5.0, or higher. If a patient has an AE of a particular severity or an AE at least possibly related to study drug, then dose modifications should be made according to the guidelines set forth in the trial protocol.

Trial Objectives:

Primary Objective:

- 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

Secondary Objectives:

- 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)

Exploratory Objectives:

- 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

Trial Endpoints:

Primary Endpoint:

- 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 Endpoints:

- 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 Endpoints:

- 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

Inclusion Criteria:

All patients must meet the following criteria for inclusion:

1. Males ≥ 18 years of age on the day of signing informed consent.
2. Metastatic CRPC with castrate levels of testosterone (≤ 50 ng/dL or ≤ 1.7 nmol/L).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Must have progressed (by PSA or radiologic criteria) during or following treatment with a novel ARSI (eg, abiraterone, enzalutamide, apalutamide, darolutamide), which may have been given for either hormone-sensitive prostate cancer or CRPC.
5. Must have received 1 to 2 prior lines of taxane chemotherapy, unless the physician and patient believe the patient is medically ineligible or the patient refuses (ineligibility or refusal must be documented in the source documents).
6. Must have progressed by PSA or radiologic criteria on or during last therapy for prostate cancer.
7. Measurable or non-measurable disease as per radiographic evaluation. Lesions situated in a previously irradiated area are considered evaluable if progression has been demonstrated in such lesions since radiation.
    - Note: If disease is considered non-measurable, a minimum PSA of 1 ng/dL is required with at least 1 confirmed rise at a minimum of a 1-week interval.
8. Washout period from the last dose of previous anticancer therapy (chemotherapy, biologic, or other investigational agent) to the first dose of study drug must be > 5 times the half-life of the agent or > 21 days, whichever is shorter. The washout period for palliative radiation (defined as ≤ 2 weeks of radiation) to non-central nervous system (CNS) disease is > 7 days.
9. Resolution of non-immune-related AEs secondary to prior anticancer therapy (excluding alopecia and peripheral neuropathy) to Grade ≤ 1 per NCI-CTCAE

version 5.0 or higher, and complete resolution of immune-related AEs secondary to prior immunotherapy.

- Note: Patients with the following clinically stable or clinically nonsignificant immune-related AEs are permitted: Controlled thyroid disorders, vitiligo, asymptomatic elevated amylase/lipase, type 1 diabetes on insulin, Grade ≤ 2 controlled rash, Grade ≤ 2 electrolyte abnormalities on stable dose of supplementation.

10. Adequate hematologic function, defined as absolute neutrophil count ≥ 1.5×10^9/L, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100×10^9/L. Transfusions are permitted to meet hemoglobin and platelet criteria. However, the patient must have a stable hemoglobin level and platelet count for ≥ 2 weeks prior to dosing without transfusion.
11. Adequate renal function, defined as serum creatinine clearance ≥ 30 mL/min per Cockcroft-Gault formula.
12. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (≤ 3 × ULN if elevated because of Gilbert's syndrome, and ≤ 2 × ULN for patients with known liver metastases).
13. Aspartate aminotransferase and alanine aminotransferase < 2.5 × ULN (< 5 × ULN if liver metastases present).
14. Prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy, in which case PT/INR or aPTT must be within therapeutic range of intended use of anticoagulants.
15. Willingness of male patients who are not surgically sterile to use medically acceptable methods of birth control for the duration of the study treatment period, including 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, whichever is later; male patients must refrain from donating sperm for 4 months after the last dose of any study drug. Sexually active men, when having sexual intercourse with a female of reproductive potential, should use an efficient barrier contraceptive (condom plus spermicide); the respective partner should also use an additional efficient contraceptive method (eg, oral pills, intrauterine device, or diaphragm, and spermicide).
16. Ability to adhere to the trial visit schedule and all protocol requirements.
17. Institutional review board/independent ethics committee-approved informed consent form signed and dated by patient (or legally acceptable representative if applicable) before any Screening procedures are performed.

Exclusion Criteria:

Patients are to be excluded from the trial if they meet any of the following criteria:

1. Currently participating in or has participated in a trial of an investigational device or has used an investigational device within 21 days before the first dose of study drug.
2. Any component of small cell or neuroendocrine histology.

3. Previously received an anti-CD39 antibody, anti-CD39 targeted therapy, or other agent targeting the adenosine pathway.
4. Prior treatment with programmed death-ligand 1 (PD-L1)/programmed death receptor-1 (PD-1) inhibitors.
5. Prior treatment with ≥ 3 lines of taxane chemotherapy administered as a single agent or as part of a combination regimen.
6. Symptomatic or untreated brain metastases (including leptomeningeal metastases). Patients previously treated for brain metastases must be at least 4 weeks from completion of radiation treatment with follow-up imaging showing no progression.
7. Current pneumonitis with or without steroid requirement or history of pneumonitis requiring steroids.
8. Another malignancy other than prostate within 2 years of trial entry, except for those with a low risk of spreading or negligible risk of death such as non-melanoma skin cancer or Ta superficial bladder cancer.
9. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
10. Medical conditions requiring chronic steroid (ie, > 10 mg/day of prednisone or its equivalent).
    - Note: Replacement therapy (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for thyroid, adrenal, or pituitary insufficiency) is allowed.
11. Concomitant therapy with agents that may have potential drug-drug interactions with etrumadenant:
    a) Known P-glycoprotein substrates with a narrow therapeutic window, administered orally (eg, digoxin) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    b) Known strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    c) Known breast cancer resistance protein substrates with a narrow therapeutic window, administered orally (eg, prazosin, rosuvastatin) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    d) Additional substrates, inhibitors, and inducers with the potential for drug-drug interactions with etrumadenant within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment. Refer to Appendix 1 and the following: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

12. History of Grade ≥ 3 allergic or anaphylactic reaction to any monoclonal antibody therapy, any excipient in the study drugs, or fusion proteins.
13. Prior hematopoietic stem cell or solid organ transplant.
14. Known current or prior infection with HIV, hepatitis B virus (HBV), or current infection with hepatitis C virus (HCV).
    - Exception: Controlled active HBV or fully treated HCV infection is permitted. Antiviral therapy as per local standard of care should be continued.
      - Controlled disease is considered HBV DNA < 500 IU/mL during the Screening Period with willingness to continue antiviral treatment during the length of the trial. The patient must be on anti-HBV treatment (per local standard of care; eg, entecavir) for a minimum of 14 days prior to trial entry.
      - For patients with HCV, only cured disease or HCV considered fully treated and no longer requiring antiviral therapy for control is permitted.
      - No co-infection with HCV and HBV is allowed. HCV and HBV co-infection is defined as HCV RNA positive and hepatitis B surface antigen (HBsAg) positive and is excluded. However, a patient who is HCV antibody positive, hepatitis B core antibody positive, but negative HBsAg is not considered co-infection and is permitted.
15. Administration of a live attenuated vaccine within 6 weeks before the first dose of study drug.
    - Exception: Health Authority approved COVID-19 vaccines are permitted.
16. Baseline QT interval corrected (QTc) with Fridericia's method (QTcF) ≥ 480 milliseconds. This criterion does not apply to patients with a right or left bundle branch block.
17. History of unstable angina or ventricular arrhythmia requiring medication or mechanical control within 6 months before Screening.
18. History of major thromboembolic event (eg, stroke, myocardial infarction, pulmonary embolism) ≤ 6 months before the first dose of study drug.
    - Exception: Patients with history of deep vein thrombosis are permitted if they are on stable anticoagulation treatment for at least 3 months before the first dose of study drug.
19. Any gastrointestinal condition that would preclude the use of oral medications (eg, difficulty swallowing, nausea, vomiting, or malabsorption).
20. Major surgery within 4 weeks before Screening.
21. Ongoing, uncontrolled, systemic bacterial, fungal, or viral infections at Screening. Oral antibiotics for a controlled infection are permitted. Patients on antimicrobial, antifungal, or antiviral prophylaxis are not excluded if all other inclusion and exclusion criteria are met. No severe infection within 4 weeks before first dose.

22. Unstable or severe, uncontrolled medical condition, important medical illness, abnormal laboratory finding, or psychological condition, that would, in the Investigator's judgment, increase the risk to the patient associated with participation in the trial or interfere with safe completion of the trial.

Dosing:

The doses of SRF617, etrumadenant, and zimberelimab are presented below and will be given on a 28-day cycle:

Study drug	**Dose**
SRF617	1400 mg intravenously (IV) every 2 weeks (q2 weeks) on Days 1 and 15
Etrumadenant	150 mg orally daily
Zimberelimab	480 mg IV every 4 weeks (q4 weeks) on Day 1

Response Assessments

Assessment of response will be evaluated by computed tomography or magnetic resonance imaging of chest/abdomen/pelvis and bone scan every 12 weeks. PSA will be performed every cycle. Patients should continue past PSA progression until clear radiologic progression or clinical progression. If osseous disease is present at Baseline, disease assessment will follow the 2+2 rule to discriminate between flare and true progressive disease in bone lesions. Patients will be permitted to continue on study drug past progression if the Investigator feels the patient is otherwise experiencing clinical benefit and Sponsor agrees.

Statistical Methodology

Sample Size Determination

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 Simon 2-stage design will be implemented. Simon 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.

Analysis Sets

The Safety Lead-in Evaluable Analysis Set is defined as the first 6 patients enrolled in the Simon stage 1 who either experienced a Grade ≥ 3 related AE during the first cycle of therapy (D1-28) or who completed at least 50% of the prescribed combination therapy doses. The SRC will review the aggregate safety data of these 6 patients during Cycle 1 and must clear the trial for further enrollment of the remaining 11 patients in Stage 1. The goal of the safety evaluation for the triplet is to evaluate for any signal of unexpected or increased toxicities when given together that would not be observed with any agent alone. As such, a Grade ≥ 3 toxicity known to be associated with any of the 3 study drugs' established safety profiles would not be considered concerning.

The Safety Analysis Set is defined as all patients who received any amount of study drug. This analysis set will be the primary analysis set for all safety endpoints, excluding safety lead-in evaluation. This analysis set will be used to assess the tolerability of SRF617 in combination with etrumadenant and zimberelimab.

The Response-Evaluable Analysis Set is defined as all patients at Baseline who received study drug and had at least 1 post-Baseline response 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 study drug. This analysis set will be the primary analysis set for the primary efficacy endpoint and other efficacy endpoints. ORR will be assessed separately by PCWG3 criteria as well as RECIST v1.1. For the primary composite response endpoint of PSA_{50} or CR/PR, ORR will be measured using PCWG3 criteria. PSA response is defined as a confirmed PSA decrease from Baseline of 50% or more based on 2 consecutive assessments measured 3 to 4 weeks apart.[1] Changes in PSA across the trial period will be described using a waterfall plot. Swimmer plots will be used to describe time on trial including timing and incidence of treatment past progression, timing of serious adverse events (SAEs) or adverse events of special interest (AESIs), and may be used to reflect the concept of no longer clinically benefiting.

The Intent-to-Treat Analysis Set is defined as all enrolled patients who received any amount of study drug.

Safety Analyses:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher and will be graded according to NCI-CTCAE version 5.0 or higher.

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 later.

TEAEs will be summarized by frequency and by MedDRA System Organ Class and Preferred Term. Separate tabulations will also be produced for TEAEs assessed as related to study drug(s), TEAEs leading to treatment discontinuation, TEAEs leading to death, AESIs, and TEAEs Grade ≥ 3 in severity. Treatment-emergent SAEs and SAEs related to study drug(s) will also be tabulated.

Shifts in grade (per NCI-CTCAE version 5.0 or higher) from Baseline to the maximum post-Baseline grade will be summarized for applicable laboratory data. Laboratory values Grade ≥ 3 in severity will be tabulated.

Incidence of SSEs per PCWG3 criteria, defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression, will be reported.[1]

Table 1: Screening Assessments Checklist

• Informed consent[a] • Inclusion/exclusion criteria • Medical history and demographics • Cancer history and Baseline disease characterization[b] • Prior/concomitant medications and procedures[c] • Full physical examination[d] • ECOG performance status • ECG (12-lead)[e] (local read only) • Blood chemistry[f] • Hematology[f] • Coagulation[f] • LDH[f]	• LFTs[f] • Amylase and lipase[f] • TSH and FT4 testing • Urinalysis[f] • Hepatitis serology (HCV Ab, HBsAg)[g] • HIV[h] • Buccal swab for pharmacogenomics • PSA • PAP • Testosterone • Tumor evaluation[i] • AE/SAE assessment[j] • Tumor biopsy[k] • Archival tumor tissue[l]

Abbreviations: AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; FT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HIV = human immunodeficiency virus; ICF = informed consent form; LDH = lactate dehydrogenase; LFT = liver function test; MRI = magnetic resonance imaging; PAP = prostatic acid phosphatase; PCWG3 = Prostate Cancer Working Group 3 criteria; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TSH = thyroid stimulating hormone

Note: All Screening assessments will be performed ≤ 30 days before the first dose. See Section 6 for details on each trial assessment.

[a] Informed consent must be obtained before performing Screening assessments (see Section 6.1.1).

[b] Include documentation of all previous treatments and treatment results (ie, best response to previous disease-specific treatments) (see Section 6.1.3).

[c] Includes medications received and medical procedures performed within the previous 30 days (previous 6 weeks for live attenuated vaccines) and any cancer treatment procedures from any time in the past (see Section 6.1.4).

[d] Full physical examination parameters described in Section 6.1.5.

[e] A 12-lead ECG will be conducted at Screening after an approximately 10-minute rest period (see Section 6.1.7). Heart rate–corrected QT interval measurements will use Fridericia's correction method. Subsequent ECGs may be performed if clinically indicated, per Investigator discretion.

[f] For a list of all blood chemistry, LDH, LFTs, amylase, lipase, hematology, and coagulation parameters and urinalysis details, see Section 6.1.8.

[g] All patients will be tested for anti-HCV Ab and HBsAg at Screening as described in Section 6.1.9.

[h] Patients without documentation of a prior negative HIV test result (eg, antibody, antigen, or polymerase chain reaction-based test) are required to undergo HIV testing during Screening. Only patients with negative HIV results will be eligible to enroll.

[i] Quantification of Baseline disease burden by PCWG3 criteria and RECIST v1.1 must be performed within 30 days before the first dose of study drug. Imaging should adequately capture all known anatomical sites of disease involvement and at a minimum must include chest, abdomen, and pelvis and bone scan. The modality (CT, MRI) chosen to evaluate each individual patient should be the same throughout the duration of the trial. See Section 6.1.10 for more information on the disease-specific imaging requirements to be conducted at Screening.

[j] SAEs for all patients will be reported from the time of signing the ICF (Section 8.1); non-serious AEs will be reported from the time of first dose. Clinically significant medical conditions observed at Screening that do not meet criteria for an SAE should be recorded as part of the patient's medical history.

[k] Fresh tumor biopsies are optional and will be performed in patients who consent to the procedure, who have non-bone metastases amenable to biopsy, and for whom the procedure is deemed safe. Biopsies in these patients will be performed at Screening and, if also done on therapy, any time after dosing during Cycle 2 or EoT, whichever visit comes first. A + 7-day window for scheduling is permitted for EoT biopsies. See Section 6.1.11 for more details.

[l] Request for collection of archival tumor tissue to be initiated at Screening including a copy of associated pathology report. Archival tumor tissue is required to be collected for all patients unless Sponsor approval is obtained. Newly obtained core or excisional biopsy of a tumor lesion not previously irradiated is preferred to archived tissue. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).

Table 2: Schedule of Assessments: SRF617 + Etrumadenant + Zimberelimab Combination Therapy

	Cycle 1 (28 ± 2 days)				Cycle 2 and Cycle 3 (28 ± 2 days)		≥ Cycle 4 (28 ± 2 days)		End of Treatment[a]	Safety Follow-up[b]
	D1	**D2**	**D8 ± 1**	**D15 ± 1**	**D1 ± 1**	**D15 ± 1**	**D1 ± 1**	**D15 ± 1**	**≤ 7 d from treatment termination**	**30 or 90 (+ 7) d from last dose**
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment[c]	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical examination[d]	X[e]		X	X	X	X	X	X	X	X
ECOG performance status	X[e]				X		X		X	X
ADA assessment[f]	See Table 3									
Pharmacokinetics[f]										
Blood chemistry, LFTs, LDH, amylase, lipase, hematology, coagulation[g]	X[e]	X	X	X[h]	X[h]	X[h]	X[g,h]	X[g,h]	X	X
TSH and FT4	X[e,h,i]				X[i]		X[i]		X	
PSA[j]	X[e,h]				X[h]		X[h]		X	
PAP	X[e,h]				X[h]		X[h]		X	
Blood for PBMC immunophenotyping[k]	X			X	X		X		X	
Blood for cytokine analysis[l]	X			X	X		X		X	
Tumor biopsy[m]					X[m]				X[m]	
SRF617 administration[n]	X			X	X	X	X	X		

	Cycle 1 (28 ± 2 days)				Cycle 2 and Cycle 3 (28 ± 2 days)		≥ Cycle 4 (28 ± 2 days)		End of Treatment[a]	Safety Follow-up[b]
	D1	**D2**	**D8 ± 1**	**D15 ± 1**	**D1 ± 1**	**D15 ± 1**	**D1 ± 1**	**D15 ± 1**	**≤ 7 d from treatment termination**	**30 or 90 (+ 7) d from last dose**
Zimberelimab administration[n]	X				X		X			
Etrumadenant administration[n]	X	X	X	X	X	X	X	X		
Etrumadenant treatment compliance assessment[n]	X			X	X	X	X		X	
Disease response assessments[o]					Response assessment every 12 wks (± 7 days) after C1D1 dosing				X	

Abbreviations: ADA = antidrug antibody; AE = adverse event; aPTT = activated partial thromboplastin time; CXDX = Cycle X Day X; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; FT4 = free thyroxine; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; LFT = liver function test; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); PAP = prostatic acid phosphatase; PSA = prostate-specific antigen; PT = prothrombin time; SAE = serious adverse event; TSH = thyroid stimulating hormone

[a] The EoT visit should occur for any patient when they discontinue the last study drug. Each assessment need not be performed if the patient had an identical assessment within the previous 2 weeks. Disease response assessment is not required for patients whose most recent scan was ≤ 6 weeks before EoT visit.

[b] All patients will have a Safety Follow-up visit 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 later. If possible, this visit should occur before the initiation of any subsequent anticancer therapy. At minimum, this visit should include collection of AEs/SAEs and concomitant medications/procedures. This can be performed by telephone call if the patient does not require laboratory and/or other procedures related to any new or ongoing AEs, in which case, a clinic visit will be required.

[c] SAEs for all patients will be reported from the time of signing the ICF through 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 initiates new anticancer therapy), whichever is later (Section 8.1). Nonserious AEs are collected and monitored from the time of first dose through 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 later. Clinically significant medical conditions observed at Screening that do not meet criteria for an SAE should be recorded as part of the patient's medical history. Pregnancies occurring in partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment period through 30 days after the patient's last dose of SRF617, 30 days after the last dose of etrumadenant, or 90 days after the last dose of zimberelimab, whichever is later.

[d] Physical examination will include an evaluation of disease-relevant systems and capture of vital signs. See Section 6.1.5 for more details.

[e] The following Screening evaluations performed within 7 days of the first dose (C1D1) can be used to meet C1D1 criteria and do not need to be repeated: physical examination, ECOG performance status, coagulation parameters, TSH, FT4, PSA, PAP, LDH, amylase, and lipase.

[f] An additional blood sample for SRF617 PK and ADA should be drawn if a patient presents with a toxicity that meets the safety stopping rules, including such a toxicity outside of Cycle 1. See Section 4.6 and Section 6.1.12 for more details.

[g] Blood chemistry, LFTs, and hematology will be performed at every trial visit prior to dosing. On C1D2, sample collection should occur 24 (± 2) hours post infusion of the last administered study drug. On each D1 and D15 infusion visit, sample should be collected within 48 hours before dosing of SRF617/the first infusion study drug. LDH, amylase, and lipase will be collected within 48 hours before dosing of SRF617/the first infusion study drug on D1of each cycle. Additional (unscheduled) assessments should be performed as clinically indicated. After Cycle 5, only hematology and blood chemistry including LFTs and LDH will be performed. Coagulation parameters will be assessed only at Screening and C1D1 and then as needed. If patient is on anticoagulation that affects PT/INR or aPTT, the appropriate parameter(s) should be measured on D1 of each cycle prior to dosing. See Section 6.1.8 for detailed parameters.

[h] Sample collection should be completed within 48 hours before dosing of SRF617/the first infusion study drug.

[i] TSH and FT4 should be collected within 48 hours of D1 of every other cycle after C1D1 (eg, C3D1, C5D1, C7D1, etc). If TSH and/or FT4 result(s) are outside of the normal range, test(s) should be repeated, treatment should be initiated if appropriate, and results recorded at each visit until they are back to Baseline.

[j] The Investigator should follow PSA every cycle. If it is standard of care to follow a biomarker at a frequency other than once per cycle, Investigator should follow standard of care.

[k] PBMC samples will be collected within 24 (+2) hours before dosing of SRF617 at C1D1, C1D15, C2D1, C3D1, C4D1, C7D1, and EoT.

[l] Blood samples for analysis of cytokines, chemokines, and other soluble factors collected at C1D1 and C3D1 should be collected before dosing of SRF617, and 6 hours ± 15 minutes post SRF617 infusion. C1D15 and all other samples on D1 of a cycle should be collected before dosing of SRF617. EoT samples may be collected at any time during the visit.

[m] Fresh tumor biopsies are optional and will be performed in patients who consent to the procedure, who have non-bone metastases amenable to biopsy, and for whom the procedure is deemed safe. Biopsies in these patients will be performed at Screening and, if also done on therapy, any time after dosing during Cycle 2 or EoT, whichever visit comes first. A + 7-day window for scheduling is permitted for EoT biopsies. See Section 6.1.11 for more details.

[n] Patients will receive SRF617 once every 2 weeks on Days 1 and 15 of each cycle and zimberelimab once every 4 weeks on Day 1 of each cycle until documented disease progression or unacceptable toxicity through Cycle 24. Patients will take etrumadenant orally once daily. On Day 1 and Day 15 infusion visit days, patients should hold etrumadenant administration until directed by trial personnel (see Section 7 for more details). On all other days, patients may take etrumadenant at home. To assess compliance with self-administration of etrumadenant, patients will be required to record the time and date they took each dose in a drug diary; missed doses will also be recorded. Patients will be instructed to bring all unused doses of etrumadenant and their drug diary to the clinic at specified visits for assessments of compliance. Patients may remain on study treatment longer than 2 years with agreement from the trial Investigator and Sponsor.

[o] To include imaging consistent with anatomic areas and modality used at Screening and response evaluation by Investigator (see Section 6.3). These evaluations will be conducted on treatment or after treatment discontinuation until the patient experiences progressive disease or discontinues the trial.

Table 3: Schedule of Pharmacokinetic and Antidrug Antibody Assessments for Combination Therapy

Cycle	Day	Scheduled time point	SRF617 PK sample[a]	Etrumadenant PK sample	Zimberelimab PK sample	SRF617 ADA sample[a]	Zimberelimab ADA sample
1	1	Predose[b,c]	X	X	X	X	X
		Immediately post SRF617 infusion (+ 30 min)	X				
	15 (± 1)	Predose[b,c]	X	X			
		Immediately post SRF617 infusion (+ 30 min)	X				
2	1 (± 1)	Predose[b,c]	X	X	X	X	X
		Immediately post SRF617 infusion (+ 30 min)	X				
	15 (± 1)	Predose[c]	X				
		Immediately post SRF617 infusion (+ 30 min)	X				
3	1 (± 1)	Predose[b,c]	X	X	X	X	
		Immediately post SRF617 infusion (+ 30 min)	X				
	15 (± 1)	Predose[b,c]	X				
		Immediately post SRF617 infusion (+ 30 min)	X				
4 and beyond[d]	1 (± 1)	Predose[b,c]	X	X	X	X	X
		Immediately post SRF617 infusion (+ 30 min)	X				
EoT	--	--	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; EoT = end of treatment; PK = pharmacokinetics

[a] An additional blood sample for SRF617 PK and ADA should be drawn if a patient presents with a toxicity that meets the safety stopping rules, including such a toxicity outside of Cycle 1. See Section 4.6 and Section 6.1.12 for more details.

[b] On infusion visit days (Day 1 and Day 15 of each cycle), patients will hold etrumadenant administration until directed by trial personnel. Predose PK and ADA samples collected on these days should be collected before dosing of any study drugs. On all other days, patients may take etrumadenant at home.
[c] Pre-dose PK samples obtained on Cycle 1 Day 1 may be collected within 24 hours before SRF617 dosing. Predose PK samples obtained after Cycle 1 Day 1 may be collected within 2 hours before SRF617 dosing.
[d] Beginning with Cycle 4, SRF617 PK and ADA samples will be collected on Day 1 of each cycle and EoT. Etrumadenant and zimberelimab PK samples and zimberelimab ADA samples will only be collected on Cycle 4 Day 1, Cycle 8 Day 1, Cycle 13 Day 1, and EoT.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARSI	androgen receptor signaling inhibitor
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
C1D1	Cycle 1 Day 1
CNS	central nervous system
CR	complete response
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DoR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ENTPD1	ectonucleoside triphosphate diphosphohydrolase-1
EoT	end of treatment
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HR	hazard ratio
HSPC	hormone-sensitive prostate cancer
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IgG4	immunoglobulin G4
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
KO	knockout
LDH	lactate dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NECA	5′-N-ethylcarboxamide adenosine
NK	natural killer
ORR	objective response rate
OS	overall survival
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cell
pCREB	cAMP response element-binding protein
PCWG3	Prostate Cancer Working Group 3
PD-1	programmed death receptor-1
PD-L1/2	programmed death-ligand 1/2
PFS	progression free survival
PK	pharmacokinetic(s)

PR	partial response/remission
PSA	prostate-specific antigen
PSA_{30}	PSA decline ≥ 30%
PSA_{50}	PSA decline ≥ 50%
PT	prothrombin time
q2 weeks	once every 2 weeks
q4 weeks	once every 4 weeks
QTc	heart rate–corrected QT interval
QTcF	QT interval corrected with Fridericia's method
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SRC	Safety Review Committee
SSE	symptomatic skeletal events
TEAE	treatment-emergent adverse event
TME	tumor microenvironment
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal

1. BACKGROUND

1.1. Castration-Resistant Prostate Cancer

Prostate cancer is the second most common cancer in incidence and the fifth leading cause of death in men worldwide.[2] It is estimated that approximately 249,000 new cases will be diagnosed in the United States in 2021, with approximately 34,000 related deaths due to metastatic disease.[3] Current approaches to the treatment of hormone-sensitive metastatic prostate cancer have changed rapidly in the last several years, with significant survival advantages achieved by adding docetaxel chemotherapy[4, 5] or novel androgen receptor signaling inhibitors ([ARSIs] eg, abiraterone, enzalutamide, apalutamide[6-9]) to standard androgen deprivation therapy upon a backbone of gonadotropin-releasing hormone analogs in patients who have not had bilateral orchiectomy. However, almost all patients will still transition to castration-resistant prostate cancer (CRPC, progression despite testosterone levels < 50 ng/dL) in approximately 15 to 19 months[5, 10], which is responsible for most of the morbidity and the mortality of prostate cancer.

While the advances in the hormone-sensitive space have translated to significant increases in overall survival (OS), they have created challenges as to the optimal sequencing of subsequent treatments for CRPC. Most patients will receive several second-line regimens for metastatic CRPC (mCRPC) ranging from taxane chemotherapy (docetaxel, cabazitaxel[11, 12]), alternative ARSIs (eg, enzalutamide or abiraterone), or the dendritic cell vaccine sipuleucel-T.[13] Selected patients may receive radium-223, if disease is predominantly represented by bone metastases[14], or PARP inhibitors (eg, olaparib, rucaparib) for tumors that contain certain DNA repair pathway mutations or alterations.[15, 16] However, prospective studies and retrospective analyses have shown that sequencing one ARSI after another or layering on an additional ARSI achieves disappointingly short times to disease progression (by prostate-specific antigen [PSA] or radiologically) on the order of 3 to 6 months, especially if the patient has already received both a taxane and an ARSI.[17-24] The randomized Phase 2 CARD trial (n = 225) investigated whether patients whose disease had had prior docetaxel exposure (minimum 3 cycles) and who had progressed within the past 12 months on an ARSI with enzalutamide or abiraterone would have a longer progression-free survival (PFS) and OS if given cabazitaxel next rather than switching to the other ARSI.[25] Receipt of cabazitaxel doubled the imaging-based median PFS (8.0 vs. 3.7 months, hazard ratio [HR] 0.54, $p < 0.001$) and significantly improved the median OS (13.6 vs 11 months, HR 0.64, $p = 0.008$) over receiving the alternative ARSI.

Prostate cancer is generally an immunologically cold tumor. Attempts at leveraging immune checkpoint inhibition with programmed death receptor-1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade, which have provided significant clinical benefit across other solid tumors, have been less fruitful in mCRPC, with an objective response rate (ORR) of < 15%.[26-29] Multiple Phase 3 trials are ongoing to evaluate PD-1 blockade with standard therapies such as docetaxel or enzalutamide. Two Phase 3 trials of the anti-CTLA-4 antibody ipilimumab did not induce a survival benefit in either the pre- or post-chemotherapy mCRPC space.[30-32] As such, immune checkpoint blockade in the form of anti-PD-1 is only approved for selected prostate cancers in which there is mismatch repair deficiency (eg, MLH1, MSH2, MSH6, PMS2) or high tumor mutational burden.[28]

Despite these advances and a multitude of drugs now approved for mCRPC, it remains uniformly fatal due to inherent or adaptive resistance mechanisms, and more effective therapies are needed.

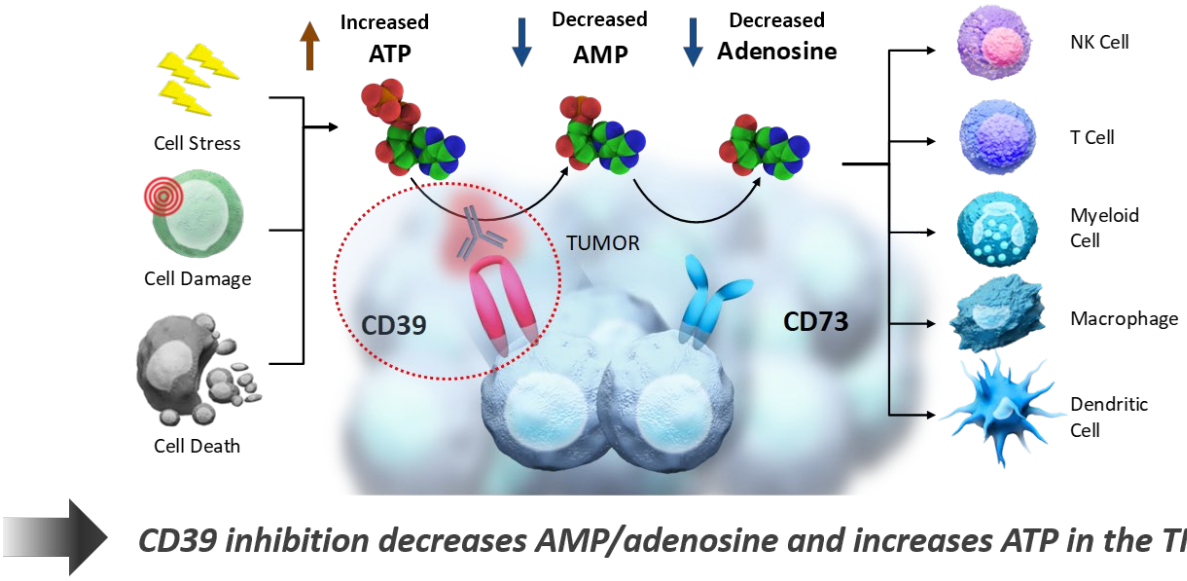
One such resistance pathway in prostate cancer may be the adenosine pathway. The tumor microenvironment (TME) contains high levels of adenosine, an immunosuppressive chemical which binds to and activates the A2a and A2b receptors on immune cells resulting in a dampened immune response against the tumor. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, A2bR is upregulated[33-35] and the activity of prostatic acid phosphatase (PAP) produces additional adenosine[36, 37], suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression.

1.2. Adenosine Pathway in Cancer

The purine nucleoside adenosine has a critical role in dampening innate and adaptive immune responses under various inflammatory conditions.[38] In contrast, high levels of extracellular adenosine triphosphate (ATP) generated as a result of tissue damage or immunogenic cell death can initiate pro-inflammatory responses.[39] Extracellular adenosine accumulates in cancerous tissues through the degradation of ATP and constitutes an important mechanism of tumor immune escape, induction of angiogenesis, and metastasis.[40] Early studies demonstrated that adenosine could inhibit $CD3^+$ T-cell and natural killer (NK) cell function, and endogenous adenosine levels in tumors would be sufficient to mediate immunosuppression.[41] Other studies have shown that high levels of ATP can act as a potent chemoattractant for innate immune cells and can mediate robust inflammation leading to activation of adaptive immune responses.[39] Thus, there is an important role for both extracellular adenosine and ATP in cancer maintenance and progression. Thus, inhibition of extracellular adenosine while maintaining high levels of ATP in the TME may have anticancer therapeutic activity.

Reduction of ATP and subsequent increase of extracellular adenosine production in the TME depends on the concerted enzymatic activity of 2 ectonucleotidases, CD73 (5'-nucleotidase ecto) and CD39 (ectonucleoside triphosphate diphosphohydrolase-1 [ENTPD1]). CD39 catalyzes the hydrolysis of ATP and adenosine diphosphate (ADP) to adenosine monophosphate (AMP) and CD73 hydrolyzes AMP to adenosine (Figure 1). The effects of adenosine are mediated via interactions with adenosine-binding G-protein coupled receptors (A1, A2A, A2B, and A3). Notably, adenosine inhibits the activation and expansion of T cells primarily via the A2A receptor. Mice that lack the A2A receptor have reduced tumor growth as compared with their wildtype littermates, providing genetic evidence for the adenosine/A2A receptor pathway in protecting tumors from antitumor T cells.[42] A2A receptor stimulation also upregulates expression of coinhibitory molecules such as CTLA-4 and PD-1[43], while stimulation of A2bR results in adenosine-driven suppression of myeloid cells through the A2bR present on dendritic cells and macrophages.

Figure 1: The adenosine pathway's role in antitumor immunity



Abbreviations: AMP = adenosine monophosphate; ATP = adenosine triphosphate; NK = natural killer; TME = tumor microenvironment
CD39 is a key enzyme modulating innate and adaptive immune responses. Extracellular adenosine suppresses tumor immunity, while extracellular ATP stimulates innate immunity. Antibody blockade of CD39 decreases AMP and adenosine and increases ATP in the TME.

Studies examining reduction of adenosine through inhibition or loss of CD73 have further validated this pathway in mediating tumor immune evasion. Host CD73 deficiency or neutralizing antibodies targeting CD73 lead to delayed tumor growth in multiple syngeneic transplantable tumor models, including ovalbumin-expressing MC38 colon cancer, EG7 lymphoma, AT-3 mammary tumors, ID8 ovarian tumors, B16F10 melanoma, and TRAMP-C1 prostate tumors.[44] Depending on the model, the tumor-protective effects of CD73 blockade were dependent on $CD8^+$ T cells, NK cells, and interferon gamma secretion.[44] Targeting CD73 also enhances the activity of anti–PD-1 and anti–CTLA-4 antibodies in mouse syngeneic tumor models.[45, 46]

Inhibition or loss of CD39 has been shown to have antitumor effects in multiple studies. Notably, in CD39 knockout (KO) mice, growth of both MC38 colon cancer cells and B16 melanoma hepatic metastatic tumors was significantly inhibited compared with growth in wild-type mice.[47] Interestingly, hepatic metastatic growth was also reduced in chimeric mice reconstituted with $CD39^{-/-}$ bone marrow–derived cells, suggesting that CD39 on immune cells alone contributes to tumor growth. In a complementary study, CD39 transgenic mice over-expressing CD39 were shown to have larger, more rapidly growing metastatic tumors after injection of CT26 colorectal cells.[48] Treatment with the CD39 inhibitor sodium polyoxotungstate or an anti-CD39 antibody was also shown to limit metastatic tumor growth, [49, 50] and direct inhibition of CD39 has been shown to inhibit tumor angiogenesis in a variety of models. [47, 49-52] Taken together, these observations demonstrate the potential for targeting CD39 in cancer treatment and serve to further validate the importance of the extracellular adenosinergic pathway in promoting tumor growth.

1.3. CD39

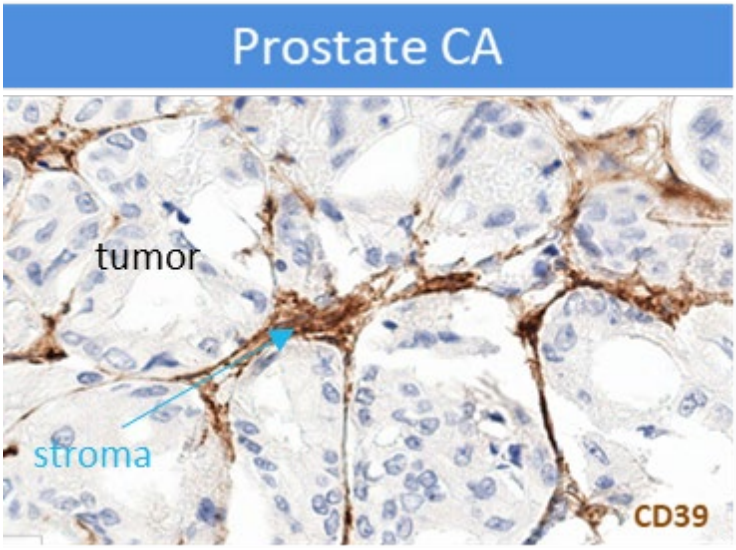
CD39 is an enzyme critical to both the production of adenosine and the breakdown of ATP. The accumulation of adenosine leads to immunosuppression, whereas maintained levels of ATP increase T-cell proliferation, dendritic cell maturation, and pro-inflammatory cytokine levels. The adenosine axis is a well-validated immune suppression pathway. CD39 is a key upstream target in the pathway modulating innate and adaptive immune responses. CD39 inhibition decreases immunosuppressive adenosine while stimulating innate immunity by potentiating ATP levels in the TME. Extracellular adenosine suppresses tumor immunity; extracellular ATP stimulates innate immunity.

1.3.1. CD39 and Prostate Cancer

Internal studies have revealed that prostate cancer can strongly express CD39 in the stromal compartment of tumors (Figure 2). In general, the TME of prostate cancer is largely devoid of immune infiltrate displaying a "cold" tumor phenotype.[53] CD39 in the stroma of cancer tissue likely contributes to the immunosuppressive barrier by degrading extracellular ATP, thereby increasing adenosine levels. Inhibiting CD39 activity in the TME could increase ATP levels and reduce available adenosine, which in turn could induce antitumor inflammation of this immunologically "cold" tissue with resultant recruitment of immune cells, and ultimately suppression of tumor growth.

PAP is a secreted glycoprotein enzyme that is widely present in prostate gland epithelial cells. While PSA is the universally tested serum biomarker for diagnosis and response assessment in prostate cancer management, serum PAP levels are also increased in patients with prostate cancer, and it was widely used as a biomarker prior to PSA testing. High PAP levels can correlate with earlier metastases, larger tumor size, higher pathological grade, and shortened survival.[54, 55] Although PAP is expressed in other tissues such as brain, kidney, and placenta, its expression in normal prostate and prostate cancer tissues is 50-5000x and 110-6000x higher, respectively.[56] Since more than 95% of prostate cancer cells express PAP, it has been used as a target antigen for prostate cancer immunotherapy.[56] Although the exact physiological function of PAP is not clear, PAP can function as an ectonucleotidase and convert AMP to adenosine.[54, 55] Together with CD39, PAP may contribute to an adenosine-rich, immunosuppressive TME in prostate cancer. A recent trial has shown that serum PAP levels can be a useful indicator of an adenosine-rich TME.[57] This is particularly important in this trial since both SRF617 and etrumadenant are therapeutics designed to decrease the immunosuppressive effect of adenosine in TME.

Figure 2: CD39 exhibits a stromal expression pattern in prostate cancer



Abbreviations: IHC = immunohistochemistry, TME = tumor microenvironment
Representative image of a human prostate cancer tissue sample demonstrating CD39 protein expression (brown staining) in the stromal component (blue arrow) of the TME by IHC.

1.4. SRF617

SRF617 is a fully human immunoglobulin G4 (IgG4) antibody against human ENTPD1, also known as CD39, that prevents CD39-mediated conversion of ATP and ADP to AMP and phosphate, leading to a reduction in adenosine levels within the TME. There is an important role for extracellular ATP and adenosine in cancer maintenance and progression. Maintaining high levels of ATP (and resultant low levels of adenosine) in the TME may have anticancer therapeutic activity.

The ability of SRF617 to inhibit CD39 enzymatic activity was demonstrated in vitro with recombinant CD39 protein and on multiple cell types expressing both human and cynomolgus monkey CD39. Functional cellular immunologic assays demonstrated that SRF617 enhances T-cell proliferation and dendritic cell maturation in vitro. In vivo, SRF617 has shown significant antitumor activity after repeated dosing as a single agent in the MOLP-8 xenograft model in mice, which expresses high levels of CD39.

1.4.1. Summary of Nonclinical Safety of SRF617

The nonclinical toxicology program conducted in support of clinical trials for SRF617 consisted of 2 in vivo repeated-dose intravenous (IV) injection studies in cynomolgus monkeys, an in vitro cytokine release study using human peripheral blood mononuclear cells (peripheral blood mononuclear cells [PBMCs]), and an in vitro off-target binding study using human HEK293 cells. The in vivo toxicology studies of SRF617 were conducted in cynomolgus monkeys, which was the only species identified as pharmacologically relevant based on SRF617 avidity for CD39. Both in vivo toxicology studies were conducted by the IV route of administration, which is the current clinical route of administration. The pivotal toxicology study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

The weight of evidence from all the pharmacology and toxicology studies conducted with SRF617 in vitro and in vivo supports its safety in the treatment of patients with advanced cancer. All the in vivo safety studies conducted with SRF617 resulted in no significant findings up to 100 mg/kg, corresponding to an average maximum serum concentration of 4,950,000 ng/mL and area under the curve of 91,400,000 h*ng/mL. Biologic activity of SRF617 in cynomolgus monkeys was confirmed by an in situ CD39 enzymatic activity assay.

Preclinical evidence implicates CD39 in murine models of thromboregulation. In CD39-haploinsufficient mice, there is an increase in thrombogenesis under certain vascular conditions.[58] Although no evidence of disordered platelet activation or thrombogenesis was detected in SRF617 nonclinical studies, including nonhuman primate toxicology studies, this clinical trial will monitor for laboratory evidence of such effects, and all thromboembolic adverse events (AEs) will be recorded and monitored as adverse events of special interest (AESIs).

SRF617 is not an immune system agonist, and no increases in cytokines were observed in vivo in the 4-week GLP toxicology study. In an in vitro cytokine release assay in PBMCs isolated from healthy human donors, SRF617 induced secretion of interleukin (IL)-8 at assay concentrations of ≥ 100 µg/mL and tumor necrosis factor alpha (TNFα) at ≥ 1000 µg/mL, up to 7.6 times and 2.8 times, respectively, compared with negative control. At the highest assay concentrations of 10,000 µg/mL, SRF617 induced secretion of IL-1β, IL-6, IL-8, and TNFα from 28.1x to 77.6x. This concentration is approximately 30x greater than the human serum concentrations achieved with the recommend Phase 2 starting dose of 1400 mg. Although cytokine release did not occur at dose levels relevant to clinical doses, these models are not necessarily predictive of the response that may be observed in patients with significant circulating tumor cells.

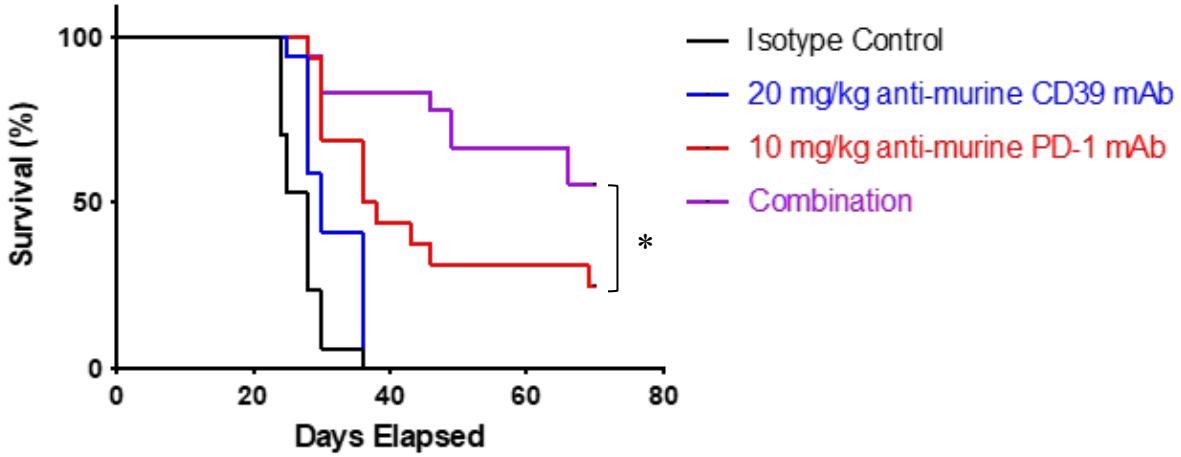
Further details on the nonclinical development of SRF617 are available in the current version of the SRF617 Investigator's Brochure.

1.4.2. Rationale to Combine SRF617 With PD-1 Blockade

There is rationale for combining SRF617 with diverse classes of anticancer agents, including immune-checkpoint inhibitors. Immune-checkpoint blockade with anti-PD-1/programmed death-ligand 1 (PD-L1) antibodies are thought to work by activating exhausted $CD8^+$ T cells in the TME, which could be further enhanced by removing immunosuppressive adenosine. Nonclinical studies have demonstrated that blocking or modulating the immune suppressive adenosine pathway in the TME can augment immune responses in combination with PD-1 blockade. A recent study showed that CD39 KO mice implanted with both B16F10 syngeneic tumors had delayed tumor growth and better survival when treated with an anti-PD-1 antibody.[49] Antibody inhibitors of CD73 and small molecule inhibitors of the adenosine receptor A2AR were also shown to have significantly increased antitumor effects when combined with anti-PD-1 or anti-PD-L1 in syngeneic murine tumor models. This further supports the utility of combining adenosine-lowering or -blocking agents with checkpoint inhibition. [45, 59, 60]

Internal nonclinical experiments have demonstrated antitumor cooperativity of anti-CD39 antibody treatment in combination with both PD-1 blockade and chemotherapeutic agents. An antimurine CD39 surrogate antibody in combination with an antimurine PD-1 antibody significantly decreased tumor growth and increased survival in syngeneic CT26 colorectal tumor-bearing mice (Figure 3).[61]

Figure 3: An antimurine-CD39 surrogate antibody in combination with an antimurine PD-1 antibody increases survival in a syngeneic CT26 tumor model



Abbreviations: BIW = twice a week; IgG1 = immunoglobulin G1; IP = intraperitoneal(ly); mAb = monoclonal antibody; n = number; PD-1 = programmed death receptor-1
Five- to 7-week-old female BALB/c mice were injected with 2.5×10^5 CT-26 tumor cells subcutaneously into the right flank and randomized into 4 treatment groups when tumors reached a mean volume of approximately 50-80 mm^3. The groups (n = 16-18 mice/group) were treated IP with either 20 mg/kg isotype control antibody (mouse IgG1), 20 mg/kg antimurine CD39 mAb, 10 mg/kg anti–mouse PD-1 antibody (RMP-14), or a combination of PD-1 with antimurine CD39 mAb BIW for 3 weeks. Tumors were measured using a caliper BIW, and tumor volumes were calculated. Animals in each group were euthanized when they reached an individual tumor volume of $\geq$ 2000 mm^3 or were necrotic. A Kaplan-Meier curve depicting overall survival is shown here. Statistical significance was calculated using the log-rank (Mantel-cox test) (*$p < 0.05$).

1.4.3. Summary of Clinical Studies of SRF617

Currently, there is 1 other ongoing SRF617 clinical trial (SRF617-101, NCT04336098), a Phase 1, open-label, first-in-human, monotherapy and combination therapy dose-escalation, safety, and tumor biopsy expansion trial in patients with advanced solid tumors. This trial will enroll approximately 100 patients. The combination therapy portion of the trial will evaluate SRF617 in combination with gemcitabine + albumin-bound paclitaxel (Abraxane®) or SRF617 in combination with pembrolizumab (Keytruda®). The primary objective of this trial is to determine the recommended Phase 2 dose (RP2D) as monotherapy and in combination therapy in patients with solid tumors, with the primary endpoint of dose-limiting toxicities.

Further details on the ongoing clinical studies of SRF617 are available in the current version of the SRF617 Investigator's Brochure.

1.5. Etrumadenant (AB928)

Etrumadenant is the first clinical stage small molecule dual antagonist of both A2aR andA2bR and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through A2aR on CD8+ T cells and NK cells) and myeloid cells (through A2bR on dendritic cells and macrophages) in the absence of any agonist activity. Developed specifically for the oncology setting, etrumadenant achieves high penetration of tumor tissue, robust potency in the presence of high adenosine concentrations, and minimal shift in potency

from non-specific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects.

Nonclinical data demonstrate potent inhibition of adenosine receptor-mediated signaling in peripheral blood immune cells at plasma levels consistent with those reached in healthy human volunteers and cancer patients. Although etrumadenant alone displayed minimal effects on tumor growth or on the nature of the immune infiltrate in various mouse models, etrumadenant enhanced the antitumor efficacy when administered in combination with standard cancer chemotherapy or immunotherapy without additive toxicity. Moreover, etrumadenant provided continued benefit in tumor growth inhibition following cessation of the T-cell activating combination partner.

Clinical data show that heavily pretreated patients with metastatic solid tumors have experienced clinical benefit with etrumadenant in combination with other anti-cancer agents as defined by objective responses or prolonged stabilization of disease.

Etrumadenant exhibits pharmacokinetics/pharmacodynamics consistent with once-daily dosing and has been well tolerated in dose-escalation studies as a single agent and in Phase 1b/2 studies administered in combination with chemo/immunotherapy across multiple advanced solid tumor indications.[62]

The advanced nature of the underlying cancer is associated with clinically significant side effects related to the disease under study. Thus far, administration of etrumadenant in cancer patients has been well tolerated and in the absence of additive toxicity. The emerging safety profile for etrumadenant, together with evidence of clinical benefit across multiple solid tumor types, supports a favorable benefit/risk assessment and provides justification for continued clinical development of this investigational therapy.[63, 64]

Further details on the ongoing clinical studies of etrumadenant are available in the current version of the etrumadenant Investigator's Brochure.

1.6. Zimberelimab (AB122)

Zimberelimab is a fully human IgG4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated pharmacokinetics (PK), pharmacodynamics (including receptor occupancy), efficacy, and safety that are consistent with currently approved anti-PD-1 therapies. The most advanced trial with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic non-small cell lung cancer, evaluating zimberelimab in combination with domvanalimab (AB154), an anti-TIGIT monoclonal antibody, and etrumadenant. Zimberelimab is also being evaluated as monotherapy in a tumor agnostic, biomarker selected Phase 1b trial for cancers with no approved anti-PD-1 treatment options.

Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function post exposure to zimberelimab.

Clinical data from monotherapy treatment in heavily pretreated patients with various advanced solid tumors has established tolerable and pharmacokinetically stable dosing regimens of zimberelimab intravenously every 2, 3, and 4 weeks. Additional studies in combination with etrumadenant and other agents have also established a tolerable combinatory dosing regimen of

zimberelimab. Although preliminary safety data from these studies are still maturing and others are ongoing, no unique safety risks have been identified for zimberelimab compared to other anti-PD-1 agents. However, the risks associated with this drug class are well established given significant experience with the approved anti-PD-1 agents such as nivolumab[65] and pembrolizumab[28] and are appropriate for zimberelimab monitoring. The emerging safety profile for zimberelimab, together with well-established clinical benefit with this class of agents with approvals across multiple tumor types, supports a favorable benefit/risk assessment and provides justification for continued clinical development of this investigational therapy.

Further details on the ongoing clinical studies of zimberelimab are available in the current version of the zimberelimab Investigator's Brochure.

1.7. Rationale for Combining Etrumadenant and Zimberelimab

The combination of etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 trial in patients with advanced solid tumors (NCT03846310). Etrumadenant administered together with zimberelimab was well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months, in heavily pretreated patients across multiple disease indications.[62]

ARC-5 (NCT03629756) is an ongoing, open-label, Phase 1 dose-escalation and dose-expansion trial evaluating the safety and tolerability of etrumadenant and zimberelimab in patients with advanced malignancies. The dose-escalation phase of the trial is evaluating etrumadenant (75 mg, 150 mg, or 200 mg QD) in combination with zimberelimab 240 mg every 2 weeks (q2 weeks). The dose-expansion phase is evaluating etrumadenant 150 mg QD and zimberelimab 240 mg q2 weeks in patients with renal cell carcinoma or mCRPC. Among 11 evaluable patients, Investigator-assessed best overall response (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) is 1 confirmed partial response (endometrial cancer), 6 stable disease (including ovarian cancer [2 patients] as well as colorectal and appendiceal cancers [1 patient each]), and 4 progressive disease. The most commonly reported AEs considered at least possibly related to etrumadenant have included fatigue, nausea, and diarrhea. The most commonly reported AEs considered related to zimberelimab have included fatigue, diarrhea, and increased alanine aminotransferase.

ARC-6 (NCT04381832) is an ongoing open-label, Phase 1b/2 trial evaluating etrumadenant plus zimberelimab with or without standard of care docetaxel or enzalutamide in patients with mCRPC. Preliminary safety data suggest a safety profile for the combination similar to what has been observed thus far in ARC-5.

1.8. Trial Rationale

While the treatment armamentarium for mCRPC has significantly improved in the last few years with next-generation androgen receptor-targeted therapies and chemotherapy, resistance is nearly universal. Engaging the patient's immune system with immune checkpoint blockade and targeting the immunosuppressive adenosine pathway that may make for a tumor-permissive microenvironment is a rational route to override innate or established resistance mechanisms in mCRPC. Dual blockade of the adenosine pathway with proximal inhibition of CD39 with SRF617 and distal targeting at the level of the adenosine receptors with the dual A2AR antagonist etrumadenant in concert with PD-1 pathway blockade has great potential to induce

significant clinical benefit in mCRPC resistant to standard therapies and improve clinical outcomes.

Anti-PD-1 antibodies activate exhausted $CD8^+$ T cells in the TME, an effect that can be dampened by the immunosuppressive adenosine within the TME. Nonclinical studies have demonstrated that blocking or modulating the adenosine pathway in the TME can augment immune responses in combination with PD-1 blockade. In CD39 KO mice implanted with both B16F10 syngeneic tumors, delayed tumor growth and better survival was observed after treatment with an anti-PD-1 antibody.[49] Antibodies against CD73 and small molecule inhibitors of the adenosine receptor A2AR have also been shown to significantly increase tumor shrinkage when combined with anti-PD-1 or anti-PD-L1 in syngeneic murine tumor models.[45, 59, 60] These effects are largely attributed to enhanced T-cell activation in the TME.

In the clinic, preliminary signs of antitumor activity in mCRPC have been observed with several adenosine pathway antagonists in combination with PD-1 pathway blockade.[66-69] These early clinical results, combined with the robust preclinical data, support co-targeting the adenosine and PD-1 pathways.[45,59,60] The combination of etrumadenant and zimberelimab has already been evaluated in early-phase studies across multiple tumor types demonstrating some tumor responses and disease stabilization as well as a favorable safety profile. While both SRF617 and etrumadenant target the adenosine pathway, the safety profile of both agents appears manageable thus far with low-grade fatigue or gastrointestinal (GI) distress as the most common overlapping side effects, which will be monitored for any cumulative toxicity and tolerability. Together, the safety profiles and strong mechanistic potential for complementary three-way reversal of immune suppression and induction of a more hospitable immune milieu provide justification for clinical development of this triplet IO therapy.

1.8.1. Selection of Patient Populations

The population to be studied in this Phase 2 trial includes patients with mCRPC who have progressed on or after prior ARSI therapy.

1.9. Determination of Dose and Schedule

The RP2D of SRF617 monotherapy from Trial SRF617-101 was determined to be 1400 mg, based on the totality of safety information, clinical PK/pharmacodynamic relationship, and the PK modeling for the biologically active dose using preclinical efficacy models. The dose of 1400 mg was investigated in Trial SRF617-101 and found to be safe and well-tolerated. Based on comprehensive modeling, a dose of 1400 mg will achieve (1) CD39 target occupancy near saturation throughout the dosing interval, (2) an SRF617 concentration that is anticipated to inhibit CD39 activity in tissues and tumors in human CD39 knock-in mice, and (3) an equivalent drug level that resulted in significant tumor growth inhibition in preclinical xenograft efficacy models. The SRF617 dose schedule in SRF617-201 will be a q2 week schedule, the same dosing frequency as that in SRF617-101; therefore, dose scaling is not planned. In addition, drug-drug interactions with SRF617 are not anticipated as etrumadenant is a synthetic, low molecular weight drug administered orally and zimberelimab is an antibody targeting the PD-1 pathway (different from SRF617's antibody blocking of the adenosine pathway). Both SRF617 and etrumadenant target the adenosine pathway at different levels and have good tolerability as single agents with low-grade fatigue and GI distress being the most common overlapping side

effects of these agents reported thus far. Cumulative toxicity of dual targeting this pathway will be monitored. Therefore, given the lack of anticipated safety or tolerability concerns with the combination of SRF617, etrumadenant, and zimberelimab, the SRF617 RP2D of 1400 mg as determined in Trial SRF617-101 will be employed as the starting dose in SRF617-201.

In order to establish the optimal SRF617 dose and schedule in SRF617-201, the Sponsor may consider evaluating an alternative dose level or dose schedule, as recommended by the Safety Review Committee (SRC)'s safety review of the monotherapy and combination therapy data.

The proposed dose of zimberelimab is 480 mg administered IV every 4 weeks (q4 weeks). In the first-in-human study of zimberelimab, AB122CSP001, zimberelimab doses of 80 mg, 240 mg, and 360 mg q2 weeks, 360 mg every 3 weeks, and 480 mg and 720 mg q4 weeks were administered as monotherapy to patients with advanced malignancies. All doses mentioned above were found to be safe and well-tolerated, and no maximum tolerated dose was reached. PK data were gathered from all subjects after first dose and at steady-state and were used to develop a population PK model. Simulations were performed using the population PK model to identify appropriate doses for Phase 2 and Phase 3 studies. The dose of 480 mg q4 weeks was found to result in steady-state concentrations at trough > 15 µg/mL in a majority of patients. This concentration was identified as the target effective concentration that would result in > 99% peripheral receptor occupancy of PD-1 receptors, a level of target occupancy that is widely believed to result in maximal efficacy.

The proposed dose of etrumadenant is 150 mg administered orally every day. In the first-in-human study of etrumadenant, AB928CSP001, doses up to 200 mg once daily were administered as a single agent. Overall, the doses were found to be safe and well-tolerated and a maximum tolerated dose for etrumadenant was not identified in the study. Subsequently, etrumadenant was administered at doses of 75 mg and 150 mg once daily in combination with pegylated liposomal doxorubicin with and without IPI-549. Overall, no major safety concerns were identified at this dose. A pharmacodynamic measure was also incorporated in these studies. Levels of phosphorylated cAMP response element-binding protein (pCREB) were assessed by flow cytometry, both in the absence of and following ex vivo stimulation with the adenosine receptor agonist 5′-N-ethylcarboxamide adenosine (NECA). The dose of 150 mg was identified as the dose for Phase 2 expansion studies since it resulted in near maximal reduction in pCREB in both healthy subjects and cancer patients. Subsequently, the dose of 150 mg has been used in other studies in cancer patients; no new concerns regarding safety of this dose have been identified.

Additional information regarding administration of SRF617, etrumadenant, and zimberelimab is described in Section 7 and in the SRF617-201 Pharmacy Manual.

2. OBJECTIVES

2.1. Primary Objectives

- 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

2.2. Secondary Objectives

- To evaluate additional preliminary efficacy parameters of the combination including ORR, PSA response, clinical benefit, duration of response (DoR), and radiologic 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)

2.3. Exploratory Objectives

- 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 TME
- 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

3. ENDPOINTS

3.1. Primary Endpoints

- The proportion of patients with a response, defined as PSA_{50} response (≥ 50% decline) and/or radiographic objective response of complete response (CR) or partial response (PR) per Prostate Cancer Working Group (PCWG3) criteria
- Incidence and severity of AEs

3.2. Secondary Endpoints

- ORR per PCWG3 criteria, ORR per RECIST v1.1, duration of response, disease control rate (DCR), 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

3.3. Exploratory Endpoints

- 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 PAP levels
- PAP expression levels in tumors in patients who undergo tumor biopsy
- PD-L1 and CD39 expression levels in tumors in patients who undergo tumor biopsy

4. TRIAL 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 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.

The trial will employ a Simon 2-stage design with an integrated safety lead-in for the triplet combination of SRF617, etrumadenant, and zimberelimab. Cycles are 28 days in duration.

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 (Section 4.7). Patients may remain on study drug longer than 2 years with agreement from the trial Investigator and Sponsor.

4.1. Stage 1

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 SRC has reviewed the aggregate safety data. Once the SRC deems it safe to proceed, an additional 11 patients will be enrolled.

To be considered evaluable for the Safety Lead-in, patients must have completed at least 50% of the prescribed doses of all 3 drugs during the review period (Day 1-28 = Cycle 1) and must not have discontinued treatment during Cycle 1 for reasons other than drug-related AEs. For example, patients who discontinued study treatment during Cycle 1 for progressive disease or for patient or physician preference but without experiencing a Grade ≥ 3 related toxicity would not be considered fully evaluable for the Safety Lead-in and would be replaced. A 'related' toxicity is defined as those toxicities assessed by the Investigator to be possibly, probably, or definitely related to any study drug.

4.2. Stage 2

Based on an evaluation of safety and response data, the trial will proceed to the Stage 2 expansion if ≥ 1 radiographic CR/PR or 2 PSA responses (defined as a ≥ 50% decline [PSA_{50}]) according to 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.

4.3. Safety Review Committee

This trial will use an SRC, which will meet regularly throughout the trial to review all available safety, PK, and preliminary efficacy data. The SRC will be composed of a medical representative from the Sponsor, a Medical/Safety Monitor from the Contract Research Organization supporting the trial (if applicable), and all Principal Investigators (or their specified delegates) at each of the enrolling sites. The SRC may recommend investigating intermediate doses or alternative schedules for administration of SRF617 to optimize combination dose determination. The SRC may recommend halting or stopping the trial at any time based on a comprehensive review of all clinical data.

4.4. Dosing Frequency

SRF617 will be administered in combination with etrumadenant and zimberelimab in 28-day cycles according to the following dosing schedule:

- SRF617 1400 mg IV q2 weeks on Days 1 and 15
- Etrumadenant 150 mg orally daily
- Zimberelimab 480 mg IV q4 weeks on Day 1

4.5. Monitoring of Adverse Events

All patients will be monitored continuously for toxicity while on study drug. AE severity will be assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0, or higher. If a patient has an AE of a particular severity or an AE at least possibly related to study drug, then dose modifications should be made according to the guidelines set forth in the trial protocol (see Section 7.4).

4.6. Trial Stopping Rules

The following safety stopping rule will also be applied during the Safety Lead-in: If 2 or more of these 6 patients experience a Grade ≥ 3 related AE (with the exception of toxicities listed in Table 4), any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1, or prolonged delay (>14 days in initiating Cycle 2 due to toxicity), the trial will be halted for SRC review.

Table 4: Stopping Rule Exceptions

The following Grade ≥ 3 toxicities considered at least possibly related to study treatment would **not** be considered to meet criteria for a safety stopping rule:	
Nausea	Any Grade ≥ 3 event responding to supportive treatment within 3 days
Vomiting	
Diarrhea	
Fatigue	Grade ≥ 3 lasting < 7 days
Asymptomatic amylase/lipase elevations	Grade ≥ 3 lasting any duration if asymptomatic and no clinical signs of pancreatitis
Thyroid function abnormalities (eg, hypo- or hyperthyroidism)	Grade ≥ 3 lasting any duration if can be controlled with treatment such as thyroid supplementation or beta blockade
Rash	Grade ≥ 3 recovering to Grade 1 with treatment (ie, steroids) within 7 days
Alopecia	Grade ≤ 2 lasting any duration
Non-hematologic laboratory abnormalities	Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, electrolytes, uric acid, etc.

4.7. Treatment Discontinuation

A patient should be discontinued from a study drug if, in the opinion of the Investigator or Sponsor, it is medically necessary or if it is the wish of the patient. Discontinuation of study treatment does not represent withdrawal from the trial.

All patients should undergo the Safety Follow-up visit when they discontinue the last study drug (Section 6.4).

Patients will be discontinued from all study drugs for any of the following reasons:

- AE(s) that requires permanent discontinuation of all study drugs
- Disease progression as measured by the appropriate response criteria
  - Note: Patients who meet criteria may continue past disease progression (see Section 6.3)
- Noncompliance with protocol
- Investigator decision (specific justification to be documented)
- Patient is lost to follow-up
- Termination of the trial by the Sponsor
- Voluntary withdrawal by patient

AEs leading to the discontinuation of study drug will be followed until resolution to Baseline or until the event is considered stable or chronic. Patients who discontinue treatment with any study drug for any reason, but who are deriving clinical benefit (objective response or stable disease) from one or both of the remaining drugs, may continue to receive those study drugs at the discretion of the Investigator and Sponsor.

The End of Treatment (EoT) visit should occur within 7 days after a patient discontinues the last study drug. Disease response assessment is not required for patients whose most recent scan was ≤ 6 weeks before the EoT visit. Other assessments previously performed within the previous 2 weeks need not be repeated at EoT. For patients who discontinue the last study drug because of a treatment interruption lasting > 56 days, the EoT visit should be completed as soon as possible.

All patients will have a Safety Follow-up visit at 30 days after the last dose of SRF617, 30 days after the last dose of etrumadenant, or 90 (+ 7) days after the last dose of zimberelimab (30 days after the last dose of zimberelimab if the patient initiates new anticancer therapy), whichever is later. If possible, this visit should occur before the initiation of any subsequent anticancer therapy. At a minimum, this visit should include collection of AEs and concomitant medications/procedures.

Response assessments will be conducted per Table 2 until the patient experiences progressive disease or discontinues the trial.

4.8. Trial Withdrawal

Patients may voluntarily withdraw from the trial at any time for any reason without prejudice.

Patients will be withdrawn from the trial for any of the following reasons:

- Patient death
- Patient lost to follow-up
- Termination of the trial by Sponsor
- Voluntary withdrawal of consent by patient

If the patient withdraws consent from the overall trial participation (and not just study drug), no further evaluations should be performed and no attempts should be made to collect additional data.

5. TRIAL POPULATION

5.1. Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Males ≥ 18 years of age on the day of signing informed consent.
2. Metastatic castration-resistant prostate cancer with castrate levels of testosterone (≤ 50 ng/dL or ≤ 1.7 nmol/L).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Must have progressed (by PSA or radiologic criteria) during or following treatment with a novel ARSI (eg, abiraterone, enzalutamide, apalutamide, darolutamide), which may have been given for either hormone-sensitive prostate cancer (HSPC) or CRPC.
5. Must have received 1 to 2 prior lines of taxane chemotherapy, unless the physician and patient believe the patient is medically ineligible or the patient refuses (ineligibility or refusal must be documented in the source documents).
6. Must have progressed by PSA or radiologic criteria on or during last therapy for prostate cancer.
7. Measurable or non-measurable disease as per radiographic evaluation. Lesions situated in a previously irradiated area are considered evaluable if progression has been demonstrated in such lesions since radiation.
    - Note: If disease is considered non-measurable, a minimum PSA of 1 ng/dL is required with at least 1 confirmed rise at a minimum of a 1-week interval.
8. Washout period from the last dose of previous anticancer therapy (chemotherapy, biologic, or other investigational agent) to the first dose of study drug must be > 5 times the half-life of the agent or > 21 days, whichever is shorter. The washout period for palliative radiation (defined as ≤ 2 weeks of radiation) to non-central nervous system (CNS) disease is > 7 days.
9. Resolution of non-immune-related AEs secondary to prior anticancer therapy (excluding alopecia and peripheral neuropathy) to Grade ≤ 1 per NCI-CTCAE version 5.0 or higher, and complete resolution of immune-related AEs secondary to prior immunotherapy.
    - Note: Patients with the following clinically stable or clinically nonsignificant immune-related AEs are permitted: Controlled thyroid disorders, vitiligo, asymptomatic elevated amylase/lipase, type 1 diabetes on insulin, Grade ≤ 2 controlled rash, Grade ≤ 2 electrolyte abnormalities on stable dose of supplementation.
10. Adequate hematologic function, defined as absolute neutrophil count (ANC) ≥ 1.5×10^9/L, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100×10^9/L. Transfusions are permitted to meet hemoglobin and platelet criteria. However, the patient must have a stable hemoglobin level and platelet count for ≥ 2 weeks prior to dosing without transfusion.

11. Adequate renal function, defined as serum creatinine clearance ≥ 30 mL/min per Cockcroft-Gault formula.
12. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (≤ 3 × ULN if elevated because of Gilbert's syndrome, and ≤ 2 × ULN for patients with known liver metastases).
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN (< 5 × ULN if liver metastases present).
14. Prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy, in which case PT/INR or aPTT must be within therapeutic range of intended use of anticoagulants.
15. Willingness of male patients who are not surgically sterile to use medically acceptable methods of birth control for the duration of the study treatment period, including 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, whichever is later; male patients must refrain from donating sperm for 4 months after the last dose of any study drug. Sexually active men, when having sexual intercourse with a female of reproductive potential, should use an efficient barrier contraceptive (condom plus spermicide); the respective partner should also use an additional efficient contraceptive method (eg, oral pills, intrauterine device, or diaphragm, and spermicide).
16. Ability to adhere to the trial visit schedule and all protocol requirements.
17. Institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) signed and dated by patient (or legally acceptable representative if applicable) before any Screening procedures are performed.

5.2. Exclusion Criteria

Patients are to be excluded from the trial if they meet any of the following criteria:

1. Currently participating in or has participated in a trial of an investigational device or has used an investigational device within 21 days before the first dose of study drug.
2. Any component of small cell or neuroendocrine histology.
3. Previously received an anti-CD39 antibody, anti-CD39 targeted therapy, or other agent targeting the adenosine pathway.
4. Prior treatment with PD-L1/PD-1 inhibitors.
5. Prior treatment with ≥ 3 lines of taxane chemotherapy administered as a single agent or as part of a combination regimen.
6. Symptomatic or untreated brain metastases (including leptomeningeal metastases). Patients previously treated for brain metastases must be at least 4 weeks from completion of radiation treatment with follow-up imaging showing no progression.
7. Current pneumonitis with or without steroid requirement or history of pneumonitis requiring steroids.

8. Another malignancy other than prostate within 2 years of trial entry, except for those with a low risk of spreading or negligible risk of death such as non-melanoma skin cancer or Ta superficial bladder cancer.
9. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
10. Medical conditions requiring chronic steroid (ie, > 10 mg/day of prednisone or its equivalent).
    - Note: Replacement therapy (eg, levothyroxine, insulin, or physiologic corticosteroid replacement therapy for thyroid, adrenal, or pituitary insufficiency) is allowed.
11. Concomitant therapy with agents that may have potential drug-drug interactions with etrumadenant:
    a) Known P-glycoprotein (P-gp) substrates with a narrow therapeutic window, administered orally (eg, digoxin) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    b) Known strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    c) Known breast cancer resistance protein (BCRP) substrates with a narrow therapeutic window, administered orally (eg, prazosin, rosuvastatin) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.
    d) Additional substrates, inhibitors, and inducers with the potential for drug-drug interactions with etrumadenant within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment. Refer to Appendix 1 and the following: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
12. History of Grade ≥ 3 allergic or anaphylactic reaction to any monoclonal antibody therapy, any excipient in the study drugs, or fusion proteins.
13. Prior hematopoietic stem cell or solid organ transplant.
14. Known current or prior infection with HIV, hepatitis B virus (HBV), or current infection with hepatitis C virus (HCV).
    - Exception: Controlled active HBV or fully treated HCV infection is permitted. Antiviral therapy as per local standard of care should be continued.
      – Controlled disease is considered HBV DNA < 500 IU/mL during the Screening Period with willingness to continue antiviral treatment during the length of the trial. The patient must be on anti-HBV treatment (per local standard of care; eg, entecavir) for a minimum of 14 days prior to trial entry.

- For patients with HCV, only cured disease or HCV considered fully treated and no longer requiring antiviral therapy for control is permitted.
- No co-infection with HCV and HBV is allowed. HCV and HBV co-infection is defined as HCV RNA positive and hepatitis B surface antigen (HBsAg) positive and is excluded. However, a patient who is hepatitis C antibody (HCV Ab) positive, hepatitis B core antibody (HBcAb) positive, but negative HBsAg is not considered co-infection and is permitted.

15. Administration of a live attenuated vaccine within 6 weeks before the first dose of study drug.
    - Exception: Health Authority approved COVID-19 vaccines are permitted.
16. Baseline QT interval corrected (QTc) with Fridericia's method (QTcF) ≥ 480 milliseconds. This criterion does not apply to patients with a right or left bundle branch block.
17. History of unstable angina or ventricular arrhythmia requiring medication or mechanical control within 6 months before Screening.
18. History of major thromboembolic event (eg, stroke, myocardial infarction, pulmonary embolism) ≤ 6 months before the first dose of study drug.
    - Exception: Patients with history of deep vein thrombosis (DVT) are permitted if they are on stable anticoagulation treatment for at least 3 months before the first dose of study drug.
19. Any gastrointestinal condition that would preclude the use of oral medications (eg, difficulty swallowing, nausea, vomiting, or malabsorption).
20. Major surgery within 4 weeks before Screening.
21. Ongoing, uncontrolled, systemic bacterial, fungal, or viral infections at Screening. Oral antibiotics for a controlled infection are permitted. Patients on antimicrobial, antifungal, or antiviral prophylaxis are not excluded if all other inclusion and exclusion criteria are met. No severe infection within 4 weeks before first dose.
22. Unstable or severe, uncontrolled medical condition, important medical illness, abnormal laboratory finding, or psychological condition, that would, in the Investigator's judgment, increase the risk to the patient associated with participation in the trial or interfere with safe completion of the trial.

6. TRIAL PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the trial can be found in the following tables:

- Table 1: Screening Assessments Checklist
- Table 2: Schedule of Assessments: SRF617 + Etrumadenant + Zimberelimab Combination Therapy
- Table 3: Schedule of Pharmacokinetic and Antidrug Antibody Assessments for Combination Therapy

A brief description of all assessments is presented in Section 6.1.

6.1. Procedures and Assessments

All potential patients will undergo Screening assessments to determine trial eligibility. Patients who do not meet Screening criteria may be rescreened later within the initial Screening Period (ie, ≤ 30 days from first dose) to confirm eligibility. If rescreening occurs after the initial Screening Period, sites should contact the trial Medical Monitor for approval. During the Screening Period, a patient number will be assigned.

6.1.1. Informed Consent

Patients potentially eligible for participation must sign an ICF before initiating any trial-specific procedures. Standard of care assessments that fulfill trial eligibility requirements may be performed before the patient signs the ICF.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential patient and documented in the patient medical record and electronic case report form (eCRF).

6.1.3. Medical History, Demographics, Disease Characterization, and Cancer History

Each patient's complete medical history will be obtained, including demographics, cancer history (eg, date of prostate cancer diagnosis, date of metastatic disease diagnosis, date when the disease became castrate resistant, and castrate-resistant status [chemical vs. surgical]), disease characterization (eg, Gleason score at diagnosis [≤ 6, 7, ≥ 8], distribution of metastatic disease at trial entry [eg, bone, lymph node, visceral disease (lung or liver), other soft tissue], number of bone metastases [0, 1 to 4, 5 to 9, 10 to 20, > 20], pain [yes/no/NA], and when available: tumor genomics [eg, microsatellite instability-high/deficient mismatch repair, DNA repair pathway alterations such as BRCA1/2, ATM, PALB2] or PD-L1 immunohistochemistry status), and documentation of all previous treatments and treatment results, ie, best response to previous prostate cancer treatments.

6.1.4. Prior/Concomitant Medications and Procedures

At Screening, concomitant and previous medications and procedures will be assessed including all medications/procedures that have occurred within the previous 30 days (previous 6 weeks for

live attenuated vaccines). In addition, any cancer treatment procedures from any time in the past (eg, radiation, surgical resection) should be captured under prior procedures. Assessment of any change in concomitant medications or procedures since the last visit will occur at all further patient visits through Safety Follow-up.

6.1.5. Physical Examination

A full physical examination will be performed at Screening and will include vital signs (temperature, blood pressure [sitting for 5 minutes], pulse, and respiratory rate), height, and weight, as well as a systematic physical examination; this will constitute the Baseline examination. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart. Clinically significant findings at Screening should be recorded as medical history.

After Screening, physical examination will be symptom directed and will include collection of vital signs; vital signs will be collected at each clinic visit. Results from the symptom-directed physical examinations will be used for assessment of disease response. Any new clinically significant abnormality or worsening conditions from Baseline should be recorded as an AE.

6.1.6. Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at Screening and frequently during the study treatment period, as well as at the EoT and 90-day Safety Follow-up visits. If the ECOG performance status assessed at Screening is performed within 7 days before the first dose (Cycle 1 Day 1 [C1D1]), the Screening assessment can be used and does not need to be repeated. Refer to Appendix 2 for a sample of the ECOG assessment.

6.1.7. Electrocardiogram

At Screening, a standard 12-lead electrocardiogram (ECG) will be conducted after an approximately 10-minute rest period in all patients and will be interpreted by the Investigator to confirm eligibility. QTc measurements will use Fridericia's correction method (QTcF). Patients with Screening/Baseline QTcF $\geq$ 480 milliseconds will be excluded from trial participation (see Section 5.2 for additional details). Subsequent ECGs will only be conducted if clinically indicated, per Investigator discretion.

6.1.8. Clinical Laboratory Tests

The following laboratory parameters will be measured as indicated at Screening (Table 1) and/or throughout the treatment period (Table 2), as appropriate for the site, and will be analyzed locally:

- Blood chemistry laboratory parameters, including sodium, potassium, chloride, bicarbonate (or carbon dioxide), blood urea nitrogen or urea, creatinine, calcium, phosphorous, magnesium, glucose, albumin, and total protein
- Liver function tests, including serum ALT, serum AST, total and direct bilirubin, and alkaline phosphatase
- Pancreatic tests, including amylase and lipase

- Hematology laboratory parameters, including hemoglobin, hematocrit, red blood cell (RBC) count, and white blood cell count with differential, including ANC, absolute lymphocyte count, platelet count, and reticulocyte count
- Coagulation laboratory parameters, including PT and aPTT
  - For patients receiving anticoagulation therapy affecting prothrombin time, an INR must be obtained. For patients receiving anticoagulation therapy affecting PT/INR or aPTT, these laboratory parameters should be monitored serially during the trial.
- Thyroid function tests, including thyroid stimulating hormone and free thyroxine
- Complete urinalysis with qualitative analysis for protein
- PSA
- PAP
- Lactate dehydrogenase (LDH)
- Testosterone

Unscheduled assessments should be done as clinically indicated.

Clinically significant laboratory findings at Screening should be recorded as medical history. Clinically significant laboratory findings identified after Screening, including but not limited to those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be reported as AEs (see Section 8.1.1 for the definition of an AE).

6.1.9. Additional Screening Laboratory Measurements

At Screening, the following assessments will be performed to determine eligibility:

Hepatitis:

- All patients will be tested for anti-HCV Ab and HBsAg at Screening. If Ab test is positive, hepatitis C RNA (viral load) or HBV DNA will be collected. Patients with a positive anti-HCV and HCV RNA titer or HBsAg test will be excluded from enrolling in the trial (except for patients with controlled viral disease as outlined in eligibility criteria). While HCV and HBV co-infection is defined as HCV RNA positive and HBsAg positive and is excluded, a patient who is HCV Ab+, HBcAb+ but negative HBsAg is not considered co-infection and is permitted.

HIV:

- Patients without documentation of a prior negative HIV test result (eg, antibody, antigen or polymerase chain reaction-based test) are required to undergo HIV testing during Screening. Only patients with negative HIV results will be eligible to enroll.

6.1.10. Tumor Evaluation

Quantification of Baseline disease burden should be performed at Screening (Table 1) and on-trial tumor response evaluated as outlined in the Schedule of Assessments (Table 2).

Assessments of Baseline disease burden, response, and disease progression will be evaluated using PCWG3 criteria and RECIST v1.1. See Section 6.3 for additional information about specific tests to be performed while on trial. See Appendix 3 for details about the PCWG3 criteria and RECIST v1.1.

6.1.11. Tumor Biopsies

Fresh tumor biopsies are optional and will be performed in patients who consent to the procedure, who have non-bone metastases amenable to biopsy, and for whom the procedure is deemed safe. Tumor biopsies may be performed for any accessible non-bone tumor during the Screening period and again any time after dosing during Cycle 2 or at EoT, whichever visit comes first. A + 7-day window for scheduling is permitted for EoT biopsies.

Fresh tumor tissue biopsies may be performed at the time points outlined in Table 1 (Screening) and Table 2.

Archival tumor tissue collection is required for all patients unless an exception is granted with Sponsor approval. Refer to the Laboratory Manual for details on sample handling procedures and shipping requirements for fresh tumor biopsy samples and archival tumor tissue samples.

6.1.12. Pharmacokinetic Sampling

PK sample collection time points are shown in Table 3. Serum samples will be analyzed for SRF617 and zimberelimab concentrations. Plasma samples will be analyzed for etrumadenant.

The date and time of each sample collection, and the date and time of the prior study drug dose, must be recorded for all collected samples.

An additional PK sample, beyond those listed in Table 3 may be requested (when feasible) at the time of any unusual safety event (ie, an AE different in type and severity from that which is expected in the setting of SRF617, etrumadenant, or zimberelimab use), or if a sample is found to be compromised.

Refer to the Laboratory Manual for details on sample handling procedures and shipping requirements for PK samples.

6.1.13. Biomarker Assessments

Samples will be collected for biomarker analysis to investigate the biological effects of SRF617 at the molecular and cellular level, as well as to evaluate how changes in the markers and immune cell populations may relate to exposure and clinical outcomes. The goal of the biomarker assessments is to provide supportive data for the clinical trial. There may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis because of either practical or strategic reasons, eg, inadequate sample number, sample quality issues precluding analysis. Therefore, sample collection and/or analysis may be omitted at the discretion of the Sponsor. The timing around collection of these assessments is outlined in Table 1 (archival tumor tissue) and Table 2.

Additional biomarker samples beyond those listed in Table 2 may be requested (when feasible) at the time of any unusual safety event (ie, an AE different in type and severity from that which

is expected in the setting of SRF617, etrumadenant, or zimberelimab use), or if a sample is found to be compromised.

The following biomarker samples may be analyzed at a central laboratory or a specialized laboratory vendor:

- Blood (PBMCs) for immunophenotyping and immune monitoring:
  - To monitor the effects of treatment on various peripheral blood immune cell populations, PBMC immunophenotyping by flow cytometry analysis will be used for quantitation and to assess relative frequency of various immune cell subsets. Subsets may include, but are not limited to, monocytes, neutrophils, myeloid-derived suppressor cells, and T/B/NK-cell populations.
- Blood for cytokine/chemokine/soluble factors:
  - For profiling of potential predictive and pharmacodynamic biomarkers of response and/or resistance to SRF617.
  - Serum levels of soluble factors associated with cancer and immunological function will be assessed. Examples include, but are not limited to, MCP-1 (CCL2), TNFα, MIP-1α (CCL3), MIP-1β (CCL4), IL-1β, interferon (IFN)γ, IL-10, IL-8, IL-6, and IL-2.
- Archival tumor tissue and fresh tumor biopsy tissues, when available:
  - For assessment of potential predictive biomarkers in the tumor and TME.
  - In situ examination of markers on tumor cells, distinct immune cell populations, and other nontumor cellular compartments (eg, stroma) by immunohistochemistry may include, but are not limited to, CD39, PD-L1, and T-cell and macrophage populations as assessed by various immune cell markers (eg, CD8 and CD68).
  - Gene expression evaluation of tumor-specific and immune-related genes and/or gene signatures.

Samples collected during the trial will banked for up to 10 years. Any remaining material, as permitted, may be used to conduct research related to either SRF617 and CD39-relevant pathways, or to cancer biology in general.

Refer to the Laboratory Manual for biomarker sample handling procedures and shipping requirements.

6.2. Safety Assessments

6.2.1. Adverse Events

Serious adverse events (SAEs) will be immediately reported from the time of signing the ICF until the Safety Follow-up visit, 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 initiates new anticancer therapy), whichever is later, or until the patient has been deemed to be a screen failure. At any time after completion of the AE reporting

period, if an Investigator becomes aware of an SAE that the Investigator considers to be related to any study drug, the event must be reported.

Nonserious AEs will be monitored from the time of the first dose of study drug through 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 later. After the patient is enrolled, all AEs will be captured on the eCRF.

See Section 8.2 for a full description of the collection and reporting of AEs during this trial.

6.2.2. Antidrug Antibody Assay

An ADA assay will be performed at a central laboratory for SRF617 immunogenicity testing. Refer to the Laboratory Manual for sample handling procedures and shipping requirements. ADA assays will also be performed for zimberelimab, with sparse sampling throughout the trial. The time points for the collection of this assessment are detailed in Table 3. An additional ADA sample, beyond those listed, may be requested (when feasible) at the time of any unusual safety event, ie, an AE different in type and severity from that which is expected in the setting of SRF617, etrumadenant, or zimberelimab use. Patients who test positive for SRF617 ADA will be tested until their ADA levels revert to Baseline or the end of the trial.

6.3. Response Assessment Procedures

For all parts of the trial, response and progression will be determined by Investigator assessment at the time points shown in Table 2 as compared with Baseline tumor evaluation (see Section 6.1.10) performed in Screening assessments (Table 1). The modality chosen to evaluate each individual patient should be the same throughout the duration of the trial. Redacted images may be collected.

Of note, for patients who achieve a CR or PR, a follow-up response assessment should be performed after at least 4 weeks to confirm the response. Patients will be expected to continue to follow the response assessment schedule as outlined in the Schedules of Assessments.

These evaluations will be conducted until the patient experiences progressive disease or discontinues the trial. See Section 6.3.1 for more information regarding the response procedures and response criteria.

Note that pseudoprogression or initial progression followed by clinical benefit/response may occur in patients treated with immune-modulating agents; therefore, treatment past progression may be considered if the Investigator and Sponsor agree and the patient is otherwise clinically stable and believed to be deriving clinical benefit. Patients who remain on trial past initial radiologic progression should have repeat imaging within 4 to 8 weeks.

6.3.1. Response Evaluation Criteria

PCWG3 criteria will be applied at the time points specified in the Schedules of Assessments (Table 2). 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). If osseous disease is present at Baseline, disease assessment will follow the 2+2 rule to discriminate between flare and true progressive disease in bone lesions. The Screening bone scan will be used as the Baseline scan. Patients will be permitted to continue on study drug past progression if the Investigator feels the patient is otherwise experiencing clinical benefit and Sponsor agrees (see Section 6.3). However, if a repeat scan 4 to 8 weeks after initial progressive disease confirms additional progression per PCWG3 criteria, the patient should discontinue study drug(s).

6.4. Safety Follow-up Visit

All patients will have a Safety Follow-up visit at 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 later. If possible, this visit should occur before the initiation of any subsequent anticancer therapy. Patients continuing to experience toxicity at this point after the discontinuation of treatment will continue to be followed at least monthly by phone/telehealth or in-person visit until resolution or determination in the clinical judgment of the Investigator that no further improvement is expected.

6.5. Long-term Follow-up for Safety

SAEs will be reported through 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 initiates new anticancer therapy), whichever is later. Pregnancy events in female partners of male trial participants will be followed for 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, whichever is later. Long-term follow-up reporting may be conducted in person or by phone.

6.6. Concomitant Medications or Procedures

6.6.1. Transfusion Support (Prophylaxis or Supportive Care)

Blood cell transfusion (packed RBCs or platelets) are permitted as clinically indicated. Transfusions are also permitted to meet hemoglobin and platelet inclusion criteria. However, the patient must have a stable hemoglobin level and platelet count for ≥ 2 weeks prior to dosing without transfusion.

6.6.2. Prohibited Medications

During the study treatment period, the following medications are prohibited:

- Any additional anticancer therapy.
- Other investigational agents.
- Systemic immunostimulatory agents (including but not limited to IFNs and IL-2).
- Systemic immunosuppressive medications (eg, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents), including

systemic corticosteroids administered at > 10 mg/day prednisone or equivalent on a long-term basis are prohibited.

  - Acute, low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of adverse events or premedication are allowed after Medical Monitor approval has been obtained.
  - Inhaled steroids for the management of asthma/chronic obstructive pulmonary disease are permitted.

- If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Medical Monitor.
  - Exception: The Sponsor is supportive of patients receiving a Health Authority approved COVID-19 vaccine if they have no known contraindications to the vaccination. If administered, the name of the vaccine, the dose, and the dates administered should be documented in the medical records as well as the concomitant medication section of the eCRF. Investigators should have an informed risk/benefit discussion with the patient in making the decision to receive the vaccine and monitor for toxicity as there could be unknown risks of (1) heightened immune response and thus toxicity or (2) diminished immune response to either the study treatment, the vaccine, or both. If a trial patient decides to pursue an approved COVID-19 vaccination, the Sponsor recommends scheduling vaccination such that the full vaccination course occurs at least 2 weeks before C1D1, when possible.
- Given potential interactions with etrumadenant, co-administration of the following medications are prohibited:
  - BCRP substrates with a narrow therapeutic window, administered orally (eg, prazosin, rosuvastatin).
  - P-gp substrates with a narrow therapeutic window, administered orally (eg, digoxin).
  - Strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and strong CYP3A4 inhibitors (eg, clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole).
  - Refer to Appendix 1 and the following for more examples of relevant substrates, inhibitors, and inducers with the potential for drug-drug interactions with etrumadenant: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

6.6.3. Other Concomitant Therapies or Procedures

- Radiation therapy to a symptomatic or progressing solitary lesion including the brain may be allowed at the Sponsor's discretion and if the Investigator feels the patient is deriving clinical benefit/disease control in the other disease sites.

- Any other medication that is considered necessary for the patient's welfare, including antimicrobial prophylaxis and growth factor support, and that is not expected to interfere with the evaluation of study drug may be given at the discretion of the Investigator.
- Supportive care medicines (eg, bisphosphonates or RANK ligand inhibitors) are allowed on trial.
- Patients may receive a COVID-19 vaccination. Because COVID-19 vaccines are reported to have side effects similar to those of an infusion reaction, the vaccination should take place at a different place and time from any trial infusion. For vaccines requiring 2 doses, both doses should be administered in this fashion. For any patient presenting to clinic or emergency department with symptoms consistent with COVID-19 infection[70], testing for the presence of the novel coronavirus is recommended, as well as isolation and quarantine following institutional and local health authority guidance[71](for experience and recommendations specific to oncology clinics). AEs or treatment discontinuation suspected to be attributable to infection with COVID-19 should be indicated as such on the relevant case report forms.

6.6.4. Contraception and Pregnancy

The effects of the study treatment on conception, pregnancy, and lactation are unknown.

Male patients with female partners of reproductive potential are required to use highly effective contraceptive measures from the first dose of study treatment until 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, whichever is later.

- A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.
- A female partner of a male patient is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.
  - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly effective contraception is defined as use of one or more methods that result in a low failure rate (ie, < 1%). Highly effective contraceptive measures include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable

- Intrauterine device
- Intrauterine hormone-releasing system in combination with a barrier method (preferably male condom)
- Surgical sterilization
  - Male patient is vasectomized (with documented medical confirmation of surgical success) and is the sole sexual partner of a female with reproductive potential
  - Female partner of the male patient has undergone bilateral tubal ligation
- Complete sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient

To ensure proper birth control, male patients, when having sexual intercourse with a female of reproductive potential, should use an efficient barrier contraceptive (condom plus spermicide); the respective partner should also use an additional efficient contraceptive method (eg, oral pills, intrauterine device, or diaphragm, and spermicide).

Patients should not donate sperm for 4 months after the last dose of any study drug.

7. STUDY DRUG MATERIALS AND MANAGEMENT

On visit days where study drug is administered in the clinic, dosing will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

7.1. SRF617

7.1.1. Description of SRF617

SRF617 drug product is a sterile filtered liquid, aseptically filled into a single-use stoppered glass vial and sealed with a flip-off seal. SRF617 drug product contains at least 2.0 mL at a target concentration of 50 mg/mL in 10 mM histidine, 280 nM sucrose, and 0.02% polysorbate 20, pH 6.0. All lots of drug product are tested to ensure product identity, strength, quality, purity, and potency. For IV infusion, the drug product will be diluted into normal saline (0.9%, Sodium Chloride Injection, US Pharmacopeia) for injection as diluent. Additional details on the preparation and administration of SRF617 drug product will be provided to the Investigator in the Pharmacy Manual.

7.1.2. SRF617 Dosage

Patients will receive SRF617 1400 mg IV q2 weeks on Days 1 and 15 of a 28-day cycle. SRF617 is administered as an IV infusion supplied by the Sponsor.

Dose reductions and discontinuations for SRF617 in individual patients may be made based on the clinical judgment of the Investigator with notification to the Medical Monitor/Sponsor (see Section 7.4).

7.1.3. SRF617 Administration

SRF617 will be administered as an IV infusion. SRF617 infusion should be administered under the supervision of a physician, or other trial personnel, experienced in the use of IV agents. The suggested infusion duration range is approximately 30 to 60 minutes. The timing of SRF617 administration relative to etrumadenant and zimberelimab is shown in Table 5.

Table 5: Timing of Administration of Study Drug on Infusion Days in Trial SRF617-201

Cycle/Day	Order/Timing of study drug administration[a]
Day 1 of each cycle[b]	• SRF617 will be administered first • Etrumadenant will be taken orally after at least a 30-minute observation period that begins at the end of the SRF617 infusion • Zimberelimab will be administered at least 30 minutes after the patient has taken etrumadenant
Day 15 of each cycle[b]	• SRF617 will be administered first • Etrumadenant will be taken orally after at least a 30-minute observation period that begins at the end of the SRF617 infusion

[a] The timing and order of administration of study drug may be changed at the direction of the trial Safety Review Committee.

[b] On Day 1 and Day 15 infusion visits, patients will hold etrumadenant administration until directed by trial personnel.

Missed doses of SRF617 or zimberelimab (more than ± 3 days) should not be made up; rather, follow the schedule for the next biweekly dose. There should be a minimum of 11 days between SRF617 infusions and between zimberelimab infusions. The ± 3-day window may be used one time per patient during the study treatment period without contacting the Sponsor. Please contact the Sponsor if a second ± 3-day window is needed.

Please refer to the Pharmacy Manual for detailed administration instructions.

7.1.4. SRF617 Storage

SRF617 is supplied in vials for single use. Each vial contains 100 mg of SRF617 for IV infusion. The drug product vials should always be stored in the container provided to the pharmacy and should be stored at -20 °C ± 5 °C (-13 °F to 5 °F) protected from light. Caution is required when handling SRF617. Pharmacists should follow standard procedures for handling investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, the individual should treat for physical exposure (skin washing) or inhalation (move to fresh air, as necessary) and, if needed, seek medical advice. During the preparation of SRF617, drug product is diluted in normal saline (0.9% Sodium Chloride for Injection, United States Pharmacopeia) as diluent. Once diluted, SRF617 should be stored at 2 °C to 8 °C or at room temperature until infusion and administered within 4 hours.

7.1.5. SRF617 Preinfusion Medications

For the first administration of SRF617 (C1D1), no preinfusion medication is required. If a Grade 1 or higher infusion-related AE is recorded at any dose, the following premedications should be administered for all subsequent doses for that patient:

- Antipyretics (oral acetaminophen 650-1000 mg)
- Antihistamine (oral or IV diphenhydramine 25-50 mg or equivalent)

Patients with a Grade 2 or higher infusion reaction should also be premedicated with a glucocorticoid (IV dexamethasone 20 mg or methylprednisolone 80 mg) for all subsequent infusions.

7.1.6. SRF617 Postinfusion Medications

No specific postinfusion medications are required for SRF617.

7.1.7. SRF617 Treatment Continuation

Patients will remain on study treatment until disease progression, unacceptable toxicity, or the completion of approximately 2 years of study treatment. Patients may remain on study treatment longer than 2 years with agreement from the trial Investigator and Sponsor.

7.2. Etrumadenant

7.2.1. Etrumadenant Dosage

Etrumadenant will be taken orally at a daily dose of 150 mg. Enough etrumadenant bottles should be dispensed to cover patient dosing through the next visit. When more than 1 bottle of etrumadenant is dispensed, patients should be instructed to open 1 bottle and consume all contents before opening another bottle. To assess compliance with self-administration of etrumadenant, patients will be required to record the time and date they took each dose in a drug diary; missed doses will also be recorded. Patients will be instructed to bring all unused doses of etrumadenant and their drug diary to the clinic at specified visits for assessments of compliance. See Table 9 for information about possible dose modifications of etrumadenant to manage drug-related toxicities.

7.2.2. Etrumadenant Administration

Etrumadenant must be taken with a full cup or glass of non-carbonated room temperature water.

All capsules for the etrumadenant dose should be taken within minutes of each other. Etrumadenant should be taken daily at approximately the same time each day. Patients should only take the prescribed dose of etrumadenant once per day. If the patient forgets to take etrumadenant at the scheduled time, they should take the dose as soon as they remember. However, if the dose is not taken by 9 PM (21:00) that same day, it should be documented as a "missed" dose in the dosing diary and the patient should resume dosing the following day at the planned dose time.

Details about the timing of etrumadenant administration on infusion days are provided in Table 5.

Formulation information for etrumadenant may be found in the etrumadenant Investigator Brochure. Additional information on the administration, distribution, storage, preparation, handling, and destruction of etrumadenant is described in the Pharmacy Manual.

7.3. Zimberelimab

7.3.1. Zimberelimab Dosage

Patients will receive zimberelimab 480 mg IV q4 weeks on Day 1 of a 28-day cycle. Zimberelimab is administered as an IV infusion supplied by the Sponsor.

There will be no dose modifications for zimberelimab in this trial. See Table 9 for additional information about management of drug-related toxicities with zimberelimab.

7.3.2. Zimberelimab Administration

Details about the timing of zimberelimab administration are provided in Table 5.

To reduce the risk of infusion reaction, patients may receive acetaminophen with or without an antihistamine or other standard therapy according to local guidelines as pre-medication prior to an infusion.

Formulation information for zimberelimab may be found in the zimberelimab Investigator Brochure. Additional information on the administration, distribution, storage, preparation, handling, and destruction of zimberelimab is described in the Pharmacy Manual.

7.4. Dose Holds, Modifications, and Discontinuations

Patients will be monitored continuously for toxicity while on study drug. Toxicity severity will be assessed using the NCI-CTCAE version 5.0 or higher. Every effort should be made to administer the study drug according to the planned dose and schedule; however, in the event of significant treatment-related toxicity, administration of study drug may need to be adjusted as described below.

Holding of 1 agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. Appropriate documentation is required regarding the drug(s) to which the Investigator is attributing the AE. If, in the opinion of the Investigator, the toxicity is related to the combination of all 3 study drugs, then all 3 drugs should be held.

If all 3 drugs have been withheld for > 56 days, then all study treatment should be discontinued.

Patients who discontinue any study drug(s) but are continuing to derive clinical benefit from any of the others may continue treatment at the discretion of the Investigator and Sponsor.

7.4.1.1. SRF617

If in the opinion of the Investigator, the patient experiences any of the toxicities outlined in Table 6 that are not clearly related to disease progression, intercurrent illness, or concomitant medications, then SRF617 dose(s) will be held until recovery of the toxicity to Grade ≤ 1 or to the patient's previous Baseline. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

Table 6: Hematologic Toxicities Leading to Dose Hold of SRF617

Toxicity	Recommended Dose Delay or Reduction
Neutropenia	
Grade 3 (ANC < 1000/μL; 1 x 10^9/L) with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4 °F) for > 1 hour	Hold until toxicity recovers to Baseline and then resume at reduced dose. If Grade ≥ 3 recurs, permanently discontinue.
Grade 4 (ANC < 500/μL; < 0.5 × 10^9/L) persisting for ≥ 7 days, and/or complicated by infection	Permanently discontinue.
Grade 4 life-threatening consequences; urgent intervention indicated	Permanently discontinue.
Platelets	
Grade 3 (platelets < 50,000-25,000/μL; < 50.0-25.0 × 10^9/L) with associated clinically significant bleeding	Permanently discontinue.
Grade 4 (platelets < 25,000/μL; < 25.0 × 10^9/L) of any duration bleeding	Permanently discontinue.
Anemia	
Grade 4 anemia defined as life-threatening consequences; urgent intervention indicated (any duration)	Permanently discontinue.
All other hematologic toxicity	
Intolerable or recurrent Grade 2	Hold until resolves to baseline and resume at reduced dose.
Grade 3	Hold until resolves to baseline and resume at reduced dose.
Recurrent Grade 3 or 4	Permanently discontinue.
Grade 4 not detailed above	Permanently discontinue.

Abbreviation: ANC = absolute neutrophil count.

Steroids may be used to manage severe (Grade ≥ 3) hematologic toxicity if thought to be immune-related. All attempts should be made to rule out other causes such as metastases, sepsis, and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, lactate dehydrogenase, haptoglobin, bone marrow biopsy, or Coomb's test, etc., should be considered to confirm the diagnosis. The AE should be reported to the Sponsor regardless of etiology.

In the unlikely event of severe bone marrow suppression, a bone marrow biopsy should be performed, if clinically feasible, to assist in determining causality.

Nonhematologic toxicities that occur during treatment with SRF617 that are not clearly related to disease progression, intercurrent illness, or concomitant medications should be managed according to the guidelines in Table 7.

Table 7: Nonhematologic Toxicities Leading to Dose Hold, Modification, or Discontinuation of SRF617

Toxicity	Recommended dose delay or reduction
Immune-mediated AEs	
Grade 2 or Grade 3 immune-mediated AEs	Hold SRF617 until resolves to Grade ≤ 1 and resume with dose reduced by 1 level.
Grade 4 immune-mediated AEs	Permanently discontinue SRF617.
Hepatotoxicity	
> 2 × ULN bilirubin AND Grade ≥ 2 ALT/AST (> 3 × ULN) in patients who enroll with Grade ≤ 1 ALT/AST OR > 2 × ULN bilirubin AND doubling of ALT/AST in patients who enroll with Grade 2 ALT/AST	In the absence of biliary obstruction or other cause responsible for the concurrent elevation, permanently discontinue SRF617.
Grade 4 ALT/AST elevation OR Grade 4 bilirubin elevation	Permanently discontinue SRF617.
Metabolic	
Grade 3 electrolyte disturbance	Hold SRF617 until resolves to Grade ≤ 1 or Baseline and resume with same dose (first occurrence) or with dose reduced by 1 level after resolution (second occurrence).
Grade 4 electrolyte disturbance	Hold SRF617 until resolves to Grade ≤ 1 or Baseline and resume with same dose if resolves in ≤ 72 hours; permanently discontinue if resolution takes > 72 hours.
Gastrointestinal	
Grade 3 vomiting, diarrhea, or nausea	Hold SRF617 until resolves to Grade ≤ 1 or Baseline and resume with same dose if resolves in ≤ 72 hours with supportive care. If it lasts > 72 hours despite optimal supportive care, resume with dose reduced by 1 level. Patients must be contacted by the Investigator or trial nurse daily until it is clear that the problem has resolved or requires additional support (eg, hospitalization).
Grade 4 vomiting or diarrhea	Permanently discontinue SRF617.

Toxicity	Recommended dose delay or reduction
Other nonhematologic toxicities	
Grade 2 or Grade 3 AEs that, in the opinion of the Investigator, require dose reduction	Hold SRF617 until resolves to Grade ≤ 1 or Baseline and resume with dose reduced by 1 level. Evaluate at least once weekly after the initial identification of the toxicity until its resolution or stabilization.
Grade 4[a] AEs that, in the opinion of the Investigator, require dose reduction	Permanently discontinue SRF617.
Other	
Treatment delays of > 56 days due to drug–related toxicities	Permanently discontinue SRF617.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
[a] Other than laboratory abnormalities that Investigator deems clinically insignificant and that last ≤ 72 hours.

For toxicities that also meet the stopping rule criteria for safety (see Section 4.6), after the first occurrence of the toxicity, the Investigator may resume SRF617 treatment at 1 dose level lower upon recovery of the toxicity to Grade ≤ 1 or Baseline value (Table 8). For toxicities that do not meet the stopping rule criteria for safety, the Investigator may resume SRF617 treatment at the same dose level upon recovery of the toxicity to Grade ≤ 1 or Baseline value. Any patient who requires more than 2 dose level reductions or requires holding of SRF617 for more than 56 days will be permanently discontinued from the study drug.

Table 8: Recommended Dose Reductions for SRF617

	Initial dose	First dose reduction	Second dose reduction
SRF617	1400 mg	700 mg	350 mg

Patients who have a dose reduction because of a toxicity may be eligible for a dose increase back to the dose level before the reduction if the following criteria are met and approved by the Sponsor:

- Patient has tolerated the lower dose level for > 1 treatment cycle
- Patient has recovered to Baseline levels from the toxicity that caused the dose reduction

Patients who have a dose reduction because of a Grade 4 nonhematologic AE may not re-escalate the dose after a dose reduction.

Infusion-Related Reactions

For infusion reactions of any grade/severity, immediately interrupt the SRF617 infusion and manage symptoms. Management of infusion reactions may require reduction in the rate of infusion or treatment discontinuation of SRF617, as outlined below:

- Grade 1 to 2 (mild or moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume in increments and at intervals clinically appropriate up to the maximum rate of 100 mL/h.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue SRF617 upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Permanently discontinue SRF617 treatment.

No dose reductions of SRF617 for infusion-related reactions are recommended.

For any patient who has a Grade ≥ 2 infusion reaction with SRF617, steroidal premedication should be used for all subsequent infusions (see Section 7.1.5).

7.4.1.2. Etrumadenant and Zimberelimab

Dose holds of etrumadenant or zimberelimab are allowed throughout the trial for no more than 56 days. If either drug has been withheld for more than 56 days, then that drug should be permanently discontinued.

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outline in Table 9. If further dose reduction below 75 mg is indicated, etrumadenant should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the Investigator's discretion with Medical Monitor approval. There will be no dose reductions for zimberelimab in this trial.

Table 9: Recommended Dose Reductions for Etrumadenant

	Initial dose	First dose reduction	Second dose reduction
Etrumadenant	150 mg	100 mg	75 mg
Zimberelimab	480 mg	N/A	N/A

Guidelines for the management of patients who experience specific AEs are provided in Table 10. For AEs for which management guidelines are not provided, patients should be managed, and study treatment should be modified as deemed appropriate by the Investigator according to best medical practice.

Table 10: Guidelines for Management of Patients who Experience Adverse Events Considered to be Related to Etrumadenant and/or Zimberelimab

Event	Severity	Etrumadenant action to be taken	Zimberelimab action to be taken
Infusion-related reaction (including hypersensitivity and anaphylaxis)	**Grade 1-2**	Continue etrumadenant at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated. Refer to the NCCN or institutional guidelines for the Management of Immune CPI Related Toxicities for symptom-directed supportive care.
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis)	**Grade 1**	Continue etrumadenant at the same dose level. Immediately institute supportive care measures for symptomatic relief.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 2	Consider etrumadenant dose modification as clinically indicated; otherwise continue at the same dose. **For suspected etrumadenant-related events:** • Immediately institute supportive measures. • If the event does not resolve to Grade 1 or better within 7 days, consider dose interruption. If event resolves to Grade 1 or better, resume etrumadenant at the same dose or with a one-level dose reduction (Table 9). • Etrumadenant dose re-escalation is permitted at the Investigator's discretion.	
	Grade 3	Withhold etrumadenant for at least 7 days until toxicity resolves to Grade 1 or better. **For suspected etrumadenant-related events:** • Immediately institute supportive measures. • If event resolves to Grade 1 or better within 56 days, resume etrumadenant with a one-level dose reduction (Table 9).[a] If not, permanently discontinue etrumadenant and contact Medical Monitor.	

Event	Severity	Etrumadenant action to be taken	Zimberelimab action to be taken
		• Etrumadenant dose re-escalation is permitted at the Investigator's discretion.	
	Grade 4	Permanently discontinue etrumadenant and contact Medical Monitor	Permanently discontinue zimberelimab and contact Medical Monitor
Hepatic toxicity (including elevations in transaminases and/or bilirubin)	**Grade 1-2** ALT/AST ≤ 5 × ULN	Continue etrumadenant at the same dose level at the Investigator's discretion. Monitor LFTs more frequently until return to < 3 × ULN or Baseline.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected non-immune-mediated transaminase elevations:** • Withhold etrumadenant and zimberelimab for up to 56 days. • Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or Baseline. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • If event resolves to Grade 1 or better within 56 days, resume etrumadenant with a one-level dose reduction (Table 9) and resume zimberelimab.[a] If not, permanently discontinue etrumadenant and zimberelimab and contact Medical Monitor. **For suspected immune-mediated transaminase elevations:** • Permanently discontinue zimberelimab and contact Medical Monitor. • Withhold etrumadenant for up to 56 days. • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better within 56 days, taper corticosteroids over ≥ 1 month and resume etrumadenant with a one-level dose reduction (Table 9).[a] If not, permanently discontinue etrumadenant and contact Medical Monitor.	
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and contact Medical Monitor. For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	Permanently discontinue zimberelimab and contact Medical Monitor. For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.
	ALT/AST > 3 × ULN with	• Permanently discontinue etrumadenant and zimberelimab and contact Medical Monitor. • Monitor liver function at least weekly until values return to Baseline.	

Event	Severity	Etrumadenant action to be taken	Zimberelimab action to be taken
	concurrent bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. • Exception: Patients with Gilbert syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.	
Fatigue	**Grade 1-2**	Continue etrumadenant at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[a] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated. Refer to the NCCN or institutional guidelines for the Management of Immune CPI Related Toxicities for symptom-directed supportive care.
Gastrointestinal toxicity (including but not limited to diarrhea and colitis)	**Grade 1**	• Continue etrumadenant at the same dose level. • Initiate symptomatic treatment and monitor closely. • Endoscopy is recommended if symptoms persist > 7 days.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 2	• Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose. • Initiate symptomatic treatment. • Referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • **1st occurrence:** If etrumadenant was withheld and event resolves to Grade 1 or better within 56 days, resume etrumadenant at the same dose level. • **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 56 days, resume etrumadenant with a one-level dose reduction (Table 9).[a] If not, permanently discontinue etrumadenant and contact Medical Monitor.	

Event	Severity	Etrumadenant action to be taken	Zimberelimab action to be taken
		• Etrumadenant dose re-escalation is permitted at the Investigator's discretion.	
	Grade 3	Withhold etrumadenant for up to 56 days after event onset. **For suspected immune-mediated events (including colitis):** • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Follow guidance for Grade 2 recurrent or persistent events.	
	Grade 4	Permanently discontinue etrumadenant and zimberelimab and contact Medical Monitor. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.	
Etrumadenant-related toxicities not described above	**Grade 1-2**	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom directed supportive care according to institutional guidelines.	Continue zimberelimab.
	Grade 3	• Withhold etrumadenant for up to 56 days after event onset. • If event resolves to Grade 1 or better within 56 days resume etrumadenant with a one level dose reduction.[a] If not, permanently discontinue etrumadenant and contact Medical Monitor. • Etrumadenant dose re-escalation is permitted at the Investigator's discretion.	Continue zimberelimab at the Investigator's discretion.

Event	Severity	Etrumadenant action to be taken	Zimberelimab action to be taken
	Grade 4	Permanently discontinue etrumadenant and contact Medical Monitor.	Withhold zimberelimab for up to 56 days after event onset. If event improves and Medical Monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 3	• Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose. • Initiate symptomatic treatment. • If etrumadenant was withheld and event resolves to Grade 1 or better within 56 days, resume etrumadenant with a one-level dose reduction.[a] • Etrumadenant dose re-escalation is permitted at the Investigator's discretion.	Refer to the NCCN or institutional guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 56 days after event onset.
	Grade 4	Permanently discontinue etrumadenant and contact Medical Monitor.	Permanently discontinue zimberelimab and contact Medical Monitor.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPI = checkpoint inhibitor; GI = gastrointestinal; IV = intravenous; LFT = liver function test; NCCN = National Comprehensive Cancer Network; ULN = upper limit of normal

[a] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, one dose level) and then from 100 mg to 75 mg for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a patient receiving the 75 mg dose of etrumadenant, then that patient should discontinue etrumadenant.

7.5. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying drug order form.

All unused study drug will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any study drug at the clinical trial site per site procedures, or if necessary, all study drug will be returned to the Sponsor, or its designee. Disposition of all study drug should be documented, including any study drug that is lost or damaged.

7.6. Assignment to Treatment

All patients will receive open-label study drug at a dose and schedule based on the trial design (see Section 4).

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with trial participation, whether or not considered related to study drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a preexisting medical condition as well as clinically significant changes from Baseline laboratory values/conditions. Worsening of the preexisting medical condition (eg, diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A preexisting condition that has not worsened during the trial is not considered an AE. Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

8.1.2. Definition of Serious Adverse Event

An AE or suspected adverse reaction is termed "serious" if according to the Investigator or Sponsor, it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Elective or preplanned treatment for a preexisting condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE.
  - Scheduled therapy for the target disease of the trial, including admissions for transfusion support or convenience, is not considered an SAE.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly/birth defect
- Is considered an important medical event
  - If an AE does not meet one of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of important medical event. Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Per NCI-CTCAE version 5.0, if death is due to an AE (eg, Cardiac disorders: Cardiac arrest; infection, pulmonary embolism), it should be reported as a Grade 5 event under that System Organ Class and Preferred Term. However, if death is due to disease progression but cannot be attributed to a specific NCI-CTCAE term associated with Grade 5, the AE should be reported as NCI-CTCAE Preferred Term "disease progression" found in the System Organ Class, "General disorders and administration site conditions." Evidence that the death was a manifestation of the underlying disease (eg, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

8.1.3. Definition of an Adverse Event of Special Interest

AESIs will be collected to evaluate potential class effects for antibodies targeting CD39. AESIs for this trial are defined as thromboembolic events, eg, DVT, pulmonary embolism, stroke, myocardial infarction.

8.2. Procedures for Recording and Reporting Adverse Events

8.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each trial visit. All SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Safety Follow-up visit, 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 later. All AEs occurring in treated patients will be recorded in the eCRF from the time of first dose through 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 later. An AE will be followed until it is either resolved, has returned to Baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of the ICF through 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 later, will be processed as outlined in Section 8.2.2.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained.
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to each study drug
- Action taken with each study drug as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause; eg, for dehydration due to diarrhea, the AE would be diarrhea. However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events; eg, for sepsis secondary to pneumonia, both events should be recorded.

The signs and symptoms of progressive disease that meet the AE criteria should be reported as specific AEs and not as disease progression.

8.2.1.1. Relationship to Study Drug

The Investigator must assess whether the AE may be related to each study drug or trial-mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is "not drug related":

- None: The event is related to an etiology other than the study drug administration (the alternative etiology must be documented in the trial patient's medical record).
- Remote: The event is unlikely to be related to the study drug and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "drug related":

- Possible: There is an association between the event and the administration of study drug, and there is a plausible mechanism for the event to be related to the study drug; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study drug, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to the study drug, and causes other than study drug have been ruled out and/or the event reappeared on re-exposure to study drug.

8.2.1.2. Adverse Event Severity

The Investigator will assess the grade of the AE per the NCI-CTCAE version 5.0 or higher. Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: life-threatening consequences; urgent intervention indicated

- Grade 5: death related to AE

Note: It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 8.1.2 above.

8.2.1.3. Abnormal Laboratory and Electrocardiogram Values

The Investigator is responsible for reviewing clinical laboratory test and ECG results and determining whether an abnormal value in a patient represents a clinically significant change from the patient's Baseline value. In general, abnormal laboratory findings and ECGs without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. In general, an abnormal laboratory test and ECG results should be reported as an AE if the laboratory result:

- Requires an adjustment or discontinuation of study drug
- Requires treatment or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

8.2.1.4. Medication Errors, Misuse, and Abuse of Study Drug

Overdose, medication error, misuse, and abuse are defined as follows:

- Medication error: refers to an unintentional error in dispensing or administration of study drug not in accordance with the protocol
- Off-label use: relates to situations where the study drug is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where the study drug is intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to the study drug because of one's professional or nonprofessional occupation

No specific information is available on the treatment of overdose of study drug. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdoses, medication errors, abuse, and misuse will be collected as part of investigational medicinal product dosing information and/or as protocol violations, as required.

8.2.2. Reporting of Serious Adverse Events and Adverse Events of Special Interest

An SAE/AESI report form will be completed in the electronic data capture (EDC) system and submitted to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug, from the time of signing the ICF through 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 initiates new anticancer therapy), whichever is later. In the event that EDC is unavailable, the SAE/AESI paper report form must be filled out by the Investigator and sent via email within 24 hours of awareness of the event to the Clinipace Pharmacovigilance Department (safetygroup@clinipace.com), and then the information entered into the EDC once available.

Please refer to the SAE/AESI report form and completion guidelines for more detailed instructions.

The initial SAE/AESI report must be as complete as possible, including details of the current illness and SAE/AESI and an assessment of the relationship between the event and study drugs. Additional information relating to a previously reported SAE/AESI must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE/AESI considered related to study drug(s) by the Investigator occurring more than 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, the SAE must be reported as described above.

8.2.2.1. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor or designee will determine expectedness for each reported SAE based on the appropriate reference safety information for the study drug per local requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator shall notify the Central Ethics Committees of serious, related, and unexpected AE(s), or significant risks to patients, per country requirements.

The Investigator will notify the appropriate IRB/Local Ethics Committees of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs/IECs.

8.2.2.2. Reporting Adverse Events of Special Interest

AESIs for this trial are defined as thromboembolic events, eg, DVT, pulmonary embolism, stroke, myocardial infarction. The Investigator should report both serious and nonserious thromboembolic events to the Sponsor using the same methods as described for reporting SAEs.

8.2.3. Pregnancy and In Utero Drug Exposure

Pregnancies occurring in partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment period through 30 days after the patient's last dose of SRF617, 30 days after the last dose of etrumadenant, or 90 days after the last dose of

zimberelimab, whichever is later. The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this trial.

Please refer to the pregnancy notification form or pregnancy outcome form and associated completion guidelines on where and how to submit the forms.

9. STATISTICAL METHODS

Details of the statistical methods for this trial will be documented in a statistical analysis plan (SAP). The SAP may modify the statistical methods outlined in the protocol; however, any major modification will also be reflected in a protocol amendment.

9.1. Sample Size

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 Simon 2-stage design will be implemented. Simon 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.

9.2. Analysis Sets

The main analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

9.2.1. Safety Lead-in Evaluable Analysis Set

The Safety Lead-in Evaluable Analysis Set is defined as the first 6 patients enrolled in the Simon Stage 1 who either experienced a Grade ≥ 3 related AE during the first cycle of therapy (D1-28) or who completed at least 50% of the prescribed combination therapy doses. The SRC will review the aggregate safety data of these 6 patients during Cycle 1 and must clear the trial for further enrollment of the remaining 11 patients in Stage 1. The goal of the safety evaluation for the triplet is to evaluate for any signal of unexpected or increased toxicities when given together that would not be observed with any agent alone. As such, a Grade ≥ 3 toxicity known to be associated with any of the 3 study drugs' established safety profiles would not be considered concerning.

9.2.2. Safety Analysis Set

The Safety Analysis Set is defined as all patients who received any amount of study drug. This analysis set will be the primary analysis set for all safety endpoints, excluding safety lead-in evaluation. This analysis set will be used to assess the tolerability of SRF617 in combination with etrumadenant and zimberelimab.

9.2.3. Response-Evaluable Analysis Set

The Response-Evaluable Analysis Set is defined as all patients at Baseline who received study drug and had at least 1 post-Baseline response 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 study drug. This analysis set will be the primary analysis set for the primary efficacy endpoint and other efficacy endpoints.

9.2.4. Intent-to-Treat Analysis Set

The Intent-to-Treat Analysis Set is defined as all enrolled patients who received any amount of study drug.

9.2.5. SRF617 Pharmacokinetics Analysis Set

The PK Analysis Set is defined as all enrolled patients who received at least 1 dose of study drug and had at least 1 measurable PK concentration after SRF617 administration.

9.2.6. Biomarker Analysis Set

The Biomarker Analysis Set is defined as all enrolled patients who received at least 1 dose of study drug and had at least 1 adequate pharmacodynamic assessment after SRF617 administration.

9.2.7. Tumor Biopsy Analysis Set

The Tumor Biopsy Analysis Set is defined as patients with non-bone metastases amenable to biopsy, who consent to optional Baseline (± on therapy) biopsies of the metastatic site, and for whom the procedure is deemed safe.

9.3. Background Characteristics

9.3.1. Patient Disposition

The number and percentage of patients in each trial population, number of cycles completed, reason for discontinuing treatment, and reason for discontinuing the trial will be summarized.

9.3.2. Demographics and Baseline Characteristics

The following demographics and Baseline characteristics will be summarized for the Safety Analysis Set: sex, race, age, tumor stage (tumor-node-metastases), ECOG performance status, time elapsed since cancer diagnosis, sites of disease at trial entry, and prior anticancer therapies. These parameters will be summarized by incidence (n, %). Additional parameters may be specified in the SAP.

9.4. Study Drug Exposure and Compliance

Total number of cycles is defined as the maximum number of treatment cycles that a patient receives. Total cumulative dose (mg) is the sum of the actual doses that the patient receives across cycles. Total planned dose (mg) is the sum of the planned doses. The total number of cycles, total cumulative dose (mg), and total planned dose (mg) will be summarized.

The study drug exposure will be summarized based on the Safety Analysis Set.

9.5. Efficacy Analyses

ORR will be assessed separately by PCWG3 criteria as well as RECIST v1.1. The primary response endpoint is defined as the proportion of patients achieving PSA_{50} and/or radiographic objective response of CR/PR measured using PCWG3 criteria. PSA 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.[1] Changes in PSA across the trial period will be described using a waterfall plot. Swimmer plots will be used to describe time on trial, including timing and incidence of treatment past progression and timing of SAEs or AESIs, and may be used to reflect the concept of no longer clinically benefiting.

For efficacy endpoints derived from progression and/or response status, disease assessments after the start of new anticancer therapy will be excluded from consideration.

The number and percentage of patients with best overall response per PCWG3 criteria and per RECIST v1.1 in each of the response categories will be presented. ORR will be estimated by the percentage of patients achieving a best overall response of CR or PR. The estimated ORR along with the 2-sided 80% and 95% exact CIs will be provided.

Time-to-event endpoints such as the following will be summarized and estimated via the Kaplan-Meier method if the number of events is adequate:

- DoR, defined as the time from the first documented response (PSA_{50} and/or CR/PR) to documented disease progression as determined by applicable disease criteria, or documented death due to any cause, whichever occurs first. PSA_{50} and objective responses (CR or PR) will also be assessed individually.
- DCR, defined as the percentage of patients with CR, PR, or stable disease lasting a minimum of 12 weeks
- PFS, defined as the time from the first treatment on trial with study drug to documented disease progression as determined by applicable disease criteria or death
- Landmark PFS, defined as the percentage of patients who have not developed PFS events (ie, death or documented disease progression as determined by applicable disease criteria) at 6 months, 12 months, 18 months, and 24 months
- Time to PSA progression
- Time to radiologic progression

Subgroup analyses for efficacy endpoints will be done when possible and will be generally descriptive. The following subgroups are prespecified for analysis, based on Baseline characteristics: PSA (above or below the median at trial Baseline), age (above or below the median at trial Baseline, ≥ 70 years or < 70 years), ECOG performance status (0 or 1), distribution of metastatic disease (bone only ± nodal disease, nodal disease only [no bone disease present]: pelvic and extrapelvic, visceral [lung, liver, adrenal, CNS] disease [± other sites]; high vs. low volume per CHAARTED criteria[5]), type of progression at trial entry (per PCWG3: PSA only, bone only ± nodal disease, nodal disease only [no bone disease present]: pelvic and extrapelvic; visceral [lung, liver, adrenal, CNS] disease [± other sites]), number of prior treatments (1, 2, or ≥ 3), class of therapy (eg, prior chemotherapy [yes/no]), alkaline phosphatase

(above or below the median at trial Baseline), LDH (above or below the median at trial Baseline), and Gleason score (> 7 or ≤ 7 at diagnosis).

9.6. Safety Analyses

The Safety Analysis Set will be used to evaluate all safety endpoints.

9.6.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher and will be graded according to the NCI-CTCAE version 5.0 or higher.

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 later.

TEAEs will be summarized by frequency and by MedDRA System Organ Class and Preferred Term. Separate tabulations will also be produced for TEAEs assessed as related to study drug(s), TEAEs leading to treatment discontinuation, TEAEs leading to death, AESIs, and TEAEs Grade ≥ 3 in severity. Treatment-emergent SAEs and SAEs related to study drug(s) will also be tabulated.

Incidence of SSEs per PCWG3 criteria, defined as symptomatic failure, radiation or surgery to bone, or spinal cord compression, will be reported.[1]

9.6.2. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System units.

Shifts in grade (per NCI-CTCAE version 5.0 or higher) from Baseline to the maximum post-Baseline grade will be summarized for applicable laboratory data. Laboratory values Grade ≥ 3 in severity will be tabulated.

A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

9.7. Pharmacokinetic Analyses

Serum samples will be analyzed for SRF617 concentrations using a validated ligand-binding-based method. PK parameters based on the actual sample collection times will be determined using standard noncompartmental methods using the PK Analysis Set. The PK parameters to be assessed include, but are not necessarily limited to:

C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration prior to administration of subsequent dose

Evaluations of PK data will include maintenance concentration, accumulation upon multiple-dose administration, and immunogenicity analysis, when appropriate. Blood samples will be collected for etrumadenant and zimberelimab concentration analysis. Due to the limitations of sparse sampling, PK evaluation of etrumadenant and zimberelimab will be limited to the maintenance concentrations and descriptive statistics. Additional details on the PK analyses will be provided in the SAP.

9.8. Biomarker Analyses

Biomarker analyses will generally be descriptive in nature. Summary tabulations may be produced if data from a sufficient number of patients are collected. Additional details on the biomarker analyses will be provided in the SAP.

Tumor and serum PAP expression levels will be correlated to estimate if serum can provide a reliable indication of tumor expression levels. Specifically, a linear regression model will be fit to estimate the tumor PAP level versus the serum PAP level. The regression estimate, along with a 95% confidence interval, will be provided. Tumor samples will also be assessed for PD-L1 and CD39 expression levels and correlation with clinical response parameters, although no formal statistical test will be performed.

Additional biomarkers measured in serum, plasma, blood, and tumor tissues will be analyzed in an exploratory fashion. These exploratory analyses may or may not be presented formally. If presented, they will be limited to biomarkers for which data from a sufficient number of patients are available.

10. TRIAL ADMINISTRATION

10.1. Good Clinical Practice Statement

This trial is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

10.2. Informed Consent

The Sponsor or its designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or his/her staff will explain the nature of the trial, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient before enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the trial at any time without any disadvantage and without having to provide a reason for this decision. After the discussion regarding the trial, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the trial. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the trial by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

10.3. Patient Confidentiality

The written ICF will explain that trial data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and trial code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the trial that include the patient's medical history.

The Investigator must ensure that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned patient number and trial code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

10.4. Institutional Review Board/Ethics Committee Requirements

The final trial protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the trial.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the trial. The protocol must be reapproved by the IRB/IEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

10.5. Case Report Forms and Source Documentation

eCRFs will be provided for the recording of all data. The Principal Investigator/subinvestigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

10.6. Sponsor Monitoring

Before the first patient is enrolled into the trial, a representative of the Sponsor will visit the trial site in person, or remotely as COVID restrictions persist, to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the trial) their responsibilities about the protocol and the responsibilities of the Sponsor

During the conduct of the trial, a representative of the Sponsor will have regular contact with the clinical trial site and have regular visits to the clinical trial site in person, or remotely as COVID restrictions persist, to:

- Provide information and support the Principal Investigator
- Confirm that the facilities remain acceptable
- Confirm that the trial team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

10.7. Data Monitoring Committee

There will be no formal Independent Data Monitoring Committee.

10.8. Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/IECs may conduct quality assurance audits at any time during or after a trial. The Investigator must agree to allow auditors direct access to all trial-related documents including source documents and must agree to allocate his or her time and the time of his or her trial staff to the auditors to discuss findings and issues.

10.9. Trial or Clinical Site Termination

The Sponsor, or designee, reserves the right to terminate the trial or a clinical trial site at any time. Conditions that may warrant termination of the trial include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the trial
- The decision on the part of the Sponsor to suspend or discontinue testing the study drug
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical trial site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the trial, the Sponsor and the Investigator(s) will ensure that adequate consideration is given to the protection of the patients' interests.

10.10. Duration of the Trial, Expected Duration of Patient Participation, and End of Trial

Patients will continue study treatment 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.

10.11. Records Retention

All correspondence related to this clinical trial should be kept in appropriate trial files. Records of patients, source documents, eCRFs, study drug inventory, and IRB and Sponsor correspondence pertaining to this trial must be kept on file. All trial documents must be kept secured for a period of 2 years after a marketing application is approved for SRF617, or until 2 years after shipment and delivery of the study drug for investigational use is discontinued, or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain trial records; therefore, the Sponsor should be contacted before removing or relocating trial records for any reason.

10.12. Publications

Publication by the clinical trial site(s) of any data from this trial must be carried out in accordance with the Clinical Trial Agreement.

11. REFERENCES

1. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.

4. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.

5. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-46.

6. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-86.

7. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.

8. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-60.

9. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017;377(4):338-51.

10. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-7.

11. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.

12. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

13. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-22.

14. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.

15. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. 2020;38(32):3763-72.

16. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091-102.

17. Attard G, Borre M, Gurney H, Loriot Y, Andresen-Daniil C, Kalleda R, et al. Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment. J Clin Oncol. 2018;36(25):2639-46.

18. Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, et al. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. Eur Urol. 2015;68(2):317-24.

19. Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol. 2019;20(12):1730-9.

20. Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol. 2013;24(7):1807-12.

21. Morris MJ, Heller G, Bryce AH, Armstrong AJ, Beltran H, Hahn OM, et al. Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2019;37(15_suppl):5008.

22. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol. 2013;24(7):1802-7.

23. Oh WK, Cheng WY, Miao R, Vekeman F, Gauthier-Loiselle M, Duh MS, et al. Real-world outcomes in patients with metastatic castration-resistant prostate cancer receiving second-line chemotherapy versus an alternative androgen receptor-targeted agent (ARTA) following early

progression on a first-line ARTA in a US community oncology setting. Urol Oncol. 2018;36(11):500 e1- e9.

24. Schrader AJ, Boegemann M, Ohlmann CH, Schnoeller TJ, Krabbe LM, Hajili T, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol. 2014;65(1):30-6.

25. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019;381(26):2506-18.

26. Antonarakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, Hoimes CJ, et al. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. J Clin Oncol. 2020;38(5):395-405.

27. Graff JN, Alumkal JJ, Drake CG, Thomas GV, Redmond WL, Farhad M, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget. 2016;7(33):52810-7.

28. KEYTRUDA. (pembrolizumab) injection [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co. Inc. 2020.

29. Petrylak DP, Loriot Y, Shaffer D, Braiteh F, Powderly J, Harshman LC, et al. Safety and Clinical Activity of Atezolizumab in Patients With Metastatic Castration-Resistant Prostate Cancer: a Phase I Study. Clin Cancer Res. 2021.

30. Beer TM, Kwon ED, Drake CG, Fizazi K, Logothetis C, Gravis G, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol. 2017;35(1):40-7.

31. Fizazi K, Drake CG, Beer TM, Kwon ED, Scher HI, Gerritsen WR, et al. Final Analysis of the Ipilimumab Versus Placebo Following Radiotherapy Phase III Trial in Postdocetaxel Metastatic Castration-resistant Prostate Cancer Identifies an Excess of Long-term Survivors. Eur Urol. 2020;78(6):822-30.

32. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700-12.

33. Li S, Huang S, Peng SB. Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. Int J Oncol. 2005;27(5):1329-39.

34. Vecchio EA, Tan CY, Gregory KJ, Christopoulos A, White PJ, May LT. Ligand-Independent Adenosine A2B Receptor Constitutive Activity as a Promoter of Prostate Cancer Cell Proliferation. J Pharmacol Exp Ther. 2016;357(1):36-44.

35. Wei Q, Costanzi S, Balasubramanian R, Gao ZG, Jacobson KA. A2B adenosine receptor blockade inhibits growth of prostate cancer cells. Purinergic Signal. 2013;9(2):271-80.

36. Wise DR, Gardner O, Gilbert HN, Rieger A, Paoloni MC, Krishnan K. A phase Ib/II, open-label, platform study evaluating the efficacy and safety of AB928-based treatment combinations in participants with metastatic castrate-resistant prostate cancer. Journal of Clinical Oncology. 2020;38(6_suppl):TPS272-TPS.

37. Zimmermann H. Prostatic acid phosphatase, a neglected ectonucleotidase. Purinergic Signal. 2009;5(3):273-5.

38. Antonioli L, Blandizzi C, Pacher P, Hasko G. Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer. 2013;13(12):842-57.

39. Di Virgilio F, Sarti AC, Falzoni S, De Marchi E, Adinolfi E. Extracellular ATP and P2 purinergic signalling in the tumour microenvironment. Nat Rev Cancer. 2018;18(10):601-18.

40. Spychala J. Tumor-promoting functions of adenosine. Pharmacol Ther. 2000;87(2-3):161-73.

41. Blay J, White TD, Hoskin DW. The extracellular fluid of solid carcinomas contains immunosuppressive concentrations of adenosine. Cancer Res. 1997;57(13):2602-5.

42. Ohta A, Gorelik E, Prasad SJ, Ronchese F, Lukashev D, Wong MK, et al. A2A adenosine receptor protects tumors from antitumor T cells. Proc Natl Acad Sci U S A. 2006;103(35):13132-7.

43. Hasko G, Linden J, Cronstein B, Pacher P. Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. Nat Rev Drug Discov. 2008;7(9):759-70.

44. Allard B, Longhi MS, Robson SC, Stagg J. The ectonucleotidases CD39 and CD73: Novel checkpoint inhibitor targets. Immunol Rev. 2017;276(1):121-44.

45. Allard B, Pommey S, Smyth MJ, Stagg J. Targeting CD73 enhances the antitumor activity of anti-PD-1 and anti-CTLA-4 mAbs. Clin Cancer Res. 2013;19(20):5626-35.

46. Hay CM, Sult E, Huang Q, Mulgrew K, Fuhrmann SR, McGlinchey KA, et al. Targeting CD73 in the tumor microenvironment with MEDI9447. Oncoimmunology. 2016;5(8):e1208875.

47. Sun X, Wu Y, Gao W, Enjyoji K, Csizmadia E, Muller CE, et al. CD39/ENTPD1 expression by CD4+Foxp3+ regulatory T cells promotes hepatic metastatic tumor growth in mice. Gastroenterology. 2010;139(3):1030-40.

48. Kunzli BM, Bernlochner MI, Rath S, Kaser S, Csizmadia E, Enjyoji K, et al. Impact of CD39 and purinergic signalling on the growth and metastasis of colorectal cancer. Purinergic Signal. 2011;7(2):231-41.

49. Perrot I, Michaud HA, Giraudon-Paoli M, Augier S, Docquier A, Gros L, et al. Blocking Antibodies Targeting the CD39/CD73 Immunosuppressive Pathway Unleash Immune Responses in Combination Cancer Therapies. Cell Rep. 2019;27(8):2411-25 e9.

50. Zhang H, Vijayan D, Li XY, Robson SC, Geetha N, Teng MWL, et al. The role of NK cells and CD39 in the immunological control of tumor metastases. Oncoimmunology. 2019;8(6):e1593809.

51. Feng L, Sun X, Csizmadia E, Han L, Bian S, Murakami T, et al. Vascular CD39/ENTPD1 directly promotes tumor cell growth by scavenging extracellular adenosine triphosphate. Neoplasia. 2011;13(3):206-16.

52. Jackson SW, Hoshi T, Wu Y, Sun X, Enjyoji K, Cszimadia E, et al. Disordered purinergic signaling inhibits pathological angiogenesis in cd39/Entpd1-null mice. Am J Pathol. 2007;171(4):1395-404.

53. Hegde PS, Chen DS. Top 10 Challenges in Cancer Immunotherapy. Immunity. 2020;52(1):17-35.

54. Kirschenbaum A, Liu XH, Yao S, Leiter A, Levine AC. Prostatic acid phosphatase is expressed in human prostate cancer bone metastases and promotes osteoblast differentiation. Ann N Y Acad Sci. 2011;1237:64-70.

55. Xu H, Wang F, Li H, Ji J, Cao Z, Lyu J, et al. Prostatic Acid Phosphatase (PAP) Predicts Prostate Cancer Progress in a Population-Based Study: The Renewal of PAP? Dis Markers. 2019;2019:7090545.

56. Kong HY, Byun J. Emerging roles of human prostatic Acid phosphatase. Biomol Ther (Seoul). 2013;21(1):10-20.

57. Subudhi SK, Wise DR, Liu ST, et al. ARC-6: A Phase 1b/2, open-label, randomized platform study evaluating the efficacy and safety of etrumadenant (AB928)-based treatment combinations in patients with metastatic castrate-resistant prostate cancer. Poster presented at: ESMO Virtual Congress 2020; September 19-21, 2020.

58. Yadav V, Chi L, Zhao R, Tourdot BE, Yalavarthi S, Jacobs BN, et al. Ectonucleotidase tri(di)phosphohydrolase-1 (ENTPD-1) disrupts inflammasome/interleukin 1beta-driven venous thrombosis. J Clin Invest. 2019;129(7):2872-7.

59. Mittal D, Young A, Stannard K, Yong M, Teng MW, Allard B, et al. Antimetastatic effects of blocking PD-1 and the adenosine A2A receptor. Cancer Res. 2014;74(14):3652-8.

60. Willingham SB, Ho PY, Hotson A, Hill C, Piccione EC, Hsieh J, et al. A2AR Antagonism with CPI-444 Induces Antitumor Responses and Augments Efficacy to Anti-PD-(L)1 and Anti-CTLA-4 in Preclinical Models. Cancer Immunol Res. 2018;6(10):1136-49.

61. Holland PM. Targeting the adenosine axis to treat cancer. Presented at the Brisbane Immunotherapy Conference; May 24, 2019; Brisbane, Australia. 2019.

62. Powderly J, Spira A, Gutierrez R, DiRenzo D, Udyavar A, Karakunnel JJ, et al. Phase 1 evaluation of AB928, a novel dual adenosine receptor antagonist, combined with chemotherapy or AB122 (anti-PD-1) in patients (pts) with advanced malignancies. Ann Oncol. 2019;30(suppl_5):v475-v532.

63. Sachdev J, Prawira A, Chaudhry A, et al Efficacy and safety of AB928 plus pegylated liposomal doxorubicin (PLD) with or without IPI-549 in participants with metastatic ovarian and triple negative breast cancer Publication Number: PS12-12 San Antonio Breast Conference Symposium 2020, in press.

64. Cecchini M, Modiano M, Braiteh F, Gardner OS, Gilbert HN, DiRenzo D, et al. Abstract LB-387: Efficacy and safety of AB928 plus modified FOLFOX-6 (mFOLFOX-6) in participants with metastatic colorectal cancer (mCRC): Initial results at the recommended dose for expansion (ARC-3). Cancer Research. 2020;80(16 Supplement):LB-387.

65. OPDIVO (nivolumab) injection [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; April 2019.

66. Bendell J, Bauer T, Patel M, Falchook G, Karlix JL, Lim E, et al. Abstract CT026: Evidence of immune activation in the first-in-human Phase Ia dose escalation study of the adenosine 2a receptor antagonist, AZD4635, in patients with advanced solid tumors. Cancer Research. 2019;79(13 Supplement):CT026.

67. Harshman LC, Chu M, George S, Hughes BGM, Carthon BC, Fong F, et al. Adenosine receptor blockade with ciforadenant +/- atezolizumab in advanced metastatic castration-resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2020;38(6_suppl):129.

68. Lim EA, Bauer TM, Patel MR, Falchook GS, Karlix JL, Choe JH, et al. A phase I, open-label, multicenter study to assess the safety, pharmacokinetics, and preliminary antitumor activity of AZD4635 both as monotherapy and in combination in patients with advanced solid malignancies: Results from prostate cancer patients (NCT02740985). Journal of Clinical Oncology. 2020;38(15_suppl):5518.

69. Siu LL, Burris H, Le DT, Hollebecque A, Steeghs N, Delord J-P, et al. Abstract CT180: Preliminary phase 1 profile of BMS-986179, an anti-CD73 antibody, in combination with nivolumab in patients with advanced solid tumors. Cancer Research. 2018;78(13 Supplement):CT180.

70. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

71. Ueda M, Martins R, Hendrie PC, McDonnell T, Crews JR, Wong TL, et al. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. J Natl Compr Canc Netw. 2020:1-4.

72. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

73. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

APPENDIX 1. LIST OF PROHIBITED OR CAUTIONARY MEDICATIONS FOR CONCOMITANT USE WITH ETRUMADENANT

Due to the potential risk for drug-drug interactions, the following medications are either prohibited or require dose modification for concomitant use with etrumadenant (Table 11). This list is intended for use as a guidance document for site staff and may not be exhaustive.

Specific details regarding the potential for etrumadenant or its active metabolites to inhibit or induce CYP-mediated metabolism as well as interact with drug transporters are provided in the etrumadenant Investigator Brochure.

For questions regarding the potential drug-drug interaction risk for medications not included herein, please follow up with the trial Medical Monitor.

Table 11: List of Prohibited or Cautionary Medications for Concomitant Use With Etrumadenant

Medication name	Concomitant use with etrumadenant	Dose modification guidance
Loperamide	Administer with caution	• Coadministration with etrumadenant may result in reduced or increased exposure to loperamide and may be associated with potential loss of efficacy or greater risk of side effects. • If initiating new antidiarrheal therapy, avoid loperamide and administer alternate treatment if possible (cholestyramine, alosetron, bismuth subsalicylate). • If loperamide is an ongoing concomitant therapy at the time etrumadenant is initiated, loperamide may be continued with more frequent monitoring for safety and/or loss of efficacy in accordance with institutional standards.
Colchicine	Prohibited for patients with renal or hepatic impairment	• Administer alternate treatment for associated symptoms.

Medication name	Concomitant use with etrumadenant	Dose modification guidance
	Administer with caution in patients without renal or hepatic impairment	• Coadministration with etrumadenant may result in reduced or increased exposure to colchicine and may be associated with potential loss of efficacy or greater risk of side effects. • Continue colchicine with more frequent monitoring for safety and/or loss of efficacy in accordance with institutional standards. Reduce colchicine dose by 50% in response to treatment-emergent side effects.
Apixaban	Administer with caution	• Continue etrumadenant at the planned dose and implement additional safety monitoring in accordance with institutional standards. • Reduce apixaban dose by 50% in response to treatment-emergent side effects.
Rivaroxaban	Administer with caution	• If initiating new anticoagulant therapy, avoid rivaroxaban and administer alternate treatment for associated symptoms. • If rivaroxaban is an ongoing concomitant therapy at the time etrumadenant is initiated, rivaroxaban may be continued with more frequent monitoring for safety and/or loss of efficacy in accordance with institutional standards.
Dabigatran	Prohibited for patients with severe renal impairment	• Administer alternate treatment for associated symptoms.
	Administer with caution in patients with moderate renal impairment	• Coadministration with etrumadenant may result in increased exposure to dabigatran. • Reduce dabigatran dose to 75 mg and implement additional safety monitoring in accordance with institutional standards.
Rosuvastatin (> 10 mg QD)	Administer with caution	• Coadministration with etrumadenant may result in increased exposure to rosuvastatin. • Implement additional safety monitoring in accordance with institutional standards.
Rosuvastatin (≤ 10 mg QD)	Permitted	N/A

Medication name	Concomitant use with etrumadenant	Dose modification guidance
Atorvastatin	Permitted	• Coadministration with etrumadenant may result in decreased exposure to atorvastatin. • Continue current dose regimen and monitor for loss of efficacy.
Simvastatin	Permitted	• Coadministration with etrumadenant may result in decreased exposure to simvastatin. • Continue current dose regimen and monitor for loss of efficacy.
Fluvastatin (> 20 mg BID)	Administer with caution	• Coadministration with etrumadenant may result in increased exposure to fluvastatin. • Implement additional safety monitoring in accordance with institutional standards.
Fluvastatin (≤ 20 mg BID)	Permitted	N/A
Opioid agonists and antagonists	Naloxegol: Administer with caution	• Coadministration with etrumadenant may result in reduced naloxegol exposure and efficacy. • If initiating new opioid therapy, avoid naloxegol and administer alternate treatment for associated symptoms. • If naloxegol is an ongoing concomitant therapy at the time etrumadenant is initiated, naloxegol may be continued with more frequent monitoring for loss of efficacy.
	Methylnaltrexone: Permitted	N/A
	Oxymorphone, Hydromorphone, Oxycodone, Hydrocodone, Codeine, Morphine: Administer with caution	• Coadministration with etrumadenant may result in reduced or increased opioid exposure. • Implement additional monitoring for supratherapeutic opioid dose-related adverse events as well as subtherapeutic opioid dose-related loss of efficacy.
	Fentanyl: Administer with caution	• Coadministration with etrumadenant may result in reduced fentanyl exposure. • Implement additional monitoring for subtherapeutic opioid dose-related loss of efficacy.

Medication name	Concomitant use with etrumadenant	Dose modification guidance
	Methadone: Prohibited	• Administer alternate treatment for associated symptoms.
Cannabinoids	Tetrahydrocannabinol, Cannabidiol (oral, intravenous, inhaled formulations): Administer with caution	• Coadministration with etrumadenant may result in reduced cannabinoid exposure. • Implement additional monitoring for loss of efficacy.
Degarelix	Administer with caution	• Coadministration with etrumadenant may result in reduced or increased exposure to degarelix and may be associated with potential loss of efficacy or greater risk of side effects. • It is recommended to avoid degarelix. If coadministration is unavoidable, stagger etrumadenant and degarelix doses by ≥ 6 hours. Implement additional monitoring for safety and/or loss of efficacy in accordance with institutional standards. If loss of efficacy is observed, increase degarelix dose to 240 mg.
Digoxin	Prohibited	• Administer alternate treatment for associated symptoms.

Abbreviations: BID = twice daily; N/A = not applicable; QD = once daily.
Note: The half-life of etrumadenant is approximately 20 hours. A washout period of at least 4 days (equivalent to approximately 5 half-lives) following the last dose etrumadenant is therefore recommended prior to initiation of any medication listed in in this table.

APPENDIX 2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al, 1982.[72]

APPENDIX 3. RESPONSE CRITERIA

Table 12: PCWG3 Baseline Assessment of Disease – Amended for Trial SRF617-201

Parameter	Assessments

Histology	• Adenocarcinoma
	• Excluded from Trial SRF617-201:
	  o Adenocarcinoma with small-cell or neuroendocrine features
	  o Small-cell carcinoma
	• Report Gleason score sum for primary tumor at diagnosis, when available
	• Consider re-biopsy of metastatic disease

Clinical	• Age, pain, analgesic use, performance status, comorbidities, history, physical examination; prior local therapy; TNM stage and Gleason score at diagnosis; and PSA
Prior systemic treatment	• Record each line of systemic therapy (single agent or combination) in order of administration, including start and stop dates, dose(s), and schedule(s), the disease state in which it was administered, and response (resistant versus sensitive) on the basis of PSA or radiologic findings, if appropriate
Prior radiation therapy	• Site, administered dose per fraction, treatment duration if applicable and when available
Blood-based biomarkers	• Host: CBC with differential, ALP, kidney/liver function, albumin, LDH, testosterone • Tumor: PSA and PSA kinetics (PSADT)[a]
Imaging	
Prostate/Prostate bed	• Endorectal MRI (cross-sectional imaging of prostate region, if applicable)
Nodal	CT or MRI: • Nodes ≥ 1.5 cm in short axis are considered measurable; nodes ≥ 1.0 and < 1.5 cm in short axis are considered pathologic according to clinical discretion, and nontarget; nodes < 1.0 cm in short axis are considered nonpathologic

Parameter	Assessments
	• Record pelvic and extra-pelvic nodal disease separately, up to 5 nodes in total; pelvic nodes should be classified as locoregional and extrapelvic (retroperitoneal, mediastinal, thoracic, or other) nodes as metastatic • Record new lesions vs growth of pre-existing lesions, and sites of new lesions
Visceral	CT or MRI: • Record individual sites of spread separately; up to 5 lesions per site • Lesions ≥ 1.0 cm in longest dimension are considered measurable • Record new lesions vs growth of pre-existing lesions, and sites of new lesions
Bone	^{99m}Tc MDP • Record new lesions and sites of new lesions
Tumor profiling for determinants of prognostic, predictive, and resistance biomarkers	• Consider re-biopsy of metastatic or locally recurrent lesion(s) for biologic characterization • Catalog prior biopsy (or cfDNA/ctDNA) genomic results

Abbreviations: ^{99m}Tc MDP = ^{99mTc} methylene diphosphate; ALP = alkaline phosphatase; CBC = complete blood count; CEA = carcinoembryonic antigen; cfDNA= cell free DNA; CT = computed tomography; ctDNA = circulating tumor DNA; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; TNM = tumor, node, metastasis.

[a] PSADT should be calculated using a linear regression model of the normal logarithm of PSA and time. The calculation should be based on (1) at least 3 consecutive PSA values with each value ≥ 0.2 ng/dL, (2) inclusion of the most recent PSA values during androgen deprivation therapy, and (3) interval between first and last PSA values of ≥ 8 weeks but ≤ 12 months.

Source: Scher, 2016.[1]

Table 13: PWCG3 Criteria for Progression at Trial Entry

Variable	Criteria
Blood-based	
PSA	• Obtain sequence of rising values at a minimum of 1-week intervals • 1 ng/mL is the minimal starting value if confirmed rise is only indication of progression • If nonmeasurable disease, estimate pretherapy PSADT if ≥ 3 values available ≥ 4 weeks apart
Imaging	

Nodes	• Nodal progression sufficient for trial entry independent of PSA
	• Measurable lesions not required for entry
	• Modified RECIST v1.1 criteria, separate pelvic and extra-pelvic disease, up to 5 nodal lesions total recorded
	• Previously normal (< 1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from Baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed
	• If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to < 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
	• For existing pathologic adenopathy, progression is defined per RECIST v1.1
	• Record presence of nodal and/or visceral disease separately
	  ○ Nodal sites:
	  ▪ Locoregional: pelvic only
	  ▪ Extra-pelvic: retroperitoneal, mediastinal, thoracic, or other

Viscera	• Visceral progression sufficient for trial entry independent of PSA (recorded separately by site of spread [lung, liver, adrenal, CNS]); up to 5 lesions per site of metastatic disease • Measurable lesions not required for entry • Use RECIST criteria to record visceral lesions as target or nontarget • Record presence of nodal and/or visceral disease separately (visceral sites: lung, liver, adrenal, CNS)
Prostate/Prostate bed (primary site)	• Record prior treatment of primary tumor (eg, surgery, radiation, cryoablation, radiofrequency ablation, none, other) • Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease

Variable	Criteria
Bone	• 2 new lesions • Confirm ambiguous results by other imaging modalities (eg, CT or MRI), but only positivity on bone scan defines metastatic disease to bone
Other sites of disease	• Patients with treated epidural lesions and no other epidural progression are eligible
Type of progression at trial entry	

	• Report separately:
	  ○ PSA only
	  ○ Bone only ± nodal disease
	  ○ Nodal disease only (no bone disease present): pelvic and extrapelvic
	  ○ Visceral (lung, liver, adrenal, CNS) disease (± other sites)
	• Record new lesions and site of new lesions versus growth of pre-existing lesions, or both

Abbreviations: CNS = central nervous system; CT = computed tomography; MRI = magnetic resonance imaging; PET =positron emission tomography; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; RECIST = Response Evaluation Criteria in Solid Tumors
Source: Scher, 2016.[1]

Table 14: RECIST Version 1.1 Lesion Response

Evaluation of target lesions	
Complete response (CR):	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis
Partial response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum of diameters
Progressive disease (PD):	At least a 20% increase in the sum of diameters of target lesions from the smallest value on trial (including Baseline, if that is the smallest). The sum of diameters must also demonstrate an absolute increase of at least 5 mm. Or, the appearance of one or more lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Evaluation of nontarget lesions	
Complete response (CR):	Disappearance of all extranodal nontarget lesions, all lymph nodes must be nonpathological in size (< 10 mm in short axis), and normalization of tumor marker level
Non-CR/non-PD:	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive disease (PD):	Unequivocal progression of existing nontarget lesions. Or, the appearance of one or more lesions

Note: Evaluations for target, nontarget, and new lesions are to be considered together to assess an overall response status at a time point as detailed in Table 15. For the overall response of CR or PR, confirmation of the response status at a subsequent time point at least 4 weeks apart from the initial observation is recommended.
Source: Eisenhauer et al, 2009.[73]

Table 15: Evaluation of Overall Response by RECIST Version 1.1

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response/ remission, SD = stable disease.
Source: Eisenhauer et al, 2009.[73]