TITLE PAGE

Protocol Title:	A Phase 1b/2, Open-Label, Randomized Platform Study Evaluating the Efficacy and Safety of AB928-Based Treatment Combinations in Patients with Metastatic Castrate Resistant Prostate Cancer
Protocol Number:	ARC-6
Investigational Product:	Etrumadenant (AB928), zimberelimab (AB122), quemliclustat (AB680), Sacituzumab govitecan (SG)
Sponsor:	Arcus Biosciences, Inc. 3928 Point Eden Way Hayward, CA 94545
Lead Principal Investigator:	PPD, MD, FACP, FASCO Johns Hopkins Sidney Kimmel Comprehensive Cancer Center 201 N. Broadway, Viragh Building 9150 Baltimore, MD 21287
Medical Monitor:	**Primary contact:** PPD, MD Medical Director, Clinical Development PPD PPD
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LIST OF ABBREVIATIONS

Abbreviation	Definition
$A_{2a}R$	adenosine 2a receptor
$A_{2b}R$	adenosine 2b receptor
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CFR	Code of Federal Regulations
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CRPC	castrate resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection

Abbreviation	Definition
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council For Harmonization
ICI	immune checkpoint inhibitor
IEC	independent ethics committee
IMC	internal monitoring committee
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LFT	liver functional test
mCRPC	metastatic castrate resistant prostate cancer
mg	milligram
mL	milliliter
mOS	median overall survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer

Abbreviation	Definition
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHA	new hormonal agent
NK	natural killer (cells)
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PAP	prostatic acid phosphatase
PCWG2	Prostate Cancer Working Group 2
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PSA	prostate-specific antigen
QD	once daily
QTc	corrected QT interval
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SG	sacituzumab govitecan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TNAP	tissue nonspecific alkaline phosphatase
TNBC	triple-negative breast cancer
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
WOCBP	woman of childbearing potential

1. PROTOCOL SYNOPSIS

SPONSOR/COMPANY:
Arcus Biosciences, Inc.

NAME OF INVESTIGATIONAL PRODUCT(S):
Etrumadenant (AB928), zimberelimab (AB122), quemliclustat (AB680), Sacituzumab govitecan (SG)

PROTOCOL NUMBER:
ARC-6

ABBREVIATED TITLE:
Adenosine Receptor Antagonist Combination Therapy for Metastatic Castrate Resistant Prostate Cancer (ARC-6)

OFFICIAL TITLE:
A Phase 1b/2, Open-Label, Randomized Platform Study Evaluating the Efficacy and Safety of AB928-Based Treatment Combinations in Patients with Metastatic Castrate Resistant Prostate Cancer

OBJECTIVES AND ENDPOINTS:

Stage 1

Primary Objective	**Corresponding Endpoint**
Efficacy: To evaluate the antitumor activity of etrumadenant-based treatment combinations in Stage 1	Objective response rate (ORR), defined as the composite proportion of participants with a PSA and/or radiographic complete and partial response determined by the investigator according to the Prostate Cancer Working Group 3 (PCWG3) criteria
Safety: To evaluate the safety of etrumadenant-based treatment combinations in Stage 1	Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
Secondary Objectives	**Corresponding Endpoints**
To evaluate prostate-specific antigen (PSA) response rate in Stage 1	Proportion of participants with a PSA complete response (CR) and partial response (PR) as defined by PCWG3
To evaluate radiographic response rate in Stage 1	Proportion of participants with radiographic CR and PR as defined by PCWG3
To evaluate clinical efficacy in Stage 1	Disease control rate (DCR)
To determine the pharmacokinetic (PK) profile for components of etrumadenant-based treatment combinations in Stage 1	Serum/plasma concentration and PK parameters for components of etrumadenant-based combination therapy
To assess immunogenicity of the biologic component(s) of combination therapy where appropriate in Stage 1	Number and percentage of participants who develop antidrug antibodies (ADAs) to the biologic component(s) of combination therapy
Exploratory Objectives	
To characterize the relationship between tumor tissue/blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy	
To use tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy for treatment of the disease under study	

Stage 2

Primary Objective	**Corresponding Endpoint**
To evaluate the antitumor activity of etrumadenant based treatment combinations in Stage 2	ORR, defined as the composite proportion of participants with a PSA and/or radiographic complete and partial response determined by PCWG3 criteria
Secondary Objectives	**Corresponding Endpoints**
To evaluate the safety of etrumadenant-based treatment combinations in Stage 2	Incidence and severity of AEs and SAEs
To evaluate PSA response rate in Stage 2	Proportion of participants with a PSA CR and PR as defined by PCWG3
To evaluate radiographic response rate in Stage 2	Proportion of participants with radiographic CR and PR as defined by PCWG3
To evaluate clinical efficacy in Stage 2	DCR
To determine the PK profile for components of etrumadenant-based treatment combinations therapy in Stage 2	Serum/plasma concentration and PK parameters for components of etrumadenant-based combination therapy
To assess immunogenicity of the biologic component(s) of combination therapy where appropriate in Stage 2	Number and percentage of participants who develop ADAs to the biologic component(s) of combination therapy
Exploratory Objectives	
Progression-free survival (PFS)	
Overall survival (OS)	
To evaluate the change from baseline in blood and tumor tissue microenvironment pharmacodynamic biomarkers in response to etrumadenant-based combination therapy	
To characterize the relationship between tumor tissue/blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy	
To use tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy for treatment of the disease under study	

OVERALL DESIGN:

This is a Phase 1b/2, open-label, multicenter platform trial to evaluate the antitumor activity and safety of etrumadenant-based combination therapy in participants with metastatic castrate resistant prostate cancer (mCRPC). Initial treatment arms will independently evaluate etrumadenant plus zimberelimab alone or in combination with a standard of care backbone (enzalutamide, docetaxel) or etrumadenant plus AB680 with or without zimberelimab (Figure 1). Participant eligibility for a specific treatment arm will be based on prior anticancer treatment history. The study is designed with the flexibility to explore additional study treatment regimens as new therapies become available, stop accrual into existing treatment regimens that demonstrate minimal clinical activity or unacceptable toxicity, or modify the participant population (eg, with regard to prior anticancer treatment or biomarker status). As of Version 6.0, etrumadenant will be administered in combination with sacituzumab govitecan with or without zimberelimab and will follow the study design described below.

The treatment arms will be conducted in 2 stages: Stage 1 and Stage 2 (Figure 1). Depending on the treatment arm and stage, enrollment may or may not involve randomization. The decision to begin randomized enrollment in a specific treatment arm will be made by the sponsor for each combination therapy. During Stage 1, approximately 15 participants will be enrolled and will receive investigational products at the single agent recommended dose for expansion; standard of care therapies will be administered according to label instructions. Initial enrollment of 6 participants followed by a pause may occur in treatment arms of novel combinations to

allow for safety evaluation. If clinical activity (eg, 1 or more responses in 15 participants) is observed in a treatment arm during Stage 1, approximately 25 additional participants may be enrolled in that arm during Stage 2. Treatment arms with insufficient clinical activity or unacceptable toxicity will not proceed to Stage 2.

During Stage 2, up to 25 additional participants will receive an etrumadenant-based combination therapy explored in Stage 1 or, for applicable arms, a standard of care control appropriate for the participant population under study (Table 1). Additional participants may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics to enable further subgroup analyses. New treatment cohorts may be added during the study via protocol amendment.

A PK substudy will be conducted in parallel to the etrumadenant + zimberelimab treatment arm in Stage 1 and will assess the relative bioavailability of etrumadenant tablets (new formulation) versus etrumadenant capsules (current formulation). A minimum of 3 and up to approximately 12 participants will be enrolled. The effect of food on etrumadenant PK will also be assessed in this substudy.

Regardless of therapy administered, all participants will complete 3 study periods: (1) Screening (up to 28 days); (2) Treatment (until discontinuation criteria are met); and (3) Follow-up (until death, study consent withdrawal, or loss to follow-up). Participants will be evaluated for response every 12 weeks via the PCWG3 criteria according to the investigator's assessment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of study consent, up to a maximum treatment duration of 2 years, death, or the end of the study. In Stage 2, participants who progress on standard of care control therapy (ie, enzalutamide or docetaxel) may be permitted to crossover to an experimental treatment arm (Figure 1).

STUDY POPULATION:

This study will enroll male participants ≥18 years of age with histologically confirmed metastatic castrate resistant adenocarcinoma of the prostate with tumor progression while on androgen deprivation therapy (including orchiectomy) with castrate levels of serum (total) testosterone (≤ 1.7 nmol/L or 50 ng/dL) defined by PSA and/or radiographic criteria according to PCWG3; measurable or non-measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; Eastern Cooperative Oncology Group performance status 0 or 1 with life expectancy ≥ 3 months; adequate organ function; and, no evidence of symptomatic or untreated central nervous system disease. Participants with measurable disease and accessible tumor must consent to undergo baseline (only if archived specimen is unavailable) and on-treatment fresh tumor biopsy (SG containing arms do not have on treatment biopsies), must be naïve to any prior treatment with immune checkpoint blockade therapies including anti-cytotoxic T-lymphocyte antigen-4 and anti-programmed cell death protein 1/ programmed death-ligand 1 therapeutic antibodies, and must satisfy all other prior anticancer therapy allowances as defined by the experimental treatment arm.

TREATMENT ARMS AND REGIMENS:

Study Treatment	Prior Cancer Therapy[a]	Approximate Number of Participants	
		Stage 1	Stage 2[b]
Etrumadenant + zimberelimab + enzalutamide[c]	Abiraterone experienced; taxane and CPI naïve	15[d]	25
Etrumadenant + zimberelimab + docetaxel[e]	NHA experienced; taxane and CPI naïve	15[d]	25
Etrumadenant + zimberelimab[f]	NHA and taxane experienced; CPI naïve	15	25
Etrumadenant + zimberelimab + AB680[f]		15[d]	25
Etrumadenant + AB680[f]		15[d]	25
Etrumadenant + zimberelimab[g]		3-12	NA
Etrumadenant + SG	NHA experienced; taxane and CPI naive	15[d]	25
Etrumadenant + zimberelimab + SG		15[d]	25

CPI = checkpoint inhibitor; NA = not applicable; NHA = new hormonal agent; SG = sacituzumab govitecan

[a] This text is intended to be an abbreviated description for ease of use and should not replace the full inclusion/exclusion criteria.

[b] If clinical activity is observed during Stage 1, up to 25 additional participants may be enrolled in Stage 2 either onto an experimental arm or a standard of care control arm to better characterize potential treatment differences between experimental arms among concurrently enrolled participants.

[c] In Stage 2, eligible participants may be randomized to receive either etrumadenant + zimberelimab + enzalutamide or enzalutamide monotherapy. Crossover to experimental treatment with either etrumadenant + zimberelimab + docetaxel or etrumadenant + zimberelimab may be permitted for participants who progress on enzalutamide monotherapy; the choice of crossover therapy is at the investigator's discretion in consultation with the sponsor.

[d] Enrollment in Stage 1 may be paused after approximately 6 participants to allow for safety evaluation.

[e] In Stage 2, eligible participants may be randomized to receive either etrumadenant+ zimberelimab + docetaxel or docetaxel monotherapy. Crossover to experimental treatment with etrumadenant + zimberelimab may be permitted for participants who progress on docetaxel monotherapy.

[f] Participants will be randomly assigned to an experimental treatment arm (etrumadenant + zimberelimab; or etrumadenant + zimberelimab + AB680; or etrumadenant + AB680). There is equal probability of assignment to any treatment combination that is open (ie, if 2 treatment arms are open, then randomization is 1:1 with a 50% probability of assignment to either arm). If clinical activity is observed in a key subgroup of participants (eg, participants with measurable disease at baseline), enrollment may continue up to a total of 40 participants from that subgroup.

[g] Pharmacokinetic substudy using a separate informed consent form.

Depending on the treatment arm, participants will receive investigational therapy as follows:

Etrumadenant: 150 mg, oral, once daily continuous dosing (21- or 28-day cycle)

Zimberelimab: 240 mg, IV, every 2 weeks (Days 1 and 15 of a 28-day cycle; AB680-containing arms only) or 360 mg, IV, every 3 weeks (Day 1 of a 21-day cycle)

AB680: 100 mg IV, every 2 weeks (Q2W) (Days 1 and 15 of a 28-day cycle).

PK substudy only/Etrumadenant (tablet formulation): 150 or 225 mg, oral, once daily

Sacituzumab govitecan: 10 mg/kg, IV, on Days 1 and 8 of a 21-day cycle

Standard of care therapy will be administered at a fixed dose according to the product label:

Enzalutamide: 160 mg, oral, once daily continuous dosing (21-day cycle)

Docetaxel: 75 mg/m^2, IV, every 3 weeks (Day 1 of a 21-day cycle)

Treatment may continue until disease progression, withdrawal from study, unacceptable toxicity, or up to a maximum of 2 years, whichever occurs first.

STATISTICAL CONSIDERATIONS:

Sample Size Considerations

This study is not designed with explicit Type I error and power considerations in mind. Rather, this is a Phase 1b/2 study intended to obtain preliminary safety, efficacy, and PK data on investigational combinations when administered to patients with mCRPC.

During Stage 1, participants will be enrolled into various treatment arms based on their prior cancer history. Enrollment may be paused after the accrual of approximately 6 participants in a treatment arm to allow for safety evaluation. A rate of toxicity of < 33% will be targeted, with toxicity being defined as the occurrence of either a treatment-related Grade 4 AE or a treatment-related Grade 3 AE that is not responsive to supportive care during Cycle 1. If 2 or more such events are observed, enrollment in that arm may not continue.

At the end of Stage 1, a futility analysis will be conducted in each treatment arm in order to guide continuation of enrollment into Stage 2. Futility gates will be arm-specific and anchored to existing standard of care historical control information for use in a beta-binomial Bayesian decision-making framework.

In the etrumadenant + zimberelimab + enzalutamide treatment arm, gating will be based on a more stringent PSA decline of > 90% (PSA90). At least 4 out of 15 evaluable participants must exhibit a percent change from baseline PSA of > 90% in order to consider opening Stage 2. Across a range of prior beta distributions, observing 3 or fewer PSA90 responses would provide greater than 80% posterior probability confidence that the PSA90 rate in the experimental arm is less than 35%. Participants must have consecutive postbaseline PSA assessments measured at least 3 to 4 weeks apart to be considered evaluable for Stage 1 decision gating.

In the remaining treatment arms, gating will be based on either radiographic or PSA response. Radiographic response is defined as either a CR or PR by RECIST v1.1, and PSA response is defined as percent change from baseline PSA of > 50%. At least 1 radiographic CR or PR or 2 PSA responses out of 15 evaluable participants must be observed in order to consider opening Stage 2. In this case, across a range of prior beta distributions, observing 1 or fewer PSA responses would provide greater than 80% posterior probability confidence that the PSA response rate is less than 20%. Participants must have at least 1 postbaseline radiographic disease evaluation or consecutive postbaseline PSA assessments measured at least 3 to 4 weeks apart to be considered evaluable for Stage 1 decision gating.

During Stage 2, up to 25 additional participants may be enrolled either onto an experimental arm or a standard of care control arm. The goal of this stage is to better characterize potential treatment differences between experimental arms and standard of care among concurrently enrolled participants. Representative estimates of 90% confidence intervals for potential differences in response between treatment arms are provided.

Safety Endpoints

Safety analyses will be conducted in the safety-evaluable population, defined as all participants who are enrolled and receive any amount of study treatment. Safety will be assessed through summaries of AEs, as well as relevant changes in laboratory test results, vital signs, and electrocardiograms. Verbatim AE terms will be mapped and coded using the Medical Dictionary for Regulatory Activities. All AEs will be assessed for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Treatment-emergent adverse events (TEAEs), defined as AEs with onset date on or after initiation of study treatment or as AEs present at baseline but which worsened after initiation of study treatment, will be summarized. Adverse events will be summarized on the participant-level using the maximum severity or grade reported. All TEAEs, SAEs, AEs leading to study treatment discontinuation, Grade 3 or higher AEs, and deaths will be listed and summarized by treatment arm with the mapped preferred terms, thesaurus level and NCI CTCAE grade, as appropriate.

In the case of crossover, participants will contribute safety information up until the time of crossover. AEs reported after crossover will be summarized separately.

Efficacy Endpoints

Efficacy analyses will be primarily conducted in the efficacy-evaluable population, defined as all participants who are enrolled and receive at least 1 dose of each drug of their assigned treatment regimen. The following prioritized efficacy endpoints will be analyzed according to PCWG3 and based on the investigator's assessment:

ORR defined as the composite proportion of participants with a PSA response or a radiographic CR or PR (defined below).

PSA response defined as the proportion of participants with a confirmed PSA decrease from baseline of 50% or more based on 2 consecutive assessments measured at least 3 to 4 weeks apart.

Radiographic response defined as the proportion of participants with a best overall response of CR or PR according to RECIST v1.1.

DCR is defined as the proportion of participants with a best overall RECIST response of CR, PR, or stable disease (SD). The duration of time required for a patient with SD to be considered in disease control is defined for treatment arm.

PFS is defined as the time from treatment assignment until first documentation of progressive disease (PSA progression, radiographic progression, bone scan progression, or other) or death, whichever occurs first. Depending on data availability, time to progression due to specific reasons (eg, PSA progression or radiographic progression) may also be presented individually.

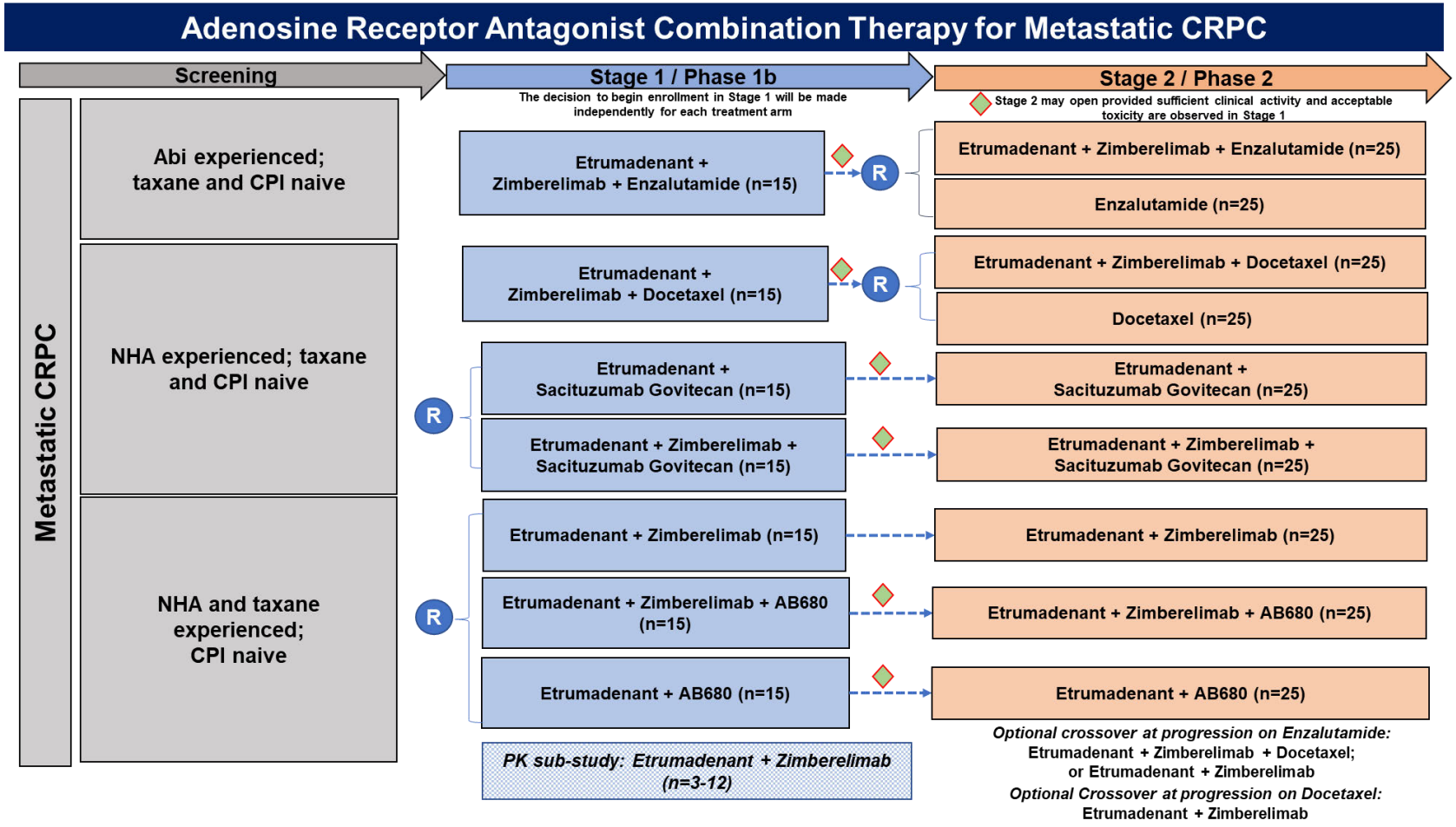
OS is defined as the time from treatment assignment until death due to any cause.

Unless otherwise specified, binary endpoints will be displayed with their exact Clopper-Pearson binomial 90% confidence intervals. Time-to-event endpoint parameters will be estimated using Kaplan-Meier techniques.

1.1. Study Schema

The study schema is depicted in Figure 1.

Figure 1: Study Schema



Abi = abiraterone; CPI = checkpoint inhibitor; CRPC = castrate resistant prostate cancer; n = number of participants; NHA = new hormonal agent R = randomization
Note: The text in Figure 1 is intended to be an abbreviated description for ease of use and should not replace the full inclusion/exclusion criteria as it relates to prior anticancer treatment history. Refer to the appropriate treatment arm section for more details related to treatment-specific criteria.

2. INTRODUCTION

2.1. Disease Overview

Prostate cancer is the most commonly diagnosed cancer and the second most frequent cause of cancer-related mortality among men in the United States (US). An estimated 174,650 new cases will be diagnosed in 2019 with 31,620 related deaths (National Cancer Institute, 2020). Adenocarcinoma comprises 95% of prostatic carcinomas (Lie, 2016). Most cases (90%) are diagnosed at a local or regional stage for which treatment options include active surveillance, surgery, or radiation. The 5-year relative survival is 98% across all stages but is 30% for disease diagnosed at an advanced stage.

Metastatic or advanced prostate cancer has a more complex treatment algorithm. Patients with locally advanced disease initially receive androgen ablation with radiation or prostatectomy, whereas first-line therapy in the metastatic setting is androgen ablation plus systemic treatment (eg, second-generation hormonal therapy or docetaxel-based chemotherapy). Disease progression in the context of androgen deprivation is known as castrate resistant prostate cancer (CRPC). Specifically, the Prostate Cancer Working Group 2 (PCWG2) defined CRPC as a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing local or metastatic disease, and/or the appearance of new metastases in the setting of castrate levels of serum testosterone (< 50 ng/dL; Scher et al., 2008).

Prognosis for CRPC is associated with several factors, including performance status, presence of bone pain, extent of disease on bone scan, and serum alkaline phosphatase (ALP) levels. Bone metastases will occur in approximately 80% of men with CRPC and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection (Saad and Hotte, 2010).

During the last decade, 6 new agents have received US Food and Drug Administration (FDA) approval for the treatment of metastatic CRPC (mCRPC) resulting in significant improvements in overall survival (OS; Fay and Antonarakis, 2019). However, the clinical benefit with each individual agent is rarely durable with a median overall survival (OS) of approximately 2 to 3 years. Due to the complexity of the disease and the challenges of successful treatment, mCRPC continues to be an area of high unmet medical need where novel therapeutic development is being actively explored.

Immune checkpoint inhibitors (ICI) have reinvigorated clinical development interest in anticancer immunotherapy. The latter relies on therapeutic modulation of the tumor microenvironment or other aspects of the immune system to overcome mechanisms of immune suppression that a tumor elicits on the host immune system. Despite their proven benefit in numerous tumor types as evidenced by the approvals of nivolumab (Opdivo Package Insert, 2019), pembrolizumab (Keytruda Package Insert, 2020), atezolizumab (Tecentriq Package Insert, 2019), and ipilimumab (Yervoy Package Insert, 2019), checkpoint inhibition has not proven effective in the treatment of metastatic prostate cancer where response rates to monotherapy are less than 5% (Antonarakis et al., 2020). These disappointing results open the door for the evaluation of novel immunotherapies for the treatment of CRPC.

2.2. Study Rationale

2.2.1. Scientific Rationale for the Adenosine Pathway as a Therapeutic Target

It has become evident that several pathways in the tumor microenvironment may play a role in the tumor immune evasion process. Adenosine is an endogenous purine nucleoside produced both intracellularly and extracellularly. Extracellular adenosine is generated by sequential enzymatic cleavage of adenosine triphosphate to adenosine monophosphate (AMP) by CD39 followed by the conversion of AMP to adenosine primarily by CD73 or tissue nonspecific alkaline phosphatase (TNAP; Borea et al., 2017; Chen et al., 2013). Within the tumor microenvironment, extracellular adenosine is highly concentrated and immunosuppressive as it binds to and activates the adenosine 2a (A_{2a}) and 2b (A_{2b}) receptors on immune cells leading to an ineffective antitumor response. Therefore, targeting adenosine receptors has emerged as a novel approach with the potential to stimulate antitumor immunity. In particular, the A_{2a} and A_{2b} receptors on T cells and myeloid cells, respectively, exhibit immunosuppressive and proangiogenic functions and have distinct biological roles in cancer.

In certain tumor types, enzymes other than CD73 or TNAP, such as prostatic acid phosphatase (PAP) in prostate cancer, can also efficiently convert AMP to adenosine (Wise et al., 2020). Increased levels of PAP are found in men with prostatic cancer, especially those with metastatic disease. In addition to PAP-derived adenosine, the A_{2b} receptor is also upregulated in prostate cancer suggesting this disease indication may be more susceptible than other malignancies to adenosine-mediated immunosuppression. In mCRPC, gene expression analysis revealed adenosine and myeloid signatures were significantly associated with poor OS, with adenosine 2b receptor ($A_{2b}R$) being one of the most prognostic genes evaluated (Abide et al., 2019). Together, this evidence provides rationale to evaluate the therapeutic potential of adenosine pathway inhibition in prostate cancer.

2.2.2. Clinical Rationale for Adenosine Pathway Inhibition

Recent clinical data demonstrated early activity of adenosine pathway inhibition in prostate cancer supporting further development in this indication (Bendell et al., 2019). In a Phase 1 trial (NCT02740985), the adenosine 2a receptor ($A_{2a}R$)-only antagonist AZD4635 demonstrated acceptable safety and antitumor responses when administered as a monotherapy or in combination with the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab to patients with advanced solid tumors. Specifically, AZD4635 with or without durvalumab resulted in radiographic and PSA responses in some patients with mCRPC. These results have led to the initiation of dose expansion cohorts to evaluate the efficacy of AZD4635-based combination therapy in mCRPC and, importantly, support clinical validation of the adenosine pathway as a novel target for therapeutic intervention in prostate cancer.

2.2.3. Etrumadenant: Small Molecule Dual Antagonist of A_{2a} and A_{2b} Receptors

Etrumadenant (AB928) is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and $A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects.

Phase 1 dose escalation established 150 mg once daily (QD) as the recommended dose for combination and confirmed receptor coverage in oncology patients at steady-state concentrations. In these early studies, etrumadenant in combination with chemotherapy and/or anti-PD-1 immunotherapy was well tolerated and demonstrated evidence of clinical benefit, including tumor responses and disease stabilization >6 months in heavily pretreated patients across multiple solid tumor disease indications.

ARC-5 (NCT03629756) is an ongoing Phase 1/1b study of etrumadenant in combination with PD-1 checkpoint inhibitor therapy (zimberelimab; AB122) in mCRPC. Eligible participants have progressed on androgen inhibition and taxane chemotherapy but are PD-1/PD-L1 treatment naïve. The primary endpoint is tolerability, with secondary endpoints of pharmacokinetics (PK), pharmacodynamics, and clinical activity.

Refer to the etrumadenant investigator brochure for additional information on preclinical and clinical studies.

2.2.4. Rationale for the 2-year Maximum Duration of Treatment for Castration Resistant Prostate Cancer

In the published literature, treatment with various ICIs for a finite duration has shown responses in patients with metastatic castration-resistant prostate cancer, and the treatment with these agents are being used for fixed durations.

Prospective data are required to guide clinical decision-making in this setting, and the pembrolizumab studies in CRPC as the Keynote-199 (Antonarakis et al, 2020) Keynote-028 (Hansen et al, 2018), Keynote-365 (Yu EY et al, 2022), Keynote-921 (Petrylak et al, 2021), and Keynote-641 (Fizazi et al, 2022) showed benefits in ORR, DOR or PFS. The ICI, in all these clinical trials, was administered for a maximum of 2 years. This approach has been shown to minimize toxicities and improve quality of life.

2.2.5. Platform Study Risk/Benefit Assessment

This is a Phase 1b/2, open-label, multicenter platform trial to evaluate the antitumor activity and safety of etrumadenant-based combination therapy (Table 1) in participants with metastatic prostate cancer. The study is designed to maintain the flexibility to open new treatment arms as new combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within a single study or master protocol may result in an overall reduction in the number of patients receiving standard of care alone and also accelerate timelines to evaluate new treatments in a patient group with a large unmet medical need. Additionally, the intent of this platform study is to provide treatment opportunities to different types of patients with resistant metastatic prostatic cancer, serving multiple lines of progressive disease.

Background information and a rationale for each treatment combination, including a benefit-risk assessment, are provided in the respective section for that treatment arm, as outlined in (Table 1).

3. OBJECTIVES AND ENDPOINTS

3.1. Stage 1

Primary Objective	Corresponding Endpoint
Efficacy: To evaluate the antitumor activity of etrumadenant-based treatment combinations in Stage 1	Objective response rate (ORR), defined as the composite proportion of participants with a PSA and/or radiographic complete and partial response determined by the investigator according to the Prostate Cancer Working Group 3 (PCWG3) criteria
Safety: To evaluate the safety of etrumadenant-based treatment combinations in Stage 1	Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
Secondary Objectives	**Corresponding Endpoints**
To evaluate PSA response rate in Stage 1	Proportion of participants with a PSA complete response (CR) and partial response (PR) as defined by PCWG3
To evaluate radiographic response rate in Stage 1	Proportion of participants with radiographic CR and PR as defined by PCWG3
To evaluate clinical efficacy in Stage 1	Disease control rate (DCR)
To determine the PK profile for components of etrumadenant-based treatment combinations in Stage 1	Serum/plasma concentration and PK parameters for components of etrumadenant-based combination therapy
To assess immunogenicity of the biologic component(s) of combination therapy where appropriate in Stage 1	Number and percentage of participants who develop antidrug antibodies (ADAs) to the biologic component(s) of combination therapy
Exploratory Objectives	
To characterize the relationship between tumor tissue/blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy	
To use tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy for treatment of the disease under study	

3.2. Stage 2

Primary Objective	Corresponding Endpoint
To evaluate the antitumor activity of etrumadenant based treatment combinations in Stage 2	ORR, defined as the composite proportion of participants with a PSA and/or radiographic complete and partial response determined by PCWG3 criteria
Secondary Objectives	**Corresponding Endpoints**
To evaluate the safety of etrumadenant-based treatment combinations in Stage 2	Incidence and severity of AEs and SAEs
To evaluate PSA response rate in Stage 2	Proportion of participants with a PSA CR and PR as defined by PCWG3
To evaluate radiographic response rate in Stage 2	Proportion of participants with radiographic CR and PR as defined by PCWG3
To evaluate clinical efficacy in Stage 2	DCR
To determine the PK profile for components of etrumadenant-based treatment combinations therapy in Stage 2	Serum/plasma concentration and PK parameters for components of etrumadenant-based combination therapy
To assess immunogenicity of the biologic component(s) of combination therapy where appropriate in Stage 2	Number and percentage of participants who develop ADAs to the biologic component(s) of combination therapy
Exploratory Objectives	
Progression-free survival	
Overall survival	
To evaluate the change from baseline in blood and tumor tissue microenvironment pharmacodynamic biomarkers in response to etrumadenant-based combination therapy	
To characterize the relationship between tumor tissue/blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy	
To use tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy for treatment of the disease under study	

4. INVESTIGATIONAL PLAN

This is a Phase 1b/2, open-label, multicenter platform trial to evaluate the antitumor activity and safety of etrumadenant-based combination therapy (Table 1) in participants with mCRPC. Initial treatment arms will independently evaluate etrumadenant plus zimberelimab alone or in combination with a standard of care backbone (enzalutamide, docetaxel) or etrumadenant plus AB680 with or without zimberelimab (Figure 1). Participant eligibility for a specific treatment arm will be based on prior anticancer treatment history. Details on the treatment regimens specified in Table 1 are provided in Section 14 through Section 20.

The study is designed with the flexibility to explore additional study treatment regimens as new therapies become available, stop accrual into existing treatment regimens that demonstrate minimal clinical activity or unacceptable toxicity, or modify the participant population (eg, with regard to prior anticancer treatment or biomarker status).

The treatment arms will be conducted in 2 stages: Stage 1 and Stage 2 (Figure 1). Depending on the treatment arm and stage, enrollment may or may not involve randomization. The decision to begin randomized enrollment in a specific treatment arm will be made by the sponsor for each combination therapy. When applicable, the randomization ratio may depend on the number of experimental treatment arms that are available (ie, if a treatment is added or enrollment in that treatment arm is suspended, pending analysis of results from Stage 1). Details regarding treatment assignment and applicable randomization are provided in Section 6.5.

4.1. Stage 1

During Stage 1, approximately 15 participants will be enrolled and will receive investigational products at the single agent recommended dose for expansion; standard of care therapies will be administered according to label instructions. The decision to begin enrollment in a specific treatment arm in Stage 1 will be made by the sponsor. The following arms are expected to initiate accrual at study start:

- Etrumadenant + zimberelimab + enzalutamide
- Etrumadenant + zimberelimab + docetaxel
- Etrumadenant + zimberelimab
- Etrumadenant + zimberelimab PK substudy

Enrollment into AB680-containing treatment arms will commence following either identification of the recommended dose for expansion or dose associated with at least 50% target coverage and an acceptable safety profile (< 33% dose-limiting toxicity [DLT] rate) as determined in the ongoing dose escalation study AB680CSP0002. The AB680 dose is defined as of Protocol Version 4.0; participant accrual into AB680-containing treatment arms may therefore begin following all necessary regulatory approvals of the aforementioned amendment. The dose of AB680 is 100 mg IV Q2W (Day 1 and Day 15 of a 28-day Cycle).

As of Protocol Version 6.0 (11 May 2022), the following arms are expected to enroll:

- Etrumadenant + Sacituzumab govitecan (SG)
- Etrumadenant + zimberelimab + SG

Initial enrollment of 6 participants followed by a pause may occur in treatment arms of novel combination to allow for safety evaluation (Section 9.1). If clinical activity (eg, 1 or more responses in 15 participants) is observed in a treatment arm during Stage 1, approximately 25 additional participants may be enrolled in that arm during Stage 2. Treatment arms with insufficient clinical activity or unacceptable toxicity will not proceed to Stage 2. Specific gating criteria (Stage 1 to Stage 2) is defined for each treatment arm in Section 9.1.

4.2. Stage 2

During Stage 2, up to 25 additional participants will receive an etrumadenant-based combination therapy explored in Stage 1 or, for applicable arms, a standard of care control appropriate for the participant population under study (Table 1). The decision to begin randomized enrollment to a control arm will be made by the sponsor based on emerging data. The sponsor may also decide to delay or suspend enrollment within a given treatment arm. Additional participants may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics to enable further subgroup analyses.

The planned treatment arms are provided in Table 1. New treatment arms may be added during the study via protocol amendment.

Table 1: ARC-6 Planned Treatment Arms

Study Treatment	Section	Prior Cancer Therapy[a]	Approximate Number of Participants	
			Stage 1	Stage 2[b]
Etrumadenant + zimberelimab + enzalutamide	Section 14	Abiraterone experienced; taxane and CPI naïve	15[d]	25[c]
Etrumadenant + zimberelimab + docetaxel	Section 15	NHA experienced; taxane and CPI naïve	15[d]	25[e]
Etrumadenant + zimberelimab[f]	Section 16	NHA and taxane experienced; CPI naïve	15	25
Etrumadenant + zimberelimab + AB680[f]	Section 17		15[d]	25
Etrumadenant + AB680[f]	Section 18		15[d]	25
Etrumadenant + zimberelimab[g]	Section 19		3-12	NA
Etrumadenant + SG	Section 20	NHA experienced; taxane and CPI naïve	15[d]	25
Etrumadenant + zimberelimab + SG	Section 20		15[d]	25

CPI = checkpoint inhibitor; NA = not applicable; NHA = new hormonal agent; SG=Sacituzumab govitecan

[a] This text is intended to be an abbreviated description for ease of use and should not replace the full inclusion/exclusion criteria (Section 5).

[b] If clinical activity is observed during Stage 1, up to 25 additional participants may be enrolled in Stage 2 either onto an experimental arm or a standard of care control arm to better characterize potential treatment differences between experimental arms and standard of care among concurrently enrolled participants (Section 9.1).

[c] In Stage 2, eligible participants may be randomized to receive either etrumadenant + zimberelimab + enzalutamide or enzalutamide monotherapy. Crossover to experimental treatment with either etrumadenant + zimberelimab + docetaxel or etrumadenant + zimberelimab may be permitted for participants who progress on enzalutamide monotherapy; the choice of crossover therapy is at the investigator's discretion in consultation with the sponsor.

[d] Enrollment in Stage 1 may be paused after approximately 6 participants to allow for safety evaluation.

[e] In Stage 2, eligible participants may be randomized to receive either etrumadenant + zimberelimab + docetaxel or docetaxel monotherapy. Crossover to experimental treatment with etrumadenant + zimberelimab may be permitted for participants who progress on docetaxel monotherapy.

[f] Participants will be randomly assigned to an experimental treatment arm (etrumadenant + zimberelimab; or etrumadenant + zimberelimab + AB680; or etrumadenant + AB680). There is equal probability of assignment to any treatment combination that is open (ie, if 2 treatment arms are open, then randomization is 1:1 with a 50% probability of assignment to either arm). If clinical activity is observed in a key subgroup of participants (eg, participants with measurable disease at baseline), enrollment may continue up to a total of 40 participants from that subgroup.

[g] Pharmacokinetic substudy using a separate informed consent form.

A PK substudy will be conducted in parallel to the etrumadenant + zimberelimab treatment arm in Stage 1 and will assess the relative bioavailability of etrumadenant tablets (new formulation) versus etrumadenant capsules (current formulation). A minimum of 3 and up to approximately 12 participants will be enrolled. The effect of food on etrumadenant PK will also be assessed in this substudy (Section 19).

Details of investigational product dosing and schedule of activities for each treatment group are provided in the respective section for each treatment arm (Section 14 through Section 20).

Regardless of therapy administered, all participants will complete 3 study periods: (1) Screening (up to 28 days; Table 2); (2) Treatment (until one of the criteria in Section 7.4.1 are met; Section 14 through Section 20); and (3) Follow-up (until death, study consent withdrawal, or loss to follow-up; Table 3). Participants will be evaluated for response every 12 weeks via the PCWG3 criteria (Scher et al., 2016) according to the investigator's assessment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of study consent, up to a maximum treatment duration of 2 years, death, or the end of the study. In Stage 2, participants who progress on standard of care control therapy (ie, enzalutamide or docetaxel) may be permitted to crossover to an experimental treatment arm as described in Section 14.3 and Section 15.3, respectively.

All participants will be closely monitored for AEs throughout study participation. Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest (AESI), performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. Planned timing for all safety assessments are provided in the schedule of activities (Section 7.1, Section 7.2, and Section 14 through Section 20). All AEs and laboratory abnormalities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Certain types of events require immediate reporting to the sponsor, as described in Section 8.2.4 and Section 8.2.5.

4.2.1. Safety Evaluation Phase

To account for potential overlapping toxicities in novel treatment arms (Table 1), enrollment may be paused after approximately 6 participants have been enrolled to allow for a safety evaluation. The safety evaluation will be based on safety data from a minimum of 6 participants who have received at least 1 dose of treatment (ie, 1 dose of each agent for a given combination) and completed safety follow-up assessments of at least 1 full treatment cycle. If a combination is determined to be sufficiently safe by the Internal Monitoring Committee (IMC; Section 9.4), enrollment will be continued in that arm.

The safety evaluation phase will be applied to specific treatment arms as defined in Section 14 through Section 20.

4.3. End of Study Definition

Treatment arms will conclude when the last participant in the treatment arm completes survival follow-up; therefore, treatment arms may conclude their evaluation while the overall study continues.

The end of this study is defined as the date when the last visit of the last participant occurs including survival follow-up visits conducted by telephone or on-site. The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately 3 to 5 years. The sponsor may establish a clinical data cutoff date for analysis reporting of a treatment arm 18 months (or based on emerging data) after the last participant has received the first dose of study treatment or after all participants have discontinued study treatment, whichever comes first.

5. ELIGIBILITY

Prospective requests for approval of protocol deviations to recruitment and enrollment criteria, also known as waivers or exemptions, are not allowed.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

General Inclusion Criteria for All Participants

1. Capable of giving signed informed consent as described in Section 11.2.2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2. Male participants ≥ 18 years of age inclusive, at the time of signing the informed consent
3. Ability to comply with the study protocol in the investigator's judgment
4. Histologically confirmed adenocarcinoma of the prostate and metastatic castrate resistant with tumor progression while on androgen deprivation therapy (ADT; including orchiectomy) with castrate levels of serum (total) testosterone (≤1.7 nmol/L or 50 ng/dL) defined by PSA and/or radiographic criteria according to PCWG3. Castrate levels of testosterone must be maintained by surgical or medical means throughout study conduct.
5. Measurable (at least 1 target lesion) or nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al., 2009). Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation
6. [Excluding SG-containing treatment arms] Participants with measurable disease and accessible tumor will be requested to consent to undergo baseline (only if archived specimen is unavailable) and on-treatment fresh tumor biopsy. The biopsy must not put participants at undue risk and the procedure must not be more invasive than a core biopsy as documented in the medical record by the investigator. Fresh biopsy of a tumor lesion not previously irradiated (tumors progressing in a prior site of radiation may be considered after sponsor consultation) should be obtained.

   Participants for biopsy should have at least 2 measurable lesions at baseline: 1 for tissue sampling and 1 for radiographic response assessment.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Life expectancy ≥ 3 months as determined by the investigator
9. Adequate hematologic and end-organ function defined by the following laboratory test results at screening:
   a. Absolute neutrophil count ≥ 1.5×10^9/L (1500/μL) without granulocyte colony stimulating factor support
   b. White blood cell counts ≥ 2.5×10^9/L (2500/μL)
   c. Lymphocyte count ≥ 0.5×10^9/L (500/μL)
   d. Platelet count ≥ 100×10^9/L (100,000/μL) without transfusion

e. Hemoglobin ≥ 90 g/L (9.0 g/dL)

   Participants must not have been transfused within 2 weeks prior to screening to meet minimum platelet and hemoglobin parameters.

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN), with the following exception:

   i. Participants with documented liver metastases: AST and ALT ≤ 5 × ULN

   ii. Participants with documented liver or bone metastases: ALP ≤ 5 × ULN

g. ALP ≤ 5 × ULN

   i. If ALP > 5 × ULN, then gamma-glutamyl transpeptidase must be within normal limits

h. Bilirubin ≤ 1.5 × ULN, with the following exception:

   i. Participants with known Gilbert syndrome: serum bilirubin level ≤ 3 × ULN

i. Albumin ≥ 25 g/L (2.5 g/dL)

j. Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 30 mL/min as determined by Cockcroft-Gault equation (Cockcroft and Gault, 1976)

10. Negative human immunodeficiency virus (HIV) test at screening. Due to safety concerns related to viral activation, development of a secondary malignancy, as well as the potential for increased treatment-related toxicity, eligible participants must not have evidence of chronic viral infection at screening

11. Negative hepatitis B surface antigen (HBsAg) test at screening. Due to safety concerns related to viral activation, development of a secondary malignancy, as well as the potential for increased treatment-related toxicity, eligible participants must not have evidence of chronic viral infection at screening

12. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. The HBV test will be performed only for participants who have a positive total HBcAb test. Due to safety concerns related to viral activation, development of a secondary malignancy, as well as the potential for increased treatment-related toxicity, eligible participants must not have evidence of chronic viral infection at screening

13. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening. The HCV RNA test will be performed only for participants who have a positive HCV antibody test. Due to safety concerns related to viral activation, development of a secondary malignancy, as well as the potential for increased treatment-related toxicity, eligible participants must not have evidence of chronic viral infection at screening

14. Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Section 14 through Section 20

Study Treatment-Specific Inclusion Criteria

Participants in a given treatment group must meet all study treatment-specific inclusion criteria as defined in the appropriate treatment arm section:

- Etrumadenant + zimberelimab + enzalutamide: Section 14
- Etrumadenant + zimberelimab + docetaxel: Section 15
- Etrumadenant + zimberelimab: Section 16
- Etrumadenant + zimberelimab + AB680: Section 17
- Etrumadenant + AB680: Section 18
- Etrumadenant + zimberelimab PK substudy: Section 19
- SG-containing treatment arms: Section 20

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

General Exclusion Criteria for All Participants

1. Prior treatment with immune checkpoint blockade therapies including anticytotoxic T-lymphocyte-associated protein-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
2. Prior anticancer treatment for the disease under study, including approved agents, systemic radiotherapy, or investigational therapy, within 4 weeks (or 5 half-lives) prior to initiation of study treatment. Prior focal radiotherapy must be completed at least 2 weeks prior to the initiation of study treatment
3. QTc ≥480 msec using Fredericia's QT correction formula (based on an average of triplicate recordings)
4. Prior allogeneic stem cell or solid organ transplantation
5. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks (or 5 half-lives), whichever is shorter, prior to initiation of study treatment
6. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:
    a. Patients who received low dose (≤ 10 mg/day prednisone or equivalent), systemic immunosuppressant medications or a 1-time pulse dose of systemic immunosuppressant medication (eg, 48 hours of corticosteroids for a contrast allergy) are eligible for the study after medical monitor approval has been obtained.
    b. Patients who received mineralocorticoids (eg, fludrocortisone), inhaled or intranasal corticosteroids for chronic obstructive pulmonary disease or asthma, or low dose corticosteroids for orthostatic hypotension or adrenal

insufficiency are eligible for the study after medical monitor approval has been obtained.

7. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the last dose of study treatment

8. Current treatment with antiviral therapy for HBV

9. Structurally unstable bone lesions suggesting impending fracture

10. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

a. Patients with a history of treated CNS metastases are eligible, if all of the following criteria are met:

i. The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

ii. Metastases are limited to the cerebellum or the supratentorial region (ie, no metastases to the midbrain, pons, medulla, or spinal cord).

iii. There is no evidence of interim progression between completion of CNS directed therapy and the screening brain scan.

iv. The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole brain radiotherapy within 14 days prior to initiation of study treatment.

v. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

b. Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan

11. History of leptomeningeal disease

12. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
b. Participants with ground-glass opacities of unknown significance may be eligible following a discussion with the medical monitor. Participants must be asymptomatic and without evidence of hypoxia on ambulation.

13. History of malignancy other than prostate cancer within 2 years prior to screening, except for malignancies with a negligible risk of metastasis or death (eg, 5-year OS rate > 90%), such as nonmelanoma skin carcinoma or ductal carcinoma in situ

14. Active tuberculosis

15. Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

a. Patients receiving prophylactic antibiotics (eg, to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

16. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia

17. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable angina or new onset angina within 3 months prior to initiation of study treatment, myocardial infarction within 6 months prior to initiation of study treatment, or unstable arrhythmia

18. Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment

19. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

a. Placement of central venous access catheter (eg, port or similar) is not considered a major surgical procedure and is therefore permitted.

20. Adverse events from prior anticancer therapy that have not improved to Grade ≤ 1 or better, except for alopecia of any grade and Grade ≤ 2 peripheral neuropathy

21. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of study treatment, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

22. Known allergy or hypersensitivity to any of the study drugs or their excipients

23. Inability to swallow medications

24. Malabsorption condition that would alter the absorption of orally administered medications

25. Evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (ie, in the absence of therapeutic anticoagulation)

26. Prior treatment with an agent targeting the adenosine pathway

Study Treatment-Specific Exclusion Criteria

Participants in a given treatment group must meet all study treatment-specific exclusion criteria as defined in the appropriate treatment arm section:

- Etrumadenant + zimberelimab + enzalutamide: Section 14
- Etrumadenant + zimberelimab + docetaxel: Section 15
- Etrumadenant + zimberelimab: Section 16
- Etrumadenant + zimberelimab + AB680: Section 17
- Etrumadenant + AB680: Section 18

- Etrumadenant + zimberelimab PK Substudy: Section 19
- SG-containing treatment arms: Section 20

5.3. Inclusion of Minorities

No restrictions regarding the inclusion of minorities are required.

5.4. Lifestyle Considerations

5.4.1. Contraception Requirements

Male participants with female partners of childbearing potential are required to use contraceptive measures that are considered highly effective.

- A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
- A female partner of is considered a woman of childbearing potential (WOCBP) following menarche and until becoming postmenopausal 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 postmenopausal 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 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
- Surgical sterilization
  - The male participant is vasectomized (with documented medical confirmation of surgical success) and is the sole sexual partner of the WOCBP participant
  - Female partner of the male participant 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 participant.

5.4.2. Meals and Dietary Restrictions

Meals and dietary restrictions, if any, are detailed in the respective section for each treatment arm (Section 14 through Section 20).

5.4.3. Activity

There are no activity restrictions for this study.

6. STUDY TREATMENT

Study treatment is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol. Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer investigational product.

Descriptions of each study treatment, its handling and storage, and dosage and administration are detailed in its treatment arm-specific section (Section 14 through Section 20). Specific instructions for each study treatment are detailed in the study pharmacy manual.

6.1. Investigational Product Dispensing, Accountability, and Disposal

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational product received and any discrepancies are reported and resolved before use of the investigational product. All investigational products must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Further guidance and information for the final disposition of unused investigational products are provided in the study pharmacy manual.

6.2. Dosage and Administration

Dosage and administration of each investigational product is detailed in the respective section for each treatment arm (Section 14 through Section 20).

6.3. Dose Modification

Changes in study therapy are detailed in the respective section for each treatment arm Section 14 through Section 20.

6.4. Prior and Concomitant Medications

Any medication or vaccine (including over the counter or prescription medicines, vitamins, vaccines, herbal or homeopathic remedies, and/or nutritional supplements) used by a participant within 14 days prior to study treatment initiation must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.4.1. Permitted Therapy

Permitted concomitant therapy is detailed in the respective section for each treatment arm (Section 14 through Section 20).

6.4.2. Prohibited Therapy

Prohibited concomitant therapy is detailed in the respective section for each treatment arm (Section 14 through Section 20).

6.5. Randomization and Blinding

6.5.1. Method of Treatment Assignment

After informed consent has been obtained, screening procedures have been completed, and eligibility has been established, a participant will be enrolled onto the study and treatment will be assigned. Depending on the study arm and stage, treatment assignment may or may not involve randomization. Regardless of the use of randomization, treatment assignment for all participants will be conducted using an Interactive Response Technology (IRT).

Method of treatment assignment, as applicable, may be further detailed in the respective section for each treatment arm (Section 14 through Section 20).

6.5.2. Blinding

This is an open-label trial; therefore, the sponsor, investigator, and participant will know the study treatment administered.

7. STUDY ASSESSMENTS

This study consists of the following:

- Screening period (Table 2)
- Treatment period
  - A schedule of activities to be performed during the treatment period is provided for each treatment arm in Section 14 through Section 20.
- End of treatment and follow-up period (Table 3)

All study activities must be performed and documented for each participant. Participants will be closely monitored for safety and tolerability throughout the study. Assessments/procedures should be completed on the day indicated; if this is not possible because of a weekend, holiday, or emergency, the assessment/procedure should be completed within the timeframe noted in the schedule of activities. On visit days where study treatment is administered in the clinic, participants should be assessed for toxicity prior to administration of study treatment; dosing will occur only if the clinical assessment and local laboratory test values are acceptable as deemed by principal investigator. All planned assessments on dosing days should be completed prior to treatment administration unless otherwise indicated in the schedule of activities.

Based on emerging data, adjustments to the planned schedule of activities may be made by the sponsor in order to protect participant safety. These decisions will be documented in writing and appropriately communicated to participating investigators prior to implementation.

7.1. Schedule of Activities: Screening

Table 2: Schedule of Activities / SCREENING

Procedure	Screening Days -28 to -1
Administrative Procedures	
Written informed consent/participant number (subject ID) assignment	X
Verify eligibility criteria	X
Demographics and medical history	X
Concomitant medications	X
Prior anticancer treatment and disease history	X
Clinical Procedures/Assessments	
Assessment of SAEs related to study procedures	X
Physical examination (full assessment including height and weight)	X
12-lead ECG[a]	X
Vital signs[b]	X
Blood pressure	X
ECOG performance status	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)	
Hematology	X
Clinical chemistry	X
Thyroid tests[c]	X
Serum (total) testosterone	X
Serology[c]	X
Efficacy Measurements	
Brain MRI (CT with contrast may be performed if MRI is contraindicated)[d]	X
Radiological disease assessment (includes CT with contrast [unless contraindicated] of the chest, abdomen, and pelvis and bone scan)[d]	X
PSA	X
Tumor Biopsies/Archival Tissue Collection	
Tumor biopsy[e]	X

CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; ID = participant identification; PSA = prostate-specific antigen; SAE = serious adverse event

[a] Participants should be supine for at least 5 minutes prior to assessment. Perform in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) using locally sourced equipment. Refer to Section 7.3.3.

[b] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws.

[c] Defined in Section 7.3.8.

[d] Radiographic imaging (CT of the chest/abdomen/pelvis, bone scan, and/or brain MRI) performed as standard of care prior to obtaining informed consent and within Day -28 to Day -1 prior to enrollment does not have to be repeated at screening.

[e] If applicable and medically appropriate as specified in Section 5.1, Section 7.3.11, Section 20.4.1, or Section 20.9.3.

7.2. Schedule of Activities: End of Treatment and Follow-Up

Table 3: Schedule of Activities / END OF TREATMENT and FOLLOW-UP

Procedure	EOT[a]	Safety Follow-up[b]	
	Within 30 days of last dose	60 (±14) days of last Zim dose	90 (±14) days of last Zim dose
Administrative Procedures			
Concomitant medications	X		
Next anticancer therapy	X	X	X
Clinical Procedures/Assessments			
Assessment of AEs/SAEs[c]	X	X	X
Physical examination[d]	X		
12-lead ECG[e]	X		
Vital signs	X		
Blood pressure	X		
ECOG performance status	X		
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)			
Hematology	X	If clinically indicated	
Clinical chemistry	X	If clinically indicated	
Thyroid tests[f]	X	If clinically indicated	
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)			
PK	X		
Pharmacodynamics	X		
Immunogenicity	X		
Efficacy Assessments			
Disease evaluation	Includes CT, bone scan, and brain MRI as appropriate Q12W until PD, the start of new anticancer therapy, or consent withdrawal		
PSA	Q4W until PD, the start of new anticancer therapy, or consent withdrawal		
Survival assessment		X	X

AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; PSA = prostate-specific antigen; Q6M = every 6 months; Q4W = every 4 weeks; Q12W = every 12 weeks; SAE = serious adverse event; Zim = zimberelimab

[a] For participants who satisfy one or more of the treatment discontinuation criteria in Section 7.4.1, perform an EOT visit within 30 days of the last dose of study treatment and prior to the start of new anticancer therapy. Procedures performed within 14 days of the EOT visit need not be repeated.

[b] Safety follow-up is applicable only for participants who receive zimberelimab until death, withdrawal of consent, or loss to follow-up.

[c] In accordance with AE reporting periods and procedures defined in Section 8.2.1 and 8.2.3, respectively.

[d] Full physical examination including weight (height not required).

[e] Single recording unless initial result is abnormal clinically significant.

[f] Defined in Section 7.3.8. Thyroid laboratory assessments are only applicable to participants who receive zimberelimab.

7.3. Study Procedure Descriptions

7.3.1. Screening Procedures

Screening evaluations are to be performed within 28 days prior to the first dose of study treatment (Cycle 1 Day 1). If an assessment was performed as part of the participant's routine clinical evaluation and not specifically for this study, it need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to the first dose of study drug. Retesting of abnormal screening values that lead to exclusion are allowed only once during the screening phase (to reassess eligibility). The last result obtained prior to the first dose of study treatment will be used to determine eligibility. The measurements collected at the time closest to, but prior to, the start of study drug administration will be defined as the baseline values for safety and PSA assessment as well as treatment decisions. Screening procedures will be performed as designated in the schedule of activities (Section 7.1) before a participant is assigned to a treatment arm. Arm-specific screening procedures, if applicable, are detailed in the relevant arm-specific section.

Procedures performed only at screening include:

- Written informed consent
- Participant number (subject ID) assignment
- Demography (age, gender, race, ethnicity)
- Medical history including baseline disease characteristics
- Prior anticancer therapy history

Informed Consent

All participants must sign and date the most recent IRB/IEC-approved ICF for participation in the study before any procedures and/or screening evaluations can be performed except where noted in the protocol in relation to standard of care procedures. The ICFs for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. A separate participant consent, either within the main informed consent or on a separate ICF, may be required for optional study procedures including future research, per local region and/or IRB/IEC requirements.

Participant Number (Subject ID) Assignment

After a participant signs the ICF, they will be assigned a unique participant number (subject ID) via the electronic data capture system. Detailed instructions on subject ID assignment are provided in the electronic case report form completion guidelines.

Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled on the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria not met, and any SAE.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants may qualify for 1 rescreening opportunity (for a total of 2 screenings per participant) at the investigator's discretion. Participants who are rescreened are not required to sign another ICF if the original consent is still the current version and the screening window has not lapsed. If a new ICF version exists at the time of rescreening or the screening window has expired, then reconsent is required. Rescreened participants should be assigned the same participant number as for the initial screening.

7.3.2. Physical Examinations

A complete physical examination will be conducted at the frequency defined in the schedule of activities and will include, at a minimum, participant's general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Any clinically significant abnormality identified prior to the first dose of study treatment should be recorded on the medical history case report form (CRF). A symptom-directed physical examination will be conducted at all other specified timepoints. Clinically significant abnormalities that are new or worsened from baseline should be recorded as AEs on the AE CRF.

Participant height will be measured at screening and as clinically indicated throughout study treatment.

Body weight will be measured at screening for all participants and subsequently throughout treatment at the indicated frequency (Section 7.1 and Section 7.2; Section 14 through Section 20) for participants who receive study therapy at a dose determined by body weight or surface area (ie, mg/kg or mg/m^2).

7.3.3. Electrocardiograms

The ECG assessments will be performed at screening (triplicate recordings; Section 7.1) and during study treatment (single recording) as outlined for each arm in the schedules of activities, as applicable (Section 14 through Section 20), and at the EOT visit (single recording; Section 7.2). The ECGs for each participant should be obtained from the same machine wherever possible with lead placement as consistent as possible. Participants must rest in a supine position for at least 5 minutes prior to ECG recording.

At each time point, 12-lead ECGs will be performed by qualified site personnel. The clinical investigator will review the printout, including ECG morphology. After screening and during study treatment, an ECG should be repeated in triplicate if clinically relevant abnormalities are noted: 3 individual ECG tracings should be obtained within a 5-minute period, at least 1 minute apart. Additional cardiovascular assessments should be performed as clinically appropriate to ensure participant safety.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the CRF and recorded as an AE if appropriate.

7.3.4. Vital Signs

Vital signs will include measurements of temperature, respiratory rate, and pulse rate. Pulse/heart rate measurements should be performed while the participant is in a seated position.

Vital signs should be measured at specified timepoints, as outlined for each arm in the schedules of activities (Section 7.1 and Section 7.2; Section 14 through Section 20), and as clinically indicated.

7.3.5. Blood Pressure

Systolic and diastolic blood pressure should be performed while the participant is in a seated position according to the frequency of assessments outlined for each arm in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20), and as clinically indicated.

7.3.6. ECOG Performance Status

ECOG performance status (Oken, 1982) will be used to evaluate changes in the participant's daily living activities. The frequency of ECOG performance status is outlined for each arm in the schedules of activities (Section 7.1 and Section 7.2; Section 14 through Section 20), and as clinically indicated.

A copy of the ECOG Performance Status scale is available at https://ecog-acrin.org/resources/ecog-performance-status.

7.3.7. Adverse Events

Adverse events will be followed by the investigator as specified in Section 8. Assessment of new and ongoing AEs will occur as described in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20).

7.3.8. Laboratory Assessments

Laboratory assessments will be performed as described in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20).

A local laboratory will be responsible for hematology, clinical chemistry, thyroid tests, and PSA (Table 4). The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The results of each test must be entered into the CRF. The laboratory reports must be available with the source documents.

Table 4: Local Laboratory Assessments

Laboratory Assessments	Parameters	

Hematology	• Hematocrit
	• Hemoglobin
	• Platelet count
	• Red blood cell count
		• White blood cell count with differential:
		  ○ Neutrophils
		  ○ Lymphocytes
		  ○ Monocytes
		  ○ Eosinophils
		  ○ Basophils

Clinical Chemistry	• ALT • Albumin • ALP • Gamma-glutamyl transpeptidase (if clinically indicated per Section 5.1) • AST • Bicarbonate • Blood urea nitrogen • Calcium • Chloride	• Creatinine • Glucose (nonfasting) • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total and direct bilirubin • Total Protein
Thyroid tests	• Thyroid stimulating hormone (TSH) • Triiodothyronine (free T3) • Thyroxine (free T4)	
Cancer Markers	• PSA	
Serologya	• HBcAb • HBsAg • HCV	• HIV-1 • HIV-2

[a] Serology only performed at Screening.

7.3.9. Pharmacokinetics

Blood samples for PK will be collected from participants at the timepoints outlined in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20). The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

Serum concentrations for novel therapies will be determined by the sponsor or central laboratory designee using validated assays. Pharmacokinetic parameters will be estimated using standard noncompartmental methods.

Blood samples remaining after the bioanalyses may be analyzed for exploratory analyses, such as drug metabolism, and/or protein binding and/or other PK/pharmacodynamics work, as deemed appropriate by the Sponsor. The results of such exploratory work may only be included in the clinical study report (CSR) if deemed appropriate by the Sponsor or may be reported in a separate exploratory report.

7.3.10. Immunogenicity

Antibodies to zimberelimab will be evaluated in blood samples collected from applicable participants at the timepoints outlined in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20). The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

Serum samples will be assessed using a validated assay by the sponsor or central laboratory designee for antibodies binding to zimberelimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of zimberelimab and evaluate neutralization activity. Anti-zimberelimab immune response analysis may also be conducted on PK samples collected at other timepoints noted in Section 7.1 and Section 7.2; Section 14 through Section 20 based on emerging data.

7.3.11. Pharmacodynamics/Biomarker Assessments

Pharmacodynamic biomarkers will be collected from all participants at the timepoints outlined in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 20). The exact dates and times of biomarker sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

Availability of tumor tissue will be assessed as part of the study eligibility evaluation (Section 5.1). It is expected that paired biopsy samples (baseline fresh [preferred] or archival [within 24 months of screening] plus on-treatment fresh tissue) will be obtained from a minimum of 5 participants with measurable disease (at least 2 lesions; Section 5.1) within a given treatment arm at the timepoints outlined in the schedule of activities (Section 7.1 and Section 7.2; Section 14 through Section 19). The exact dates of sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection and processing requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual. Provided emerging data demonstrates favorable risk/benefit, sample size assumptions for one or more treatment arms may be adjusted to ensure the minimum number of participants providing paired biopsies are enrolled.

The biomarker objectives of this study are exploratory. Evaluation of baseline levels and/or changes with study treatment may be performed on peripheral blood samples and tumor tissue to determine association with clinical outcomes, including clinical response and resistance, and to inform development of diagnostic tests related to use of etrumadenant-based combination therapy for the disease under study. Biomarker scope may include but is not limited to assessment of:

- DNA
- RNA

- Protein (eg, enzymes, cytokines, antibodies, and/or markers associated with immune characteristics and activation or cancer)
- Immune cell profiling (eg, immune cell phenotyping, enumerations, and/or activation state)

Sample Collection, Storage, and Analysis

Blood and tissue samples will be collected and stored in accordance with applicable law for research purposes. Samples may be sent to one or more central laboratories, collaborators, or research partners of the sponsor. Analysis may be performed by the sponsor or sponsor's designee; samples not analyzed during study conduct may be stored for up to fifteen (15) years after the end of the main study.

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

The data generated from this research is exploratory in nature and is not expected to provide clinically meaningful information. Therefore, the sponsor will not provide the investigator, participant, or anyone else (eg, family members, study investigators, primary care physicians, insurers, or employers) with the results of this research, unless required by law.

Protection of Data Privacy

Biomarker samples will be labeled (or "coded") with a study-specific number that can be traced or linked back to the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name, date of birth, or social security number).

The specimens and data generated from the specimens will be made available for inspection upon request by representatives of national or local health authorities and, if stored or sent to third parties, by the sponsor and its representatives or agents.

Consent for Future Biomarker Research

Participants will be asked to consent to provide blood and tumor tissue samples described above for future biomedical research. Such research is for hypothesis testing to address emerging scientific questions about the investigational treatment(s) and/or disease under study not described elsewhere in the protocol. This research may include evaluation of DNA, RNA, and/or protein in blood and tumor tissue samples.

The collection and submission of biological samples to be stored for long-term future biomedical research must be detailed in the IRB/IEC-approved ICF. Participants who do not wish to participate in the future biomedical research may still participate in the study.

Withdrawal of Consent for Future Biomarker Research

Participants have the right to withdraw their consent for the future biomarker research of his/her specimens at any time for any reason and request that their specimens be destroyed. If the participant wishes to withdraw consent for this testing, the investigator must inform the sponsor

in writing. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received. In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.3.12. Disease and Response Assessment

Participants will undergo tumor assessments every 12 weeks (± 7 days) from start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study. At the investigator's discretion, tumor assessments may be repeated at any time if disease progression is suspected. All participants who discontinue study treatment for reasons other than disease progression (eg, AEs) will continue tumor assessments until death, disease progression, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, or study termination, whichever occurs first.

Measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to enrollment do not have to be repeated at screening.

Baseline disease assessments for all participants will include:

- CT scan with contrast of the chest and abdomen/pelvis,
- Full-body bone scan (technetium-99m [TC-99m]), and
- MRI scan of the brain.

Postbaseline disease assessments for all participants will include:

- CT scan with contrast of the chest and abdomen/pelvis,
- Full-body bone scan (TC-99m) for participants with bone disease documented at baseline and for participants with clinical signs or symptoms of new osseous disease, and
- MRI scan of the brain only for participants with CNS disease documented at baseline and for participants with clinical signs or symptoms of new CNS disease.

All scans should be performed in accordance with RECIST v1.1 and with contrast. If contrast is medically contraindicated, a chest CT without contrast and an abdomen/pelvis MRI without contrast may be performed. If a brain MRI is contraindicated, a brain CT with contrast should be performed. If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with standard for a full contrast diagnostic CT scan.

All measurable and evaluable lesions identified at baseline should be reassessed at each subsequent postbaseline tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (eg, same contrast

protocol for CT scans). Response will be assessed by the investigator using PCWG3. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across disease evaluations. Results must be reviewed by the investigator before dosing at the next planned study treatment cycle.

Sites may be required to provide electronic copies of radiographic imaging (ie, CT, Bone Scan, MRI) to assess centrally. Additional instruction will be provided in the study imaging manual.

Treatment After Initial Disease Progression

Antitumor response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents. Therefore, the investigator may decide to continue study treatment beyond disease progression as defined by PCWG3.

Once the PCWG3 criteria for disease progression are met, a repeat efficacy evaluation should be performed at the next protocol scheduled assessment timepoint or earlier, if clinically necessary, (but no sooner than 4 weeks from the previous assessment) in order to confirm disease progression.

While awaiting confirmation of disease progression, participants should continue to receive study treatment, if their clinical status is considered to be stable by the investigator, based on the following criteria:

- Absence of clinical signs and symptoms indicative of disease progression
- Clinical disease progression not requiring immediate therapeutic intervention

The decision to continue study treatment after the first evidence of disease progression is at the discretion of the investigator and requires that the participant agree to this treatment plan, and that the shared decision to treat beyond progression is documented. This study will utilize a Treatment Beyond Progression informed consent form. Table 5 provides guidelines to continue or discontinue study drug based on the initial and subsequent assessments of tumor and clinical status.

Table 5: Study Treatment after First Evidence of Progressive Disease

	Initial Assessment	Overall Response at Repeat Assessment	
	First Evidence of Progressive Disease	Progressive Disease	SD, PR, or CR
Disease evaluation	Repeat assessment[a]	No additional evaluations	Continue evaluations[c]
Study treatment	Continue[b]	Discontinue[e]	Continue[d]

CR = complete response; PR = partial response; SD = stable disease

[a] The repeat disease evaluation may be performed at the next protocol scheduled assessment timepoint or earlier if clinically necessary; the time interval from the initial to the confirmatory assessment should be at least 4 weeks.

[b] Participants should continue study treatment while awaiting confirmatory disease evaluation.

[c] For participants continuing study treatment, scheduled disease evaluations will continue until confirmed disease progression.

[d] Participants should continue study treatment in accordance with the schedule of activities for their treatment arm (Section 14 through Section 20). The investigator may discuss with the sponsor restarting study treatment that was stopped due to progressive disease in the initial assessment provided SD, PR, or CR is observed in the confirmatory assessment.

[e] The investigator may discuss with the sponsor continuing study treatment in a participant who is receiving benefit but has confirmed disease progression.

7.3.13. End of Treatment Assessments

Participants who satisfy one or more of the criteria in Section 7.4.1 will complete an EOT visit within 30 days of the last dose of any study treatment. The procedures to be performed at the EOT visit are detailed in Table 3. All participants are expected to complete an EOT visit.

Participants who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each treatment arm. Additional treatment arm-specific procedures or assessments, if applicable, are defined in their relevant arm-specific section (Section 14 through Section 20).

7.3.14. Safety Follow-Up

Safety follow-up visits will only occur for participants enrolled in zimberelimab-containing arms. Subjects enrolled in treatment arms that do not include zimberelimab will move directly into long-term follow-up after completion of the EOT visit.

Participants in zimberelimab-containing arms should return to the study center at 60 and 90 days after the last dose of zimberelimab for safety follow-up visits. The procedures to be performed at safety follow-up visits are detailed in Table 3. Additional treatment arm-specific procedures or assessments, if applicable, are defined in their relevant treatment arm-specific section (Section 14 through Section 20).

7.4. Discontinuation of Study Treatment and/or Withdrawal from the Study

7.4.1. Discontinuation from Study Treatment

- Study treatment should be discontinued if any of the following criteria are met:
- The participant has confirmed progressive disease according to the PCWG3 criteria (Scher et al., 2016; available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4872347/)
  - Note: The investigator may discuss with the sponsor continuing study treatment in a participant who is receiving benefit but has met the criteria for confirmed disease progression (Section 7.3.12).
- The participant experiences intolerable toxicity
- The investigator determines it is in the best interest of the participant
- The participant withdraws consent for further study treatment
- The participant completes study treatment regimen for a maximum of 2 years treatment duration after Cycle 1 Day 1
- The sponsor terminates the study

If 1 study treatment is discontinued, then all study treatment should be discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

When a participant's study treatment ends, this will not result in automatic withdrawal of the participant from the study. Following treatment discontinuation, the participant should complete the EOT visit within 30 days of their last study treatment dose as described in Section 7.3.13 and continue follow-up assessments as outlined. The primary reason for study treatment discontinuation will be documented in the CRF.

7.4.2. Study Discontinuation

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Death
- Loss to follow-up
- Withdrawal of study consent
- Study termination by the sponsor
- The investigator determines it is in the best interest of the participant

If a participant requests to be withdrawn from the study, the request must be documented in the source documents and signed by the investigator. The primary reason for withdrawal from study should be documented on the appropriate CRF page. If the participant withdraws from study, the sponsor may retain and continue to use any data collected before such the withdrawal of consent. In addition, the study staff may use a public information source (eg, county records) to obtain information about survival status only. However, participants who withdraw consent will not be followed for any reason after consent has been withdrawn.

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented. Loss to follow-up is defined as the absence of communication after no less than 2 phone calls and 1 couriered message by certified mail; follow-up attempts must be documented in the source documents.

8. ADVERSE EVENT REPORTING

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For each AE, the investigator will make an assessment of seriousness (Section 8.1.2), causality (Section 8.1.3), and severity (Section 8.1.4). Investigators will seek information on AEs at each participant contact as defined by the schedule of assessments (Section 14 through Section 20). Adverse events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or noted by study personnel, will be recorded in the participant's medical record and on the AE CRF page.

8.1. Definitions and Classifications

8.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Events that are related to a protocolmandated intervention, including those that occur prior to assignment of study treatment (eg, invasive screening procedures such as biopsies)

8.1.2. Serious Adverse Events

An SAE is any AE that meets any of the following criteria:

- Is fatal (ie, the AE actually causes or leads to death)
- Is life threatening (ie, the AE, in the view of the investigator, places the participant at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

- Is a significant medical event in the investigator's judgment (eg, may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe, or according to the National Cancer Institute [NCI] CTCAE; see Section 8.1.4); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

Serious AEs are required to be reported by the investigator or designee to the sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 8.2.5 for reporting instructions).

8.1.3. Assessment of Causality

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (Table 6):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event

Table 6: Causal Attribution Guidance

Is the AE suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of study treatment, and the AE cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study treatment; and/or the AE abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge. "Related" means that the event is at least possibly related to study treatment.
NO	*An AE will be considered related, unless it fulfills the criteria specified below.* Evidence exists that the AE has an etiology other than study treatment (eg, pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of study treatment (eg, cancer diagnosed 2 days after first dose of study treatment). "Unrelated" means that the event is unlikely related to study treatment.

For participants receiving combination treatment, causality will be assessed individually for each protocol-mandated therapy.

8.1.4. Assessment of Severity

An assessment of severity grade will be made by the investigator according to the NCI CTCAE (Version 5.0). Table 7 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 7: Adverse Event Severity Grading Scale for Events not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to AE[d]

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event", it must be reported as an SAE (see Section 8.2.5 for reporting instructions), per the definition of SAE in Section 8.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 8.2.5 for reporting instructions) should the event meet the definition of SAE in Section 8.1.2.

8.2. Reporting

The investigator is responsible for ensuring that all AEs are recorded on the AE CRF and reported to the sponsor in accordance with instructions provided in this section.

8.2.1. Adverse Event Reporting Period

The time periods for collection of AE, SAE, and other reportable safety event information for this protocol are defined in Table 8. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, the participant is lost to follow-up, or the participant withdraws consent in accordance with the specified time periods.

Table 8: Time Period for Collecting AE, SAE, and Other Reportable Safety Event Information

Reportable Safety Event	Time Period[a]
SAEs related to a protocol-mandated procedure[b]	Signed informed consent until the first dose of study treatment
SAEs regardless of causality	**Zimberelimab-containing regimens:** First dose of study treatment until 90 days after the last dose of zimberelimab or AB680, or 30 days after the last dose of etrumadenant or SG or other study treatment until initiation of new anticancer therapy, whichever occurs first. **Non-zimberelimab-containing regimens:** First dose of study treatment until 90 days after the last dose of AB680, 30 days after the last dose of etrumadenant or SG, or other study treatment until initiation of new anticancer therapy, whichever occurs first.
AEs	**Zimberelimab-containing regimens:** First dose of study treatment until 90 days after the last dose of zimberelimab or AB680, or 30 days after the last dose of etrumadenant or SG, or other study treatment until initiation of new anticancer therapy, whichever occurs first. **Non-zimberelimab-containing regimens:** First dose of study treatment until 90 days after the last dose of AB680, 30 days after the last dose of etrumadenant or SG or other study treatment until initiation of new anticancer therapy, whichever occurs first.
Pregnancy in female partner of a study participant	Refer to the respective section for each treatment regimen (Section 14 through Section 20).

[a] Investigators are not obligated to actively seek AE or SAE information after the end of the reporting period. However, if the investigator learns of any SAE, including a death, at any time after the end of the reporting period, and he/she considers the event to be reasonably related to study treatment or study participation, the event should be promptly reported to the sponsor or its designee according to Section 8.2.5. Every effort should be made to follow AEs and SAEs considered related to study treatment or protocol-related procedures until a final outcome can be reported.

[b] Other clinically relevant medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history CRF.

8.2.2. Method of Eliciting Adverse Event Information

A consistent methodology of nondirective questioning should be adopted for eliciting AE information at all participant evaluation time points. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Examples of nondirective questions include: “How have you felt since your last clinic visit?”, “Have you had any new or changed health problems since you were last here?”

8.2.3. Procedure for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the AE CRF. Only 1 AE term should be recorded in the event field on the AE CRF.

Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE CRF and/or SAE Form rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE CRF and/or SAE Form. If a diagnosis is subsequently established, all previously reported AEs/SAEs based on signs and symptoms should be nullified and replaced by 1 AE/SAE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first sign or symptom of the eventual diagnosis.

Disease-Related Events and/or Worsening of Metastatic Prostate Cancer

An event which is part of the natural course of the disease under study (ie, disease progression, death due to disease progression) should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the AE or SAE definition (Section 8.1.1 and Section 8.1.2).

In most cases, the expected pattern of progression will be based on PCWG3. In rare cases, the determination of clinical progression will be based on physician decision. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (Section 8.2.1) that are attributed by the investigator solely to progression of the disease under study should be recorded on the Death CRF. All other deaths that occur during the AE reporting period, regardless of relationship to study treatment, must be recorded on the AE CRF and immediately reported to the sponsor (Section 8.1.2).

Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an AE or SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (eg, for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The participant has not experienced an AE related to the pre-existing condition.
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

Overdose

For this study, overdose is defined as any dose of investigational product greater than the planned dose to be administered in accordance with the protocol.

Refer to the respective investigator brochure or prescribing information for guidance on specific treatment for an overdose.

In the event of an overdose, the investigator should:

2. Contact the medical monitor immediately.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
4. Institute symptom-directed supportive care in accordance with institutional standard practice.
5. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.2.4. Events Requiring Expedited Reporting to the Sponsor

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator becomes aware of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours of becoming aware of the event, regardless of relationship to investigational product:

- All SAEs (defined in Section 8.1.2)
- Pregnancies (see Section 8.2.8 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the sponsor immediately (ie, no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

8.2.5. Serious Adverse Event Reporting Requirements

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to the sponsor **no more than 24 hours after site personnel become aware of the event**. Any follow-up information on a previously reported SAE will also be reported to the sponsor **no more than 24 hours after becoming aware of the new information**.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the appropriate data collection tool. The investigator will always provide an **assessment of causality** at the time of the initial report as described in Section 8.1.3.

Serious AEs will be reported to the sponsor using the Safety Notification Form, which will be completed and submitted, along with any applicable supporting documents, by email or facsimile, if email is not available:

Email: ArcusPV@ubc.com

Fax: Please refer to the SAE form for the region-specific numbers.

Serious AE information recorded on the Safety Notification Form must also be entered on the AE CRF.

8.2.6. Sponsor Contact Information

Arcus Biosciences, Inc. medical monitor contact information:

Medical Monitor: PPD MD
Medical Director, Clinical Development
PPD
Mobile: PPD

Alternate medical monitor contact information is provided in the study manual.

8.2.7. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of an

investigational product under clinical investigation are met. Investigators must also comply with local requirements for reporting SAEs to the IRB/IEC or other local health authorities.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The sponsor will promptly evaluate all SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to relevant health authorities based on applicable legislation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

Upon receipt of a suspected unexpected serious adverse reaction (SUSAR) report from the sponsor or designee, the investigator must comply with all applicable requirements related to the reporting of SUSARs per institutional guidelines.

8.2.8. Collection of Pregnancy Information

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Reporting requirements for all pregnancies in female partners of male participants are described for each treatment regimen in the respective section for that combination therapy (Section 14 through Section 20). Monitoring of the mother should continue until conclusion of the pregnancy. The newborn should be monitored for up to 12 weeks for a healthy newborn or at least 1 year for a newborn with complications.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

In addition, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the SAE form.

8.3. Adverse Events of Special Interest

No AESIs have been defined for this study. All AEs and SAEs should be reported as described in Section 8.2.3 and Section 8.2.5, respectively.

8.4. Protocol-Specific Events that Qualify as Serious Adverse Events

All laboratory abnormalities meeting Hy's Law case criteria, defined below, qualify as SAEs, and must be reported as per Section 8.2.5.

Participants meeting the following criteria will meet Hy's Law case criteria:

- ALT or AST $\geq 3 \times$ ULN concurrent with serum total bilirubin $> 2 \times$ ULN and serum ALP $< 2 \times$ ULN, and

- No other reason is found to explain the combination of increased ALT/AST and serum total bilirubin, such as evidence of new or worsening liver disease/metastasis, pre-existing liver disease, viral hepatitis, alcohol abuse, ischemia, or another drug capable of causing the observed injury.

9. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on participant data collected from the time of screening though study discontinuation. Unless otherwise stated, analysis results will be summarized by the treatment that participants actually received. Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

Statistical considerations and analysis plan for all SG-containing treatment arms can be found in Section 20.12.

9.1. Sample Size Determination

This study is not designed with explicit Type I error and power considerations in mind. Rather, this is a Phase 1b/2 study intended to obtain preliminary safety, efficacy, and PK data on investigational combinations when administered to patients with mCRPC. Unless otherwise specified, assessment of efficacy will focus primarily on measures of direct antitumor activity such as PSA response or radiographic response among participants receiving study treatment.

During Stage 1, participants will be enrolled into various treatment arms based on their prior cancer history. Enrollment may be paused after the accrual of approximately 6 participants in a treatment arm to allow for safety evaluation. A rate of toxicity of < 33% will be targeted, with toxicity being defined as the occurrence of either a treatment-related Grade 4 AE or a treatment-related Grade 3 AE that is not responsive to supportive care during Cycle 1. If 2 or more such events are observed, enrollment in that arm may not continue.

A futility analysis will be conducted in each treatment arm in order to guide continuation of enrollment from Stage 1 into Stage 2. Futility gates will be arm-specific and anchored to existing standard of care historical control information for use in a beta-binomial Bayesian decision-making framework (Thall and Simon, 1994; Thall et al., 1995).

In the etrumadenant + zimberelimab + enzalutamide treatment arm, gating will be based on a more stringent PSA decline of > 90% (PSA90). At least 4 out of 15 evaluable participants must exhibit a percent change from baseline PSA of > 90% in order to consider opening Stage 2. Across a range of prior beta distributions, observing 3 or fewer PSA90 responses would provide greater than 80% posterior probability confidence that the PSA90 rate in the experimental arm is less than 35% (Khalaf et al., 2019). Participants must have at least 2 consecutive postbaseline PSA assessments measured at least 3 to 4 weeks apart to be considered evaluable for Stage 1 decision gating.

In the remaining treatment arms, gating will be based on either radiographic or PSA response. Radiographic response is defined as either a CR or PR by RECIST v1.1, and PSA response is defined as percent change from baseline PSA of > 50%. At least 1 radiographic CR or PR or 2 PSA responses out of 15 evaluable participants must be observed in order to consider opening Stage 2. In this case, across a range of prior beta distributions, observing 1 or fewer responses would provide greater than 80% posterior probability confidence that the response rate is less than 20%. Participants must have at least 1 postbaseline radiographic disease evaluation or at

least 2 consecutive postbaseline PSA assessments measured at least 3 to 4 weeks apart to be considered evaluable for Stage 1 decision gating.

During Stage 2, up to 25 additional participants may be enrolled either onto an experimental arm or a standard of care control arm. The goal of this stage is to better characterize potential treatment differences between experimental arms and standard of care, among concurrently enrolled participants. Without loss of generality when benchmarking to either binomial endpoints such as radiographic or PSA response, Table 9 shows estimated differences in response rates (without corrections for continuity) between an experimental arm and a control arm with 25 participants each during Stage 2. When appropriate, data may be pooled across Stage 1 and Stage 2 in order to more broadly characterize safety and efficacy data using a total sample size of 40 participants in a given experimental arm.

Table 9: Estimated Differences in Binomial (Response) Rates Between Experimental and Control Arms in Stage 2

No. (%) of Responders		Difference in Response Rate (%) (90% CI)
Experimental Arm (n = 25)	Control Arm (n = 25)	
4 (16.0%)	0 (0.0%)	16.0% (3.9%, 28.1%)
5 (20.0%)	1 (4.0%)	16.0% (–1.3%, 30.1%)
6 (24.0%)	2 (8.0%)	16.0% (–0.1%, 32.6%)
7 (28.0%)	3 (12.0%)	16.0% (–2.3%, 34.2%)
9 (36.0%)	4 (16.0%)	20.0% (0.1%, 39.9%)
10 (40.0%)	5 (20.0%)	20.0% (–0.8%, 40.8%)

9.2. Populations for Analysis

For purposes of analysis, the following populations are defined:

Table 10: Populations for Analysis

Population	Description
Enrolled Population	All participants who sign the ICF, complete screening, and are deemed eligible for treatment in the study
Efficacy-evaluable Population	All participants who are enrolled and receive at least 1 dose of each drug of their assigned treatment regimen
Safety-evaluable Population	All participants who are enrolled and receive any amount of study treatment

Participants who are enrolled onto the study and assigned treatment but never receive investigational product will be summarized separately.

Additional analysis populations may be defined on the basis of sample availability. Analyses of PK, ADAs, and pharmacodynamic or other tumor-based or blood-based biomarkers will occur in subsets of participants with applicable and suitable pre- or post-treatment samples collected at relevant time points.

9.3. Statistical Analyses

9.3.1. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be performed in the efficacy-evaluable population as defined in Table 10. Participants who are enrolled onto the study and assigned treatment but never receive investigational product will be summarized separately. Unless otherwise specified, binary endpoints will be displayed with their exact Clopper-Pearson binomial 90% confidence intervals. Time-to-event endpoint parameters will be estimated using Kaplan-Meier techniques.

Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR, defined as the composite proportion of participants with a PSA response or a radiographic complete or partial response determined by the investigator according to the PCWG3 criteria. PSA response and radiographic complete or partial response may be reported individually. For clarity, PSA response is defined as the proportion of participants with a confirmed PSA decrease from baseline of 50% or more based on 2 consecutive assessments measured 3 to 4 weeks apart. Radiographic response is defined as the percentage of participants with measurable disease at baseline who achieve a best overall response of CR or PR according to RECIST v1.1.

Unless otherwise specified, participants with missing or no postbaseline response assessments will be considered nonresponders. The ORR, PSA response rate, and radiographic response rate will be calculated for each treatment arm, as appropriate, along with exact Clopper-Pearson 90% Cis. The difference in ORR between treatment arms in Stage 2 will also be calculated and presented with exact 90% Cis. Response rates for the experimental arms may also be presented pooling data across Stage 1 and Stage 2.

Secondary Efficacy Endpoints

Secondary efficacy endpoints include PSA response rate (defined above), radiographic response rate (defined above), and DCR. Radiographic endpoints will be assessed according to RECIST v1.1.

Disease control rate (DCR), defined as the percentage of participants with measurable disease at baseline who achieve a best overall RECIST response of CR, PR, or SD, will be calculated for each treatment arm. The duration of time required for a patient with SD to be considered in disease control for each treatment arm is referenced Section 14 through Section 19. Differences in DCR between treatment arms will be presented with exact 90% Cis. The Wald method may also be used.

Exploratory Efficacy Endpoints

Progression-free survival (PFS) is defined as the time from treatment assignment until first documentation of progressive disease (PSA progression, radiographic progression, bone scan

progression, or other) or death, whichever occurs first. Depending on data availability, time to progression due to specific reasons (eg, PSA progression or radiographic progression) may also be presented individually.

Overall survival (OS) is defined as the time from treatment assignment until death due to any cause.

Median PFS and OS will be estimated in each treatment arm using Kaplan-Meier methodology. Depending on data maturity, hazard ratios may also be estimated using Cox proportional hazards modeling for participants enrolled into Stage 2. PFS and OS may also be estimated at specific milestones, eg, at 6 months or 12 months, or other time points as appropriate.

Based on available data, additional sensitivity analysis estimates of OS may also be obtained by censoring participants who crossover to an applicable experimental regimen (i) at the time of initial disease progression or (ii) at the time of initiation of crossover therapy. A sensitivity analysis for OS censoring any patient who has progressed and stopped receiving study treatment at the time of subsequent follow-on anticancer therapy may also be performed.

Exploratory Efficacy Endpoints (Crossover)

For participants who crossover from standard of care control monotherapy to an etrumadenant-based experimental regimen, the clinical activity of the crossover experimental regimen may also be analyzed based on available data:

ORR-2 is defined as the composite proportion of participants with a PSA response or a radiographic complete or partial response determined by the investigator according to the PCWG3 criteria beginning from the initiation of crossover therapy.

PSA response rate-2 is defined as the proportion of participants with a confirmed PSA decrease from baseline of 50% or more based on 2 consecutive assessments measured 3 to 4 weeks apart beginning from the initiation of crossover therapy.

Radiographic response-2 is defined as the percentage of participants with a best overall response of CR or PR according to RECIST v1.1 beginning from the initiation of crossover therapy.

PFS-2 is defined as the time from initiation of crossover therapy to the earliest time of next documented disease progression or death, whichever comes first.

9.3.2. Safety Analyses

Unless otherwise specified, safety analyses will be conducted in the safety-evaluable population, as defined in Table 10. Safety will be assessed through summaries of AEs, as well as changes in laboratory test results, vital signs, and ECGs. Verbatim AE terms will be mapped and coded using the Medical Dictionary for Regulatory Activities. Adverse events will be assessed for severity according to NCI CTCAE v5.0.

Treatment-emergent adverse events (TEAEs), defined as AEs with onset date on or after initiation of study treatment or as AEs present at baseline but which worsened after initiation of study treatment, will be summarized. Adverse events will be summarized on the participant-level using the maximum severity or grade reported. All TEAEs, SAEs, AEs leading to study treatment discontinuation, Grade 3 or higher AEs, and deaths will be listed and summarized by

treatment arm with the mapped preferred terms, thesaurus level and NCI CTCAE grade, as appropriate.

Relevant laboratory, vital sign, and ECG data will be displayed by time and with grades applied where appropriate. Shift tables of selected laboratory will be used to summarize the baseline and maximum postbaseline grade. Changes in vital signs and ECGs will also be summarized.

In the case of crossover, participants will contribute safety information up until the time of crossover. AEs reported after crossover will be summarized separately.

9.3.3. Pharmacokinetic and Biomarker Analyses

The following additional analyses will be conducted in populations of treated participants determined by sample availability and suitability. Specifically, analyses of PK, ADAs, and pharmacodynamic or other tumor-based or blood-based biomarkers will occur in subsets of participants with analyzable samples collected at relevant analysis time points.

Pharmacokinetic Analyses

Individual concentration-time plots for etrumadenant, zimberelimab, AB680, and SG will be presented for participants per treatment assignment. PK parameters will be estimated using noncompartmental methods. Summary statistics will be generated for each PK parameter for each arm. A population PK analysis may also be performed to obtain additional PK parameters.

Immunogenicity Analyses

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of participants who develop detectable anti-zimberelimab and/or anti-SG antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-zimberelimab antibodies. Samples confirmed positive may also be evaluated for neutralizing antibody activity.

Immunogenicity may be reported for ADA-positive status (such as persistent positive, transient positive, only last sample positive, baseline positive) and ADA-negative status, relative to baseline for participants. The effect of immunogenicity on safety, efficacy, biomarkers, and PK may be explored, pending data availability and suitability.

Pharmacodynamic and Exploratory Biomarker Analyses

Descriptive statistics will be used to evaluate the exploratory biomarkers. Samples collected for exploratory biomarker analysis (including but not limited to analysis of DNA, RNA, protein, and/or immune cell profiling) may be examined to determine pharmacodynamic changes that may occur relative to baseline. Possible PK/pharmacodynamic relationships may also be explored. If relevant data are available, relationships between biomarker changes and clinical outcome will be explored. Tumor biopsy data may also be analyzed and presented depending on available data, particularly in relationship to clinical outcomes.

9.4. Interim Analyses

There will be 2 planned interim analyses in each treatment arm, with the exception of only 1 interim analysis in the etrumadenant + zimberelimab arm. The first interim analysis will occur in Stage 1 after 6 participants have completed 1 cycle of the study treatment in all treatment

arms, excluding the etrumadenant + zimberelimab arm. The second interim analysis will assess safety and early efficacy data in order to determine treatment arm advancement from Stage 1 to Stage 2.

In the etrumadenant + zimberelimab arm, there will only be 1 planned interim analysis to determine treatment arm advancement from Stage 1 to Stage 2.

Data monitoring will be conducted by an IMC that will meet to review accumulating safety and efficacy data and to make recommendations regarding the conduct of the trial. The IMC will be composed of members from the sponsor or delegate, including, at a minimum, a clinician independent of the study team, the medical monitor, a safety representative, and a biostatistician. The IMC may bring in other internal or external scientific and clinical expertise as needed. Details of the IMC, including membership, timing, scope, and communication of committee recommendations are further described in a separate IMC charter.

10. STUDY OVERSIGHT

10.1. Data Monitoring

10.1.1. Source Documentation

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

When clinical observations are entered directly into a study site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Source documents that are required to verify the validity and completeness of data entered into the CRFs must not be obliterated or destroyed and must be retained as described in Section 10.

10.1.2. Data Protection

The sponsor maintains confidentiality standards by assigning a unique participant identification number to each participant enrolled in the study. This means that participant names are not included in data sets that are transmitted to any sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant or as permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

10.1.3. Data Quality Assurance

All participant data relating to the study will be collected via electronic data collection (EDC) on an electronic CRF unless transmitted to the sponsor or designee electronically (eg, central laboratory data, biomarker, and other biological sample data). Sites will be responsible for data entry into the EDC system and will receive training for appropriate CRF completion. The

investigator is responsible for verifying that data entries are accurate and correct by electronically signing and dating the CRF.

The investigator must maintain accurate documentation (source data, see Section 10.1.1) that supports the information entered in the CRF.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Council for Harmonization Good Clinical Practice (ICH GCP), and all applicable regulatory requirements.

At the end of the study, the investigator will receive participant data for his/her site in a readable format on a compact disc (or other readable digital format) that must be kept with the study records. Acknowledgement of receipt of the data is required.

10.2. Study Monitoring

10.2.1. Administrative Structure

This trial will be sponsored and managed by Arcus Biosciences, Inc. The sponsor will provide clinical operations management, data management, and medical monitoring.

Central facilities will be used for certain study assessments throughout the study (eg, specified laboratory tests, and PK and biomarker analyses), as specified in Section 7. Accredited local laboratories will be used for clinical laboratory safety assessments; local laboratory ranges will be collected.

10.2.2. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- Discontinuation of further investigational product development
- The incidence or severity of AEs in this or other studies indicate the potential hazard to participants
- Participant enrollment is unsatisfactory

The sponsor will notify the investigator if the sponsor decides to discontinue the study.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines

- No study activity (ie, all participants have completed the study and all obligations have been fulfilled)

10.3. Site Inspection and Audits

For the purpose of compliance, the investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, sponsor monitors, representatives and collaborators, and the IRB/IEC for each study site, as appropriate.

Site visits will be conducted by the sponsor or an authorized representative for inspection of study data, participants' medical records, and CRFs. The investigator will permit national and local health authorities; sponsor monitors, representatives, and collaborators; and the IRBs/Ecs to inspect facilities and records relevant to this study.

11. ETHICS

11.1. Compliance with Laws and Regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and applicable laws and regulations. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the US or under a US Investigational New Drug application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU) or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

11.2. Institutional Review Board or Independent Ethics Committee

11.2.1. Institutional Review Board or Independent Ethics Committee

The protocol, protocol amendments, ICF(s), investigator brochure, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials (eg, advertisements) must be approved by the IRB/IEC.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Promptly documenting and reporting any deviations that might have an impact on participant safety and data integrity to the sponsor and to the IRB/IEC in accordance with established requirements, policies, and procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of Part 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.2.2. Informed Consent

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

Participants must be re-consented to the most current version of the ICF(s) (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. The medical record should document the reconsent process and that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. All signed and dated ICFs must remain in the participant's study file or in the site study file and must be available for verification by study monitors at any time.

The final revised IRB/IEC-approved ICFs must be provided to the sponsor for the purpose of health authority submission.

12. RECORD RETENTION

Records and documents pertaining to the conduct of this study and distribution of the investigational medicinal product, including signed CRFs, electronic or paper participant-reported outcomes data (if applicable), signed ICFs, laboratory test results, and medication inventory records, must be retained by the investigator for the maximum period required by applicable regulations of relevant national or local health authorities. No records may be disposed of without the written approval of the sponsor. The sponsor will notify the investigator when the records are no longer needed. Following notification from the sponsor, the documents may be destroyed, subject to local regulations.

Written notification should be provided to the sponsor prior to transferring any records to another party or moving them to another location.

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14. ETRUMADENANT + ZIMBERELIMAB + ENZALUTAMIDE TREATMENT ARM

14.1. Introduction

This treatment arm combines 2 investigational agents in development by Arcus Biosciences, etrumadenant and zimberelimab, with enzalutamide.

14.1.1. Background for Etrumadenant + Zimberelimab + Enzalutamide

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

Zimberelimab, a fully human immunoglobulin G4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated PK, pharmacodynamics including receptor occupancy, efficacy, and safety that is consistent with currently approved anti-PD-1 therapies. Arcus in-licensed zimberelimab to enable development of precision combination regimens with full line-of-sight to the commercialization of innovative therapies for all patients who may benefit. The most advanced study with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic NSCLC, evaluating zimberelimab in combination with 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.

Enzalutamide is an androgen receptor inhibitor approved by the US FDA and other global regulatory agencies for the treatment of CRPC.

Refer to the etrumadenant investigator brochure, the zimberelimab investigator brochure, and the package insert for enzalutamide for complete discussion of the agents and additional information on preclinical and clinical studies.

14.1.2. Rationale for Combining Etrumadenant + Zimberelimab + Enzalutamide

The opportunity to combine etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 study in participants with advanced solid tumors (NCT03846310). Emerging

data show that etrumadenant administered together with zimberelimab was well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months (Powderly et al., 2019), in heavily pretreated participants across multiple disease indications.

Active cohorts in mCRPC and advanced clear cell renal cell carcinoma (RCC) are currently under study. This investigational doublet regimen is also the base for other anticancer combinations with chemotherapy in current and planned studies in NSCLC, colorectal cancer, a d head and neck cancers, as well the backbone for numerous cohorts in this platform trial in mCRPC. The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents.

Recent clinical data from KEYNOTE-199 has shown minimal response activity but potential survival advantage for NHA and taxane experienced mCRPC participants treated with the anti-PD-1 antibody pembrolizumab (Antonarakis et al., 2019). This, coupled with the early activity signal seen when AZD4635, an adenosine $A_{2a}R$ antagonist, was combined with the anti-PD-L1 antibody durvalumab in late-line mCRPC (Bendell et al., 2019), help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and supports the evaluation of etrumadenant and zimberelimab together with AB680 in this study. Specifically, mCPRC participants treated with AZD4635 with or without durvalumab showed radiographic and PSA responses. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

Androgen receptor amplification is a major mechanism of resistance to ADT and thus the evolution of prostate cancer from a hormone-sensitive to castrate-resistant disease state. Enzalutamide was previously shown to render prostate tumor cells more sensitive to T-cell-mediated killing (Ardiani et al., 2014); moreover, these enzalutamide-induced immunomodulatory effects were also shown to occur in androgen receptor-dependent manner and provide supportive rationale for its use in combination with immunotherapy in CRPC, especially for patients with minimal response to NHA monotherapy or patients with acquired resistance to ADT. Indeed, early results in abiraterone experienced or intolerant frontline mCRPC show that treatment enzalutamide in combination with pembrolizumab results in sustained clinical activity (33% DCR) after a median (95% CI) follow-up time of 9 (7-13) months (Fong et al., 2019).

Despite these treatment advances, clinical benefit was not observed in most patients and additional experimental therapeutic approaches are needed. Because adenosine is highly immunosuppressive, NHAs with or without checkpoint inhibitors may be less effective in adenosine-rich tumors such as prostate cancer. Therefore, the addition of an adenosine receptor antagonist to combination NHA/immunotherapy may result in enhanced antitumor activity. To test this hypothesis, the efficacy and safety of etrumadenant together with zimberelimab and enzalutamide will be evaluated in this treatment arm.

14.1.3. Risk/Benefit Assessment for Etrumadenant + Zimberelimab + Enzalutamide

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

Zimberelimab is currently being evaluated in for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function after 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 and every 3 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. However, the risks associated with this drug class given experience with the approved anti-PD-1 agents, nivolumab (Opdivo Package Insert, 2019) and pembrolizumab (Keytruda Package Insert, 2020), are appropriate for zimberelimab.

The combination of etrumadenant and zimberelimab has been evaluated in early-phase studies across multiple tumor types illustrating both tumor response and disease stabilization. Current and future evaluation of this combination with additional chemotherapy or investigational agents added onto this backbone are ongoing to assess efficacy in specific tumor types. This 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.

Enzalutamide is a US Food and Drug Administration-approved medication that is used in accordance with its label in this study (Xtandi Package Insert).

In summary, the safety and early activity of the combination of etrumadenant and zimberelimab in cancer patients supports its evaluation in this study as part of triplet regimen with enzalutamide. Considering the activity signals seen with similar mechanistic combinatory regimens in mCRPC and other PD-1 resistant tumor types with etrumadenant and zimberelimab,

it is hypothesized that treatment with etrumadenant, zimberelimab, and enzalutamide has promising therapeutic potential in mCRPC.

14.2. Objectives and Endpoints

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + zimberelimab + enzalutamide treatment arm are described in Section 3 with the exception of those that are treatment arm-specific and described below.

14.2.1. Stage 1 (Etrumadenant + Zimberelimab + Enzalutamide)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate of at least 6 months
To determine the PK profile for etrumadenant, zimberelimab, and enzalutamide when administered as part of a combination regimen in Stage 1	Serum/plasma concentration and PK parameters for etrumadenant, zimberelimab, and enzalutamide when administered as part of a combination regimen in Stage 1

14.2.2. Stage 2 (Etrumadenant + Zimberelimab + Enzalutamide)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate of at least 6 months
To determine the PK profile for etrumadenant, zimberelimab, and enzalutamide when administered as part of a combination regimen in Stage 2	Serum/plasma concentration and PK parameters for etrumadenant, zimberelimab, and enzalutamide when administered as part of a combination regimen in Stage 2
Exploratory Objectives	
To evaluate the clinical activity of etrumadenant + zimberelimab + docetaxel in participants who crossed over from treatment with enzalutamide monotherapy (may include PSA and/or radiographic response rate according to PCWG3, PFS, and OS depending on available data)	
To evaluate the clinical activity of etrumadenant + zimberelimab in participants who crossed over from treatment with enzalutamide monotherapy (may include PSA and/or radiographic response rate according to PCWG3, PFS, and OS depending on available data)	

14.3. Investigational Plan

The etrumadenant + zimberelimab + enzalutamide treatment arm will be conducted as described in Section 4.

In Stage 2, crossover to experimental treatment with either etrumadenant + zimberelimab + docetaxel or etrumadenant + zimberelimab may be permitted for participants who progress on enzalutamide monotherapy; the choice of crossover therapy is at the investigator's discretion in consultation with the sponsor. Participants who crossover will initiate a second study treatment period (ie, Cycle 1 Day 1) at the time of first crossover dose, following the applicable schedules of activities (Section 15.8.2 or Section 16.8.2), and will remain on study treatment until one of

the criteria in Section 7.4.1 are met. Thereafter, crossover participants will enter the follow-up period (Table 3).

14.4. Eligibility

14.4.1. Inclusion Criteria for Enzalutamide with or without Etrumadenant + Zimberelimab

All participants receiving enzalutamide with or without etrumadenant + zimberelimab must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving enzalutamide with or without etrumadenant + zimberelimab must satisfy the following:

A.1 Disease progression after prior treatment with abiraterone

A.2 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of enzalutamide, whichever is longer

14.4.2. Exclusion Criteria for Enzalutamide with or without Etrumadenant + Zimberelimab

All participants receiving enzalutamide with or without etrumadenant + zimberelimab must not meet any of the main study exclusion criteria in Section 5.2. Participants are excluded from receiving enzalutamide with or without etrumadenant + zimberelimab if any of the following criteria apply:

A.1 Prior treatment with docetaxel, cabazitaxel, or other taxane chemotherapy administered as a single agent or as part of a combination regimen

Note: Participants may have received prior docetaxel (up to 6 cycles) for hormone-sensitive prostate cancer provided that the last dose of chemotherapy was administered at least 6 months prior to the first dose of study treatment.

A.2 Prior treatment with enzalutamide or other second-generation NHA therapy.

A.3 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain Barré syndrome, or multiple sclerosis with the following exceptions:

A.3.1: Patients with a history of autoimmune related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

A.3.2: Patients with controlled Type 1 diabetes mellitus who, in the judgment of the investigator, are on a stable insulin regimen are eligible for the study.

A.3.3: Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

Rash must cover < 10% of body surface area.

Disease is well controlled at baseline and requires only low potency topical corticosteroids.

A.3.4: There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency corticosteroids within the previous 12 months

A.4 History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins

A.5 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

A.5.1: Treatment with 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

A.5.2: Treatment with 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

A.5.3: Treatment with known strong cytochrome P450 3A4 (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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment

Refer to 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

14.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant and zimberelimab may be found in the respective investigator brochure. Refer to the enzalutamide package insert for a formulation description.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

14.5.1. Dosage and Administration: Etrumadenant, Zimberelimab, Enzalutamide

Etrumadenant + Zimberelimab + Enzalutamide

All participants in Stage 1 and participants randomized to the etrumadenant + zimberelimab + enzalutamide treatment arm in Stage 2 will receive:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (21-day cycle)
- **Enzalutamide:** 160 mg, oral, once daily continuous dosing (21-day cycle)
- **Zimberelimab:** 360 mg, IV, every 3 weeks (Day 1 of a 21-day cycle)

Study treatment will continue until progressive disease, unacceptable toxicity, withdrawal of consent, or up to a maximum of 2 years, whichever occurs first.

Table 11: Etrumadenant + Zimberelimab + Enzalutamide Administration

Product Name[a]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Capsule	QD	150 mg	Oral	
Enzalutamide[b]	Capsule	QD	160 mg	Oral	
Zimberelimab	C mg/mL solution	Q3W	360 mg	IV	

IV = intravenous; Q3W = every 3 weeks; QD = once daily
[a] Product names are listed in order of administration.
[b] Participants should also receive gonadotropin-releasing hormone analog concurrently or should have bilateral orchiectomy.

On zimberelimab infusion days, participants will hold etrumadenant and enzalutamide administration until directed by study personnel. Etrumadenant and enzalutamide should be taken together at least 30 minutes prior to the start of IV infusion of zimberelimab. Participants will be administered etrumadenant and zimberelimab for a maximum of 2 years following Cycle 1 Day 1.

On study visit days when PK samples are collected, participants should take their etrumadenant and enzalutamide dose in the clinic, when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant and enzalutamide, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant, zimberelimab, and enzalutamide is described in the study pharmacy manual.

Enzalutamide

Participants randomized to the enzalutamide treatment arm in Stage 2 will receive:

- **Enzalutamide:** 160 mg, oral, once daily continuous dosing (21-day cycle)

Table 12: Enzalutamide Administration

Product Name	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI [redacted]
Enzalutamide[a]	Capsule	QD	160 mg	Oral	

QD = once daily
[a] Participants should also receive gonadotropin-releasing hormone analog concurrently or should have bilateral orchiectomy.

On clinic visit days when PK samples are collected, participants should take their enzalutamide dose in the clinic, when directed by study personnel.

To assess participant compliance with self-administration of enzalutamide, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Additional information regarding administration of enzalutamide is described in the study pharmacy manual.

For all participants receiving enzalutamide with or without etrumadenant + zimberelimab, guidelines for dose modification and safety management guidelines are provided in Section 14.9.

14.6. Method of Treatment Assignment

During Stage 1, participants will be enrolled into treatment arms based on their prior anticancer treatment history. Investigational product will be assigned according to the treatment arm in which the subject has enrolled. During Stage 2, patients may be randomized in a 1:1 ratio to enzalutamide standard of care control therapy using a permuted block method. Participants will be stratified based on the presence of measurable disease at baseline.

In Stage 2, participants who progress on enzalutamide monotherapy may be permitted to crossover to experimental treatment with etrumadenant + zimberelimab + docetaxel or etrumadenant + zimberelimab at the investigator's discretion and in consultation with the medical monitor. As this is an open-label trial, documented evidence of disease progression as

defined by PCWG3 is required prior to permitting a randomized participant in the enzalutamide arm to be deemed eligible for crossover.

14.7. Concomitant Medications

14.7.1. Permitted Therapy for Enzalutamide with or without Etrumadenant + Zimberelimab

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 14.7.2.

- Participants receiving enzalutamide should also receive a gonadotropin-releasing hormone analog concurrently or should have had bilateral orchiectomy.
- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including international normalized ratio (INR), according to institutional guidelines. If enzalutamide is administered with warfarin, conduct additional INR monitoring in accordance with the prescribing information (Xtandi USPI).
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

14.7.2. Prohibited Therapy for Enzalutamide with or without Etrumadenant + Zimberelimab

- Use of the following concomitant therapies while receiving enzalutamide with or without etrumadenant + zimberelimab is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.
- Concurrent experimental or investigational therapy.
- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.

- Co-administration of:
  - Strong CYP2C8 inhibitor (eg, gemfibrozil and clopidogrel). If patients must be co-administered a strong CYP2C8 inhibitor, reduce the enzalutamide dose to 80 mg once daily.
  - Known CYP3A4 (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (eg, phenytoin, warfarin) and CYP2C19 substrates (eg, S-mephenytoin, clopidogrel) with a narrow therapeutic index
  - 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 inhibitors of BCRP and P-gp
  - 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)
  - Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4.
  - Sensitive substrates of BSEP, MATE1 and OCT2.

Use of the following concomitant therapies with caution while receiving etrumadenant:

- Investigators should use caution when administering etrumadenant concomitantly with strong inhibitors or inducers of CYP2C8.

Refer to 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

14.8. Study Assessments and Schedule of Activities

14.8.1. Screening Procedures for Enzalutamide with or without Etrumadenant + Zimberelimab

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving enzalutamide with or without etrumadenant + zimberelimab.

14.8.2. Treatment Procedures for Enzalutamide with or without Etrumadenant + Zimberelimab

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for participants receiving enzalutamide with or without etrumadenant + zimberelimab.

Refer to Table 13 for the schedule of activities during the treatment period for participants receiving enzalutamide with or without etrumadenant + zimberelimab.

Table 13: Schedule of Activities / TREATMENT PERIOD for Enzalutamide with or without Etrumadenant + Zimberelimab

Procedure[h]	Cycle 1[n]					Cycle 2[n]			Cycle 3[n]	Cycle ≥4[n]
	D1[a]	D2	D4	D8 (±1)	D15 (±1)	D1	D2	D8 (±1)	D1	D1
Administrative Procedures										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments										
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X					X			X	X
Vital signs[c]	X	X	X	X		X		X	X	X
Blood pressure[d]	X	X	X	X		X		X	X	X
12-lead ECG[e]	X					X				
ECOG performance status	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]										
Hematology[g]	X	X	X	X		X		X	X	X
Clinical chemistry[g]	X	X	X	X		X		X	X	X
Thyroid tests[g]	X									X[q]
PSA	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]										
PK for etrumadenant [i]	X	X		X		X	X		X	X[o]
PK for zimberelimab[i]	X	X	X	X	X	X			X	X[o]
PK for enzalutamide[i]	X	X		X		X			X	X[o]
Pharmacodynamics[j]	X							X		Cycle 5
Immunogenicity[k]	X					X			X	X[p]
Tumor biopsy[l]								X		

Table 13: Schedule of Activities / TREATMENT PERIOD for Enzalutamide with or without Etrumadenant + Zimberelimab

Procedure[h]	Cycle 1[n]					Cycle 2[n]			Cycle 3[n]	Cycle ≥4[n]
	D1[a]	D2	D4	D8 (±1)	D15 (±1)	D1	D2	D8 (±1)	D1	D1
Efficacy Measurements										
Disease assessment[r]	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.									
Investigational Product Administration										
Etrumadenant administration[m]	X	X	X	X	X	X	X	X	X	X
Zimberelimab administration[m]	X					X			X	X
Enzalutamide[m]	X	X	X	X	X	X	X	X	X	X
Medication diary review	X					X			X	X

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to zimberelimab infusion start), every 20 minutes (± 5 minutes) from the start of the zimberelimab infusion until infusion end, and thereafter as clinically indicated until visit completion. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of zimberelimab infusion, and as clinically indicated thereafter until visit completion. On non-infusion days, collect vital signs prior to dosing with oral study treatment.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion days, for applicable participants, 3 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) approximately 30 minutes (±15 minutes) after administration of etrumadenant and prior to zimberelimab infusion start, and 3) 30 minutes (±15 minutes) after the end of the zimberelimab infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated. For participants randomized to enzalutamide monotherapy, ECGs during the treatment period will be completed only if clinically indicated.

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8. Thyroid tests during study treatment are only applicable to participants that receive etrumadenant + zimberelimab + enzalutamide.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints. PK samples will be collected only from participants that receive etrumadenant + zimberelimab + enzalutamide.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.
[k] Refer to the central laboratory manual for immunogenicity sampling timepoints. Immunogenicity samples will be collected only from participants that receive etrumadenant + zimberelimab + enzalutamide.
[l] On-treatment biopsy may be obtained at Cycle 2 Day 8 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 8 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 8, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.
[m] On visit days when etrumadenant is administered together with enzalutamide and zimberelimab, etrumadenant and enzalutamide may be taken together at least 30 minutes prior to the start of IV infusion of zimberelimab. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.
[n] Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (zimberelimab). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.
[o] Cycles 4, 5, 6, 8, 12 and 16 only.
[p] Cycles 4, 6, 8, 12 and 16 only.
[q] Cycle 4 and every 4 cycles thereafter.
[r] Participants randomized to enzalutamide monotherapy may be permitted to crossover to etrumadenant + zimberelimab + docetaxel or etrumadenant + zimberelimab; the choice of crossover therapy is at the investigator's discretion in consultation with the sponsor. Participants who are deemed eligible for crossover will initiate a second study treatment period beginning with Cycle 1 Day 1 in accordance with the schedule of activities in Table 22 (etrumadenant + zimberelimab + docetaxel) or Table 30 (etrumadenant + zimberelimab). Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1. Refer to Section 14.8.3.

14.8.3. Crossover Procedures following Enzalutamide Monotherapy

Following documentation of confirmed progressive disease as defined in Section 7.4.1, participants randomized to enzalutamide monotherapy may be permitted to crossover to etrumadenant + zimberelimab + docetaxel (Section 15) or etrumadenant + zimberelimab (Section 16). The choice of crossover therapy is at the investigator's discretion in consultation with the sponsor. Upon enzalutamide discontinuation, participants should perform an EOT visit (ie, EOT-1) in accordance with Table 3. Following EOT-1, participants must undergo screening procedures (ie, Screening-2) in accordance with Table 2 within 28 days of the first planned dose of crossover therapy. Eligibility to receive crossover therapy requires the participant to satisfy inclusion/exclusion criteria for the applicable crossover treatment:

- Etrumadenant + zimberelimab + docetaxel: Section 5 and Section 15.4
- Etrumadenant + zimberelimab: Section 5 and Section 16.4

Assessments performed at EOT-1 may be used for Screening-2 provided they are performed within the allowable window. However, all potential crossover participants must undergo radiographic disease evaluation at Screening-2 to reset baseline tumor burden (Table 2). All measurable and evaluable lesions identified at Screening-2 should be reassessed at each postbaseline tumor evaluation as described in Section 7.3.12.

Participants who are deemed eligible for crossover based on Screening-2 results will initiate a second study treatment period beginning with Cycle 1 Day 1 in accordance with the schedule of activities in Table 22 (etrumadenant + zimberelimab + docetaxel) or Table 30 (etrumadenant + zimberelimab). Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

14.9. Dose Modification and Safety Management Guidelines

The safety plan for participants receiving enzalutamide with or without etrumadenant + zimberelimab may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and zimberelimab or other anti-PD-1 antibodies (ie, class effects), respectively. The combination of etrumadenant + zimberelimab + enzalutamide may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and zimberelimab, and the package insert for detailed safety information for enzalutamide.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

14.9.1. Dose Modifications for Enzalutamide with or without Etrumadenant + Zimberelimab

Dose Modifications for Etrumadenant

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outlined in Table 14. 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.

Table 14: Recommended Dose Reductions for Etrumadenant

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant	150 mg	100 mg	75 mg

Dose Modifications for Zimberelimab

There will be no dose modifications for zimberelimab in this study.

Dose Modifications for Enzalutamide

For management of drug-related toxicities, the dose of enzalutamide may be reduced up to 2 times as outlined in Table 15. If further dose reduction below 80 mg is indicated, enzalutamide should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

Table 15: Recommended Dose Reductions for Enzalutamide

	Initial Dose	First Dose Reduction	Second Dose Reduction
Enzalutamide	160 mg	120 mg	80 mg

14.9.2. Study Treatment Interruptions for Enzalutamide with or without Etrumadenant + Zimberelimab

Treatment interruptions of etrumadenant, zimberelimab, and enzalutamide are allowed throughout the study for no more than 42 days. Holding of one 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 treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + zimberelimab + enzalutamide, then all drugs should be held.

If etrumadenant, zimberelimab, enzalutamide or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

14.9.3. Management Guidelines for Adverse Events: Enzalutamide with or without Etrumadenant + Zimberelimab

Guidelines for the management of participants who experience specific AEs are provided below in Table 16. In addition, guidelines for the management of participants who experience dermatologic toxicities associated with zimberelimab, etrumadenant, or enzalutamide are provided in Table 17, Table 18, and Table 19, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue enzalutamide at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.
	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.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	Consider enzalutamide dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue enzalutamide at the same dose level at the investigator's discretion. Monitor LFTs more frequently until return to < 3 × ULN or baseline.
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected nonimmune-mediated transaminase elevations:** Withhold etrumadenant and zimberelimab for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction (Table 14) and resume zimberelimab.[1,2,4] If not, permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] **For suspected immune-mediated transaminase elevations:** Permanently discontinue zimberelimab. Withhold etrumadenant for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant with a 1-level dose reduction.[1,2,4] If not, permanently discontinue etrumadenant and contact medical monitor.[3,5]		Withhold enzalutamide for at least 7 days or until toxicity resolves to Grade 2 or better. Monitor as described for etrumadenant and zimberelimab. If event resolves to Grade 1 or better within 42 days, resume enzalutamide at the same or reduced dose (Table 15).[6,7] If not, permanently discontinue enzalutamide and contact medical monitor.[8] Enzalutamide dose re-escalation is permitted at the investigator's discretion.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action Taken
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and contact medical monitor.[3] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	Permanently discontinue zimberelimab and contact medical monitor.[5] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	**For participants receiving Etrumadenant + zimberelimab + Enzalutamide:** Permanently discontinue enzalutamide and contact medical monitor[8] **For participants receiving Enzalutamide only:** Follow Grade 3 management guidelines
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,5,8] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. Exception: Participants 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue enzalutamide at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[2] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	Consider enzalutamide dose modification as clinically indicated, otherwise continue at the same dose.[7] Institute symptom-directed supportive care according to institutional guidelines.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue enzalutamide at the same dose level.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action Taken
	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 and withhold etrumadenant for up to 42 days after event onset. **1st occurrence:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant at the same dose level.[1] **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.		Continue enzalutamide at the same dose level.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.		Withhold enzalutamide for at least 7 days or until toxicity resolves to Grade 2 or better. Monitor as described for etrumadenant. If event resolves to Grade 1 or better within 42 days, resume enzalutamide at the same or reduced dose (Table 15).[6,7] If not, permanently discontinue enzalutamide and contact medical monitor.[8] Enzalutamide dose re-escalation is permitted at the investigator's discretion.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action Taken
	Grade 4	Permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] Refer participant 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.		**For participants receiving Etrumadenant + Zimberelimab + Enzalutamide:** Permanently discontinue enzalutamide and contact medical monitor[8] **For participants receiving Enzalutamide only:** Follow Grade 3 management guidelines
Seizure	**Any Grade**	Consider etrumadenant dose modification as clinically indicated2, otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Permanently discontinue enzalutamide
Hypersensitivity related to Enzalutamide	**Any Grade**	Consider etrumadenant dose modification as clinically indicated[2], otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Permanently discontinue enzalutamide
Posterior reversible encephalopathy syndrome	**Any Grade**	Consider etrumadenant dose modification as clinically indicated[2,] otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Permanently discontinue enzalutamide
Ischemic heart disease	**Any Grade**	Consider etrumadenant dose modification as clinically indicated[2], otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Permanently discontinue enzalutamide
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.	If applicable, continue enzalutamide.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.	If applicable, continue enzalutamide at the investigator's discretion.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action Taken
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]	If applicable, withhold enzalutamide for up to 42 days after event onset.[6] If event improves and medical monitor agrees that enzalutamide should be continued, resume at the same or reduced dose (Table 15);[7] otherwise, permanently discontinue enzalutamide.[8]
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	If applicable, continue enzalutamide.
	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	If applicable, continue enzalutamide at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]	If applicable, withhold enzalutamide for up to 42 days after event onset.[6] If event improves and medical monitor agrees that enzalutamide should be continued, resume at the same or reduced dose (Table 15);[7] otherwise, permanently discontinue enzalutamide.[8]
Enzalutamide-related toxicities	**Grade 1-2**	Continue etrumadenant at the same dose level.	Continue zimberelimab.	Continue enzalutamide at the same dose level.

Table 16: Guidelines for Management of Participants who Experience Adverse Events While Receiving Enzalutamide with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Enzalutamide Action Taken
not described above	**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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Withhold enzalutamide for at least 7 days or until toxicity resolves to Grade 2 or better. Initiate symptomatic treatment. If event resolves to Grade 1 or better within 42 days, resume enzalutamide at the same or reduced dose (Table 15).[6,7] If not, permanently discontinue enzalutamide and contact medical monitor.[8] Enzalutamide dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]	**For participants receiving Etrumadenant + Zimberelimab + Enzalutamide:** Permanently discontinue enzalutamide and contact medical monitor[8] **For participants receiving Enzalutamide only:** Follow Grade 3 management guidelines

[1] Etrumadenant may be withheld for a longer period (ie, > 42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.

[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or ≤ Grade 1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[4] Zimberelimab may be withheld for a longer period (ie, > 42 days after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[5] Resumption of zimberelimab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with zimberelimab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[6] Enzalutamide may be withheld for a longer period (ie, > 42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[7] The dose of enzalutamide can be reduced from 160 mg to 120 mg (ie, 1 dose level) and then from 120 mg to 80 mg for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a participant receiving the 80-mg dose of enzalutamide, then that participant should discontinue enzalutamide.

[8] Resumption of enzalutamide may be considered in participants who are deriving benefit and who have fully recovered (to baseline or ≤ Grade 1) from the toxicity. Participants can be re-challenged with enzalutamide only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 17: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab	Topical emollient Oral antihistamine for pruitus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab with intensified antipruritic therapy Consider holding in select cases	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Consider resuming after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume

Table 17: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 18: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 18: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (e.g. pruritis, burning, tightness)
[b] Macules/papules covering 10-30% BSA with or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental ADLs
[c] Macules/papules covering >30% BSA with or without symptoms (e.g. pruritis, burning, tightness) limiting ADLs
[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 19: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Enzalutamide

Event	Severity	Enzalutamide Action Taken
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis)	**Grade 1**	Continue enzalutamide at the same dose level.
	Grade 2	Continue enzalutamide at the same dose level.
	Grade 3	Withhold enzalutamide for at least 7 days or until toxicity resolves to Grade 1 or better. Institute supportive care measures. If event resolves to Grade 2 or better within 42 days, resume enzalutamide at the same or reduced dose (Table 15).[1,2] If not, permanently discontinue enzalutamide and contact medical monitor.[3] Enzalutamide dose re-escalation is permitted at the investigator's discretion.
	Grade 4	**For participants receiving Etrumadenant + Zimberelimab + Enzalutamide:** Permanently discontinue enzalutamide and contact medical monitor[3] **For participants receiving Enzalutamide only:** Follow Grade 3 management guidelines

[1] Enzalutamide may be withheld for a longer period (ie, > 42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of enzalutamide can be reduced from 160 mg to 120 mg (ie, 1 dose level) and then from 120 mg to 80 mg for management of drug-related toxicities. Additional dose reductions are not allowed. If a dose reduction is indicated for a participant receiving the 80-mg dose of enzalutamide, then that participant should discontinue enzalutamide.

[3] Resumption of enzalutamide may be considered in participants who are deriving benefit and who have fully recovered (to baseline or ≤ Grade 1) from the toxicity. Participants can be re-challenged with enzalutamide only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

14.10. Collection of Pregnancy Information

14.10.1. Collection of Pregnancy Information for Enzalutamide with or without Etrumadenant + Zimberelimab

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of enzalutamide, whichever is longer.

15. ETRUMADENANT + ZIMBERELIMAB + DOCETAXEL TREATMENT ARM

15.1. Introduction

This treatment arm combines 2 investigational agents in development by Arcus Biosciences: etrumadenant and zimberelimab, with docetaxel.

15.1.1. Background for Etrumadenant + Zimberelimab + Docetaxel

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

Zimberelimab, a fully human immunoglobulin G4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated PK, pharmacodynamics including receptor occupancy, efficacy, and safety that is consistent with currently approved anti-PD-1 therapies. Arcus in-licensed zimberelimab to enable development of precision combination regimens with full line-of-sight to the commercialization of innovative therapies for all patients who may benefit. The most advanced study with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic NSCLC, evaluating zimberelimab in combination with 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.

Docetaxel is a microtubule inhibitor approved by the US FDA and other global regulatory agencies for the treatment of mCRPC in combination with prednisone.

Refer to the etrumadenant investigator brochure, the zimberelimab investigator brochure, and the package insert for docetaxel for complete discussion of the agents and additional information on preclinical and clinical studies.

15.1.2. Rationale for Combining Etrumadenant + Zimberelimab + Docetaxel

The opportunity to combine etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 study in participants with advanced solid tumors (NCT03846310). Emerging

data show that etrumadenant administered together with zimberelimab was well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months (Powderly et al., 2019), in heavily pretreated participants across multiple disease indications.

Active cohorts in mCRPC and advanced clear cell RCC are currently under study. This investigational doublet regimen is also the base for other anticancer combinations with chemotherapy in current and planned studies in NSCLC, colorectal cancer, and head and neck cancers, as well the backbone for numerous cohorts in this platform trial in mCRPC. The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents.

Recent clinical data from KEYNOTE-199 has shown minimal response activity but potential survival advantage for NHA and taxane experienced mCRPC participants treated with the anti-PD-1 antibody pembrolizumab (Antonarakis et al., 2019). This, coupled with the early activity signal seen when AZD4635, an adenosine $A_{2a}R$ antagonist, was combined with the anti-PD-L1 antibody durvalumab in late-line mCRPC (Bendell et al., 2019), help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and supports the evaluation of etrumadenant and zimberelimab together with AB680 in this study. Specifically, mCPRC participants treated with AZD4635 with or without durvalumab showed radiographic and PSA responses. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

The antitumor effects of cytotoxic chemotherapy have historically been associated with direct tumor cell killing. However, data from recent studies suggests that the antitumor mechanism of action for these modalities may also involve immunomodulatory effects through direct action on tumor and/or immune cells (Garnett et al., 2004; Garnett et al., 2008). For example, docetaxel was previously shown to modulate CD4+, CD8+, CD19+, natural killer, and T-regulatory cells populations in nontumor-bearing mice in addition to enhancing interferon-γ production by CD8+ T cells (Garnett et al., 2008). In cancer cell lines, Hodge et al. demonstrated that treatment with docetaxel functionally enhanced antigen-specific cytotoxic T-lymphocyte (CTL)-mediated cell killing and that this immunomodulatory effect was observed in both docetaxel-sensitive and resistant tumor cells (Hodge et al., 2013). These observations are distinct and complementary to those of immunogenic cell death and provide scientific rationale supporting the use of chemotherapy in combination with immunotherapy. Indeed, in prostate cancer clinical trials, docetaxel has shown evidence of clinical benefit in the metastatic, castrate-resistant setting when combined with PSA-directed vaccine therapy (Arlen et al., 2006), sipuleucel-T (Petrylak, 2006), and, more recently, pembrolizumab (Hansen et al., 2018; Massard et al., 2019).

Despite these treatment advances, clinical benefit was not observed in most patients and additional experimental therapeutic approaches for late-line patients are needed. Because adenosine is highly immunosuppressive, docetaxel together with immunotherapy may be less effective in adenosine-rich tumors such as prostate cancer. Therefore, the addition of an adenosine receptor antagonist to combination chemo/immunotherapy may result in enhanced antitumor activity. To test this hypothesis, the efficacy and safety of etrumadenant together with zimberelimab and docetaxel will be evaluated in this treatment arm.

15.1.3. Risk/Benefit Assessment for Etrumadenant + Zimberelimab + Docetaxel

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

Zimberelimab is currently being evaluated in for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function after 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 and every 3 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. However, the risks associated with this drug class given experience with the approved anti-PD-1 agents, nivolumab (Opdivo Package Insert, 2019) and pembrolizumab (Keytruda Package Insert, 2020), are appropriate for zimberelimab.

The combination of etrumadenant and zimberelimab has been evaluated in early-phase studies across multiple tumor types illustrating both tumor response and disease stabilization. Current and future evaluation of this combination with additional chemotherapy or investigational agents added onto this backbone are ongoing to assess efficacy in specific tumor types. This 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.

Docetaxel is a US Food and Drug Administration-approved medication that is used in accordance with its label in this study (Taxotere Package Insert).

In summary, the safety and early activity of the combination of etrumadenant and zimberelimab in cancer patients supports its evaluation in this study as part of triplet regimen with docetaxel. Considering the activity signals seen with similar mechanistic combinatory regimens in mCRPC and other PD-1 resistant tumor types with etrumadenant and zimberelimab, it is hypothesized that treatment with etrumadenant, zimberelimab, and docetaxel has promising therapeutic potential in mCRPC.

15.2. Objectives and Endpoints

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + zimberelimab + docetaxel treatment arm are described in Section 3 with the exception of those that are treatment arm-specific and described below.

15.2.1. Stage 1 (Etrumadenant + Zimberelimab + Docetaxel)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and zimberelimab when administered as part of a combination regimen with docetaxel in Stage 1	Serum/plasma concentration and PK parameters for etrumadenant and zimberelimab when administered as part of a combination regimen with docetaxel in Stage 1

15.2.2. Stage 2 (Etrumadenant + Zimberelimab + Docetaxel)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and zimberelimab when administered as part of a combination regimen with docetaxel in Stage 2	Serum/plasma concentration and PK parameters for etrumadenant and zimberelimab when administered as part of a combination regimen with docetaxel in Stage 2
Exploratory Objectives	
To evaluate the clinical activity of etrumadenant + zimberelimab in participants who crossed over from treatment with docetaxel monotherapy (may include PSA and/or radiographic response rate according to PCWG3, PFS, and OS depending on available data)	

15.3. Investigational Plan

The etrumadenant + zimberelimab + docetaxel treatment arm will be conducted as described in Section 4.

In Stage 2, crossover to experimental treatment with etrumadenant + zimberelimab may be permitted for participants who progress on docetaxel monotherapy at the investigator's discretion in consultation with the sponsor. Participants who crossover will initiate a second study treatment period (ie, Cycle 1 Day 1) at the time of first crossover dose, following the Schedules

of Activities in Section 16.8.2, and will remain on study until one of the criteria in Section 7.4.1 are met. Thereafter, crossover participants will enter the follow-up period (Table 3).

15.4. Eligibility

15.4.1. Inclusion Criteria for Docetaxel with or without Etrumadenant + Zimberelimab

All participants receiving docetaxel with or without etrumadenant + zimberelimab must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving docetaxel with or without etrumadenant + zimberelimab must satisfy the following:

B.1 Disease progression after prior NHA therapy (first- or second-generation nonsteroidal antiandrogens, abiraterone)

B.2 Treatment with taxane chemotherapy is medically appropriate in the judgment of the investigator

B.3 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of docetaxel, whichever is longer

15.4.2. Exclusion Criteria for Docetaxel with or without Etrumadenant + Zimberelimab

All participants receiving docetaxel with or without etrumadenant + zimberelimab must not meet any of meet the main study exclusion criteria in Section 5.2. Participants are excluded from receiving docetaxel with or without etrumadenant + zimberelimab if any of the following criteria apply:

B.1 Prior treatment with docetaxel, cabazitaxel, or other taxane chemotherapy administered as a single agent or as part of a combination regimen

B.2 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain Barré syndrome, or multiple sclerosis with the following exceptions:

B.2.1 Patients with a history of autoimmune related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

B.2.2 Patients with controlled Type 1 diabetes mellitus who, in the judgment of the investigator, are on a stable insulin regimen are eligible for the study.

B.2.3 Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

Rash must cover < 10% of body surface area.

Disease is well controlled at baseline and requires only low potency topical corticosteroids.

B.2.4 There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency corticosteroids within the previous 12 months

B.3 History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins

B.4 History of severe hypersensitivity reactions to drugs formulated with polysorbate 80

B.5 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

B.5.1 Treatment with known 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

B.5.2 Treatment with known 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.5.3 Treatment with known 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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment

Refer to 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

15.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant and zimberelimab may be found in the respective investigator brochure. Refer to the docetaxel package insert for a formulation description.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

15.5.1. Dosage and Administration: Etrumadenant, Zimberelimab, Docetaxel

All participants in Stage 1 and participants randomized to the etrumadenant + zimberelimab + docetaxel treatment arm in Stage 2 will receive:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (21-day cycle)
- **Zimberelimab:** 360 mg, IV, every 3 weeks (Day 1 of a 21-day cycle)
- **Docetaxel:** 75 mg/m^2, IV, every 3 weeks (Day 1 of a 21-day cycle)

Table 20: Etrumadenant + Zimberelimab + Docetaxel Administration

Product Name[a]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Capsule	QD	150 mg	Oral	
Zimberelimab	C mg/mL solution	Q3W	360 mg	IV	
Docetaxel[b]	40 mg/mL solution	Q3W	75 mg/m^2	IV	

IV = intravenous; Q3W = every 3 weeks; QD = once daily
[a] Product names are listed in order of administration.
[b] Concurrent prednisone (5 mg, oral, twice daily continuous dosing) should be administered throughout study treatment in accordance with the docetaxel prescribing information.

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of zimberelimab. Docetaxel infusion will follow completion of zimberelimab administration. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

On study visit days when PK samples are collected, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant, zimberelimab, and docetaxel is described in the study pharmacy manual.

Docetaxel

Participants randomized to the docetaxel treatment arm in Stage 2 will receive:

- **Docetaxel:** 75 mg/m^2, IV, every 3 weeks (Day 1 of a 21-day cycle)

Table 21: Docetaxel Administration

Product Name	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Docetaxel[a]	40 mg/mL solution	Q3W	75 mg/m^2	IV	

IV = intravenous; Q3W = every 3 weeks
[a] Concurrent prednisone (5 mg, oral, twice daily continuous dosing) should be administered throughout study treatment in accordance with the docetaxel prescribing information.

Additional information regarding administration of docetaxel is described in the study pharmacy manual.

For all participants receiving docetaxel with or without etrumadenant + zimberelimab, guidelines for dose modification and safety management guidelines are provided in Section 15.8.3.

15.6. Method of Treatment Assignment

During Stage 1, participants will be enrolled into treatment arms based on their prior anticancer treatment history. Investigational product will be assigned according to the treatment arm in which the subject has enrolled. During Stage 2, patients may be randomized in a 1:1 ratio to docetaxel standard of care control therapy using a permuted block method. Participants will be stratified based on the presence of measurable disease at baseline.

In Stage 2, participants who progress on docetaxel monotherapy may be permitted to crossover to experimental treatment with etrumadenant + zimberelimab at the investigator's discretion and in consultation with the medical monitor. As this is an open-label trial, documented evidence of disease progression as defined by PCWG3 is required prior to permitting a randomized participant in the docetaxel arm to be deemed eligible for crossover.

15.7. Concomitant Medications

15.7.1. Permitted Therapy for Docetaxel with or without Etrumadenant + Zimberelimab

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 15.7.2.

- For applicable participants, continued ADT will be allowed for the duration of the study.

- Participants receiving docetaxel should receive continuous oral prednisone (5 mg, twice daily continuous dosing) throughout study treatment in accordance with the label instructions.
- Growth factor support for the management of treatment-emergent hematological toxicity as recommended according to the National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer guidelines.
- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including INR, according to institutional guidelines.
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

15.7.2. Prohibited Therapy for Docetaxel with or without Etrumadenant + Zimberelimab

Use of the following concomitant therapies while receiving docetaxel with or without etrumadenant + zimberelimab is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.
- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.
- Co-administration of:
  - 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 inhibitors of BCRP and P-gp
  - 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)

- Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4.
- Sensitive substrates of BSEP, MATE1 and OCT2.

Use of the following concomitant therapies with caution while receiving etrumadenant:

- Investigators should use caution when administering etrumadenant concomitantly with strong inhibitors or inducers of CYP2C8.

Refer to 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.

15.8. Schedule of Activities

15.8.1. Screening Procedures for Docetaxel with or without Etrumadenant + Zimberelimab

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving docetaxel with or without etrumadenant + zimberelimab.

15.8.2. Treatment Procedures for Docetaxel with or without Etrumadenant+ Zimberelimab

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for participants receiving docetaxel with or without etrumadenant + zimberelimab.

Refer to Table 22 for the schedule of activities during the Treatment period for participants receiving docetaxel with or without etrumadenant + zimberelimab.

Table 22: Schedule of Activities / TREATMENT PERIOD for Docetaxel with or without Etrumadenant + Zimberelimab

	Cycle 1[n]					Cycle 2[n]			Cycle 3[n]	Cycle ≥4[n]
Procedure[h]	**D1[a]**	**D2**	**D4**	**D8 (±1)**	**D15 (±1)[s]**	**D1**	**D2[s]**	**D8 (±1)**	**D1**	**D1**
Administrative Procedures										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments										
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X					X			X	X
Vital signs[c]	X	X	X	X		X		X	X	X
Blood pressure[d]	X	X	X	X		X		X	X	X
12-lead ECG[e]	X					X				
ECOG performance status	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]										
Hematology[g]	X	X	X	X		X		X	X	X
Clinical chemistry[g]	X	X	X	X		X		X	X	X
Thyroid tests[g]	X									X[q]
PSA	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]										
PK for etrumadenant [i]	X	X		X		X	X		X	Xo
PK for zimberelimab[i]	X	X	X	X	X	X			X	Xo
Pharmacodynamics[j]	X							X		Cycle 5
Immunogenicity[k]	X					X			X	X[p]
Tumor biopsy[l]								X		
Efficacy Measurements										
Disease assessment[r]	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.									
Investigational Product Administration										
Etrumadenant administration[m]	X	X	X	X	X	X	X	X	X	X
Zimberelimab administration[m]	X					X			X	X
Docetaxel[m]	X					X			X	X
Medication diary review	X					X			X	X

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to zimberelimab infusion start, if applicable), every 20 minutes (± 5 minutes) from the start of the zimberelimab and/or docetaxel infusions until infusion end, and thereafter as clinically indicated until visit completion. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of study treatment infusion (zimberelimab and/or docetaxel), and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with etrumadenant.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion days for applicable participants, 4 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to zimberelimab infusion start, 3) 30 minutes (±15 minutes) after the end of the zimberelimab infusion, and 4) 30 minutes (±15 minutes) after the end of the docetaxel infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated. For participants randomized to docetaxel monotherapy, ECGs during the treatment period will be completed only if clinically indicated.

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8. Thyroid tests during study treatment are only applicable to participants who receive etrumadenant + zimberelimab + docetaxel.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints. PK samples will be collected only from participants who receive etrumadenant + zimberelimab + docetaxel. Based on emerging data, samples collected for etrumadenant PK evaluation may also be analyzed for docetaxel PK assessment.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[k] Refer to the central laboratory manual for immunogenicity sampling timepoints. Immunogenicity samples will be collected only from participants who receive etrumadenant + zimberelimab + docetaxel.

[l] On-treatment biopsy may be obtained at Cycle 2 Day 8 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 8 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 8, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.

[m] On visit days when etrumadenant is administered together with docetaxel and zimberelimab, etrumadenant will be given at least 30 minutes prior to the start of IV administration zimberelimab; docetaxel infusion will follow zimberelimab. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[n] Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (zimberelimab and/or docetaxel as appropriate). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[o] Cycles 4, 5, 6, 8, 12 and 16 only.

[p] Cycles 4, 6, 8, 12 and 16 only.

[q] Cycle 4 and every 4 cycles thereafter.

[r] Participants randomized to docetaxel monotherapy may be permitted to crossover to receive etrumadenant + zimberelimab at the investigator's discretion in consultation with the sponsor. Participants who are deemed eligible for crossover will initiate a second study treatment period beginning with Cycle 1 Day 1 in

accordance with the schedule of activities in Table 30. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[s] For Docetaxel monotherapy participants this visit may be conducted remotely/via phone and documented per local practice.

15.8.3. Crossover Procedures Following Docetaxel Monotherapy

Following documentation of confirmed progressive disease as defined in Section 7.4.1, participants randomized to docetaxel monotherapy may be permitted to crossover to etrumadenant + zimberelimab (Section 16). Upon docetaxel discontinuation, participants should perform an EOT visit (ie, EOT-1) in accordance with Table 3. Following EOT-1, participants must undergo screening procedures (ie, Screening-2) in accordance with Table 2 within 28 days of the first planned dose of crossover therapy. Eligibility to receive crossover therapy requires the participant to satisfy inclusion/exclusion criteria for etrumadenant + zimberelimab (Section 5 and Section 16.4).

Assessments performed at EOT-1 may be used for Screening-2 provided they are performed within the allowable window. However, all potential crossover participants must undergo radiographic disease evaluation at Screening-2 to reset baseline tumor burden (Table 2). All measurable and evaluable lesions identified at Screening-2 should be reassessed at each postbaseline tumor evaluation as described in Section 7.3.12.

Participants who are deemed eligible for crossover based on Screening-2 results will initiate a second study treatment period beginning with Cycle 1 Day 1 in accordance with the schedule of activities in Table 30 (etrumadenant+ zimberelimab).

15.9. Dose Modification and Safety Management Guidelines

The safety plan for participants receiving docetaxel with or without etrumadenant + zimberelimab may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and zimberelimab or other anti-PD-1 antibodies (ie, class effects), respectively. The combination of etrumadenant + zimberelimab + docetaxel may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and zimberelimab, and the package insert for detailed safety information for docetaxel.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

15.9.1. Dose Modifications for Docetaxel with or without Etrumadenant + Zimberelimab

Dose Modifications for Etrumadenant

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outlined in Table 23. 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.

Table 23: Recommended Dose Reductions for Etrumadenant

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant	150 mg	100 mg	75 mg

Dose Modifications for Zimberelimab

There will be no dose modifications for zimberelimab in this study.

Dose Modifications for Docetaxel

The following treatment delay and dose modification guidelines are derived from the prescribing information for docetaxel. The package insert should be referenced for additional information.

Docetaxel should be administered only when the following criteria are met:

- Absolute neutrophil count ≥1500 cells/mm^3
- Bilirubin < ULN
- ALT and/or AST should be less than 1.5 × ULN if concomitant ALP is > 2.5 × ULN

If the participant does not meet these criteria by the next scheduled infusion, docetaxel treatment should be delayed until these criteria are met.

For management of drug-related toxicities, the dose of docetaxel may be reduced as outlined in Table 24. If further dose reduction below 60 mg/m^2 is indicated, docetaxel should be discontinued.

Table 24: Recommended Dose Reductions for Docetaxel

	Initial Dose	Dose Reduction
Docetaxel	75 mg/m^2	60 mg/m^2
	60 mg/m^2	Not applicable

15.9.2. Study Treatment Interruptions for Docetaxel with or without Etrumadenant + Zimberelimab

Treatment interruptions of etrumadenant, zimberelimab, and docetaxel are allowed throughout the study for no more than 42 days. Holding of one 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 treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + zimberelimab + docetaxel, then all drugs should be held.

If etrumadenant, zimberelimab, docetaxel or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

15.9.3. Management Guidelines for Adverse Events: Docetaxel With or Without Etrumadenant + Zimberelimab

Guidelines for the management of participants who experience specific AEs are provided below in Table 25. Guidelines for the management of dermatologic toxicity associated with zimberelimab, etrumadenant, or docetaxel are provided in Table 26, Table 27, and Table 28, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue docetaxel at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.
	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.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	Consider docetaxel dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue docetaxel at the same dose level at the investigator's discretion. Monitor LFTs more frequently until return to < 3 × ULN or baseline.
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected <u>non</u>immune-mediated transaminase elevations:** Withhold etrumadenant and zimberelimab for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction (Table 23) and resume zimberelimab.[1,2,4] If not, permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] **For suspected immune-mediated transaminase elevations:** Permanently discontinue zimberelimab. Withhold etrumadenant for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant with a 1-level dose reduction.[1,2,4] If not, permanently discontinue etrumadenant and contact medical monitor.[3,5]		Withhold docetaxel. Monitor as described for etrumadenant and zimberelimab. If event resolves to Grade 1 or better within 42 days, resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[7]

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action Taken
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and contact medical monitor.[3] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	Permanently discontinue zimberelimab and contact medical monitor.[5] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	**For participants receiving Etrumadenant + Zimberelimab + Docetaxel:** Permanently discontinue docetaxel and contact medical monitor[7] **For participants receiving Docetaxel only:** Follow Grade 3 management guidelines
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,5,7] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. Exception: Participants 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue docetaxel at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[2] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	Consider docetaxel dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue docetaxel at the same dose level.
	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		Continue docetaxel at the same dose level.

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action Taken
		corticosteroids equivalent to 1-2 mg/kg/day oral prednisone and withhold etrumadenant for up to 42 days after event onset. **1st occurrence:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant at the same dose level.[1] **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.		
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.		Withhold docetaxel for up to 42 days after event onset. Monitor as described for etrumadenant. If event resolves to Grade 1 or better within 42 days[6], resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[7]
	Grade 4	Permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] Refer participant 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.		**For participants receiving Etrumadenant + Zimberelimab + Docetaxel:** Permanently discontinue docetaxel and contact medical monitor[7] **For participants receiving Docetaxel only:** Follow Grade 3 management guidelines

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action Taken
Febrile neutropenia	**Any Grade**	Consider etrumadenant dose modification as clinically indicated[2], otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Withhold docetaxel and institute supportive care measures. If fever resolves and neutrophils recover to ≥ 1500 cells/mm^3 within 42 days[6], resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[7] If the participant continues to experience febrile neutropenia at 60 mg/m^2, permanently discontinue docetaxel.
Neutrophils <500 cells/mm^3 for >1 week	**--**	Consider etrumadenant dose modification as clinically indicated[2], otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Withhold docetaxel and institute supportive care measures. If neutrophils recover to ≥ 1500 cells/mm^3 within 42 days,[6] resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[7] If the participant continues to experience prolonged severe neutropenia, permanently discontinue docetaxel.
Peripheral neuropathy	**Grade 3-4**	Consider etrumadenant dose modification as clinically indicated,[2] otherwise continue at the same dose. Continue zimberelimab at the investigator's discretion. Institute symptom-directed supportive care according to institutional guidelines.		Permanently discontinue docetaxel.
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.	If applicable, continue docetaxel.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.	If applicable, continue docetaxel at the investigator's discretion.

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action Taken
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]	If applicable, withhold docetaxel for up to 42 days after event onset.[6] If event improves and medical monitor agrees that docetaxel should be continued, resume at the same or reduced dose (Table 24); otherwise, permanently discontinue docetaxel.[7]
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	If applicable, continue docetaxel.
	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	If applicable, continue docetaxel at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]	If applicable, withhold docetaxel for up to 42 days after event onset.[6] If event improves and medical monitor agrees that docetaxel should be continued, resume at the same or reduced dose (Table 24); otherwise, permanently discontinue docetaxel.[7]

Table 25: Guidelines for Management of Participants who Experience Adverse Events While Receiving Docetaxel with or without Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	Docetaxel Action Taken
Docetaxel-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Continue zimberelimab.	Continue docetaxel at the same dose level.
	Grade 3 (except alopecia)	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Withhold docetaxel. Initiate symptomatic treatment. If event resolves to Grade 1 or better within 42 days[6], resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[7] If the participant continues to experience recurrent and clinically significant symptoms at 60 mg/m^2, permanently discontinue docetaxel.
	Grade 4 (except alopecia)	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]	**For participants receiving Etrumadenant + Zimberelimab + Docetaxel:** Permanently discontinue docetaxel and contact medical monitor[7] **For participants receiving Docetaxel only:** Follow Grade 3 management guidelines

[1] Etrumadenant may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.

[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[4] Zimberelimab may be withheld for a longer period (ie, > 42 days after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[5] Resumption of zimberelimab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with zimberelimab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[6] Docetaxel may be withheld for a longer period (ie, > 42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[7] Resumption of docetaxel may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with docetaxel only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 26: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab	Topical emollient Oral antihistamine for pruitus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab with intensified antipruritic therapy Consider holding in select cases	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold zimberelimab	Treatment with high potency topical steroids to affected areas ▪ Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Consider resuming after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume

Table 26: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 27: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 27: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Table 27: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (e.g. pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (e.g. pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 28: Guidelines for Management of Participants who Experience Dermatologic Toxicity While Receiving Docetaxel

Event	Severity	Docetaxel Action Taken
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis)	**Grade 1**	Continue docetaxel at the same dose level.
	Grade 2	Continue docetaxel at the same dose level.
	Grade 3	Withhold docetaxel and institute supportive care measures. If event resolves to Grade 1 or better within 42 days[1], resume docetaxel at 60 mg/m^2. If not, permanently discontinue docetaxel and contact medical monitor.[2] If the participant continues to experience severe or cumulative cutaneous reactions at 60 mg/m^2, permanently discontinue docetaxel.
	Grade 4	**For participants receiving Etrumadenant + Zimberelimab + Docetaxel:** Permanently discontinue docetaxel and contact medical monitor[2] **For participants receiving Docetaxel only:** Follow Grade 3 management guidelines

[1] Docetaxel may be withheld for a longer period (ie, > 42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] Resumption of docetaxel may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with docetaxel only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

15.10. Collection of Pregnancy Information

15.10.1. Collection of Pregnancy Information for Docetaxel with or without Etrumadenant + Zimberelimab

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of docetaxel, whichever is longer.

16. ETRUMADENANT + ZIMBERELIMAB TREATMENT ARM

16.1. Introduction

This treatment arm combines 2 investigational agents in development by Arcus Biosciences: etrumadenant and zimberelimab.

16.1.1. Background for Etrumadenant + Zimberelimab

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

Zimberelimab, a fully human immunoglobulin G4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated PK, pharmacodynamics including receptor occupancy, efficacy, and safety that is consistent with currently approved anti-PD-1 therapies. Arcus in-licensed zimberelimab to enable development of precision combination regimens with full line-of-sight to the commercialization of innovative therapies for all patients who may benefit. The most advanced study with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic NSCLC, evaluating zimberelimab in combination with 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.

Refer to the etrumadenant investigator brochure and the zimberelimab investigator brochure for complete discussion of the agents and additional information on preclinical and clinical studies.

16.1.2. Rationale for Combining Etrumadenant + Zimberelimab

The opportunity to combine etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 study in participants with advanced solid tumors (NCT03846310). Emerging data show that etrumadenant administered together with zimberelimab was well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months (Powderly et al., 2019), in heavily pretreated participants across multiple disease indications.

Active cohorts in mCRPC and advanced clear cell RCC are currently under study. This investigational doublet regimen is also the base for other anticancer combinations with chemotherapy in current and planned studies in NSCLC, colorectal cancer, and head and neck cancers, as well the backbone for numerous cohorts in this platform trial in mCRPC. The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents.

Recent clinical data from KEYNOTE-199 has shown minimal response activity but potential survival advantage for NHA and taxane experienced mCRPC participants treated with the anti-PD-1 antibody pembrolizumab (Antonarakis et al., 2019). This, coupled with the early activity signal seen when AZD4635, an adenosine $A_{2a}R$ antagonist, was combined with the anti-PD-L1 antibody durvalumab in late-line mCRPC (Bendell et al., 2019), help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and supports the evaluation of etrumadenant and zimberelimab in this study. Specifically, mCPRC participants treated with AZD4635 with or without durvalumab showed radiographic and PSA responses. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

Standard of care treatment options for mCRPC that has progressed following NHA therapy and docetaxel (ie, third and subsequent lines) include an NHA not previously administered, chemotherapy (either cabazitaxel or docetaxel re-challenge), Radium-223 (limited to treatment of symptomatic bone metastases in the absence of visceral disease), pembrolizumab (limited to treatment of microsatellite instability-high or deficient mismatch repair disease), an investigational agent, or best supportive care. Novel therapies for late-line mCRPC, most notably tolerable ones that are efficacious for both bony and visceral metastases, are greatly needed, hence the evaluation of etrumadenant and zimberelimab in this platform study.

16.1.3. Risk/Benefit Assessment for Etrumadenant + Zimberelimab

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

Zimberelimab is currently being evaluated in for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function after 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 and every 3 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. However, the risks associated with this drug class given experience with the approved anti-PD-1 agents, nivolumab (Opdivo Package Insert, 2019) and pembrolizumab (Keytruda Package Insert, 2020), are appropriate for zimberelimab.

The combination of etrumadenant and zimberelimab has been evaluated in early-phase studies across multiple tumor types illustrating both tumor response and disease stabilization. Current and future evaluation of this combination with additional chemotherapy or investigational agents added onto this backbone are ongoing to assess efficacy in specific tumor types. This 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.

In summary, the safety and early activity of the combination of etrumadenant and zimberelimab in cancer patients supports its evaluation in this study as a novel investigational doublet regimen. Considering the activity signals seen with similar mechanistic combinatory regimens in mCRPC and other PD-1 resistant tumor types with etrumadenant and zimberelimab, it is hypothesized that treatment with etrumadenant and zimberelimab has promising therapeutic potential in late-line mCRPC.

16.2. Objectives and Endpoints

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + zimberelimab treatment arm are described in Section 3 with the exception of those that are arm-specific and described below.

16.2.1. Stage 1 (Etrumadenant + Zimberelimab)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and zimberelimab when administered as part of a combination regimen in Stage 1	Serum/plasma concentration and PK parameters for etrumadenant and zimberelimab when administered as part of a combination regimen in Stage 1

16.2.2. Stage 2 (Etrumadenant + Zimberelimab)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and zimberelimab when administered as part of a combination regimen in Stage 2	Serum/plasma concentration and PK parameters for etrumadenant and zimberelimab when administered as part of a combination regimen in Stage 2

16.3. Investigational Plan

The etrumadenant + zimberelimab treatment arm will be conducted as described in Section 4.

If clinical activity (> 10% radiographic response rate by PCWG3) is observed in a key subgroup of participants (eg, those with measurable disease at baseline), enrollment from that subgroup may continue up to a total of 40 participants (Stage 1 and Stage 2 combined).

16.4. Eligibility

16.4.1. Inclusion Criteria for Etrumadenant + Zimberelimab

All participants receiving etrumadenant in combination with zimberelimab must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving etrumadenant in combination with zimberelimab must satisfy the following:

C.1 Disease progression after prior NHA treatment (first- or second-generation nonsteroidal antiandrogens, abiraterone) and up to 2 prior lines of taxane chemotherapy, unless the physician and participant consider a taxane-containing regimen to be inappropriate (the latter must be documented in the source documents)

C.2. Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, whichever is longer

16.4.2. Exclusion Criteria for Etrumadenant + Zimberelimab

All participants receiving etrumadenant in combination with zimberelimab must not meet any of the main study exclusion criteria in Section 5.2. Additional exclusion criteria for participants receiving etrumadenant in combination with zimberelimab are:

C.1 Prior treatment with 3 or more lines of taxane chemotherapy administered as a single agent or as part of a combination regimen

C.2 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain Barré syndrome, or multiple sclerosis with the following exceptions:

C.2.1 Patients with a history of autoimmune related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

C.2.2 Patients with controlled Type 1 diabetes mellitus who, in the judgment of the investigator, are on a stable insulin regimen are eligible for the study.

C.2.3 Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

Rash must cover < 10% of body surface area.

Disease is well controlled at baseline and requires only low potency topical corticosteroids.

C.2.4 There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency corticosteroids within the previous 12 months

C.3 History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins

C.4 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

C.4.1 Treatment with known 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

C.4.2 Treatment with known 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

C.4.3 Treatment with known 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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment

Refer to 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

16.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant and zimberelimab may be found in the respective investigator brochure.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

16.5.1. Dosage and Administration: Etrumadenant and Zimberelimab

All participants in Stage 1 and Stage 2 randomized to the etrumadenant+ zimberelimab treatment arm will receive:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (21-day cycle)
- **Zimberelimab:** 360 mg, IV, every 3 weeks (Day 1 of a 21-day cycle)

Table 29: Etrumadenant + Zimberelimab Administration

Product Name[a]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Capsule	QD	150 mg	Oral	
Zimberelimab	C mg/mL solution	Q3W	360 mg	IV	

IV = intravenous; Q3W = every 3 weeks; QD = once daily

[a] Product names are listed in order of administration.

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of zimberelimab. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

On study visit days when PK samples are collected, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will

also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant and zimberelimab is described in the study pharmacy manual.

For all participants receiving etrumadenant in combination with zimberelimab, guidelines for dose modification and safety management guidelines are provided in Section 16.9.

16.6. Method of Treatment Assignment

Beginning in Stage 1 and continuing into Stage 2, participants may be randomized 1:1:1 to 1 of 3 treatment arms:

- Etrumadenant + zimberelimab
- Etrumadenant + zimberelimab + AB680 (Section 17)
- Etrumadenant + AB680 (Section 18)

A permuted block randomization method will be employed with stratification based on the presence of measurable disease at baseline.

16.7. Concomitant Medications

16.7.1. Permitted Therapy for Etrumadenant + Zimberelimab

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 16.7.2.

- For applicable participants, continued ADT will be allowed for the duration of the study.
- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including INR, according to institutional guidelines.
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

16.7.2. Prohibited Therapy for Etrumadenant + Zimberelimab

Use of the following concomitant therapies while receiving etrumadenant in combination with zimberelimab is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.
- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.

- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; acute, low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.
- Co-administration of:
  - 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 inhibitors of BCRP and P-gp
  - 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)
  - Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4
  - Sensitive substrates of BSEP, MATE1 and OCT2

Use of the following concomitant therapies with caution while receiving etrumadenant:

- Investigators should use caution when administering etrumadenant concomitantly with strong inhibitors or inducers of CYP2C8

Refer to 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

16.8. Schedule of Activities

16.8.1. Screening Procedures for Etrumadenant + Zimberelimab

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving etrumadenant in combination with zimberelimab.

16.8.2. Treatment Procedures for Etrumadenant + Zimberelimab

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for participants receiving etrumadenant in combination with zimberelimab.

Refer to Table 30 for the schedule of activities during the treatment period for participants receiving etrumadenant in combination with zimberelimab.

Table 30: Schedule of Activities / TREATMENT PERIOD for Etrumadenant in Combination with Zimberelimab

Procedure[h]	Cycle 1[n]					Cycle 2[n]			Cycle 3[n]	Cycle ≥4[n]
	D1[a]	D2	D4	D8 (±1)	D15 (±1)	D1	D2	D8 (±1)	D1	D1
Administrative Procedures										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments										
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X					X			X	X
Vital signs[c]	X	X	X	X		X		X	X	X
Blood pressure[d]	X	X	X	X		X		X	X	X
12-lead ECG[e]	X					X				
ECOG performance status	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]										
Hematology[g]	X	X	X	X		X		X	X	X
Clinical chemistry[g]	X	X	X	X		X		X	X	X
Thyroid tests[g]	X									X[q]
PSA	X					X			X	X
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]										
PK for etrumadenant [i]	X	X		X		X	X		X	X[o]
PK for zimberelimab[i]	X	X	X	X	X	X			X	X[o]
Pharmacodynamics[j]	X	X		X	X	X		X	X	Cycle 4 & 5
Immunogenicity[k]	X					X			X	X[p]
Tumor biopsy[l]								X		
Efficacy Measurements										
Disease assessment	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.									
Investigational Product Administration										
Etrumadenant administration[m]	X	X	X	X	X	X	X	X	X	X
Zimberelimab administration[m]	X					X			X	X
Medication diary review	X					X			X	X

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to zimberelimab infusion start), every 20 minutes (± 5 minutes) from the start of the zimberelimab infusion until infusion end, and thereafter as clinically indicated until the participant completes all planned study visit assessments. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of the zimberelimab infusion, and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with etrumadenant.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion days for applicable participants, 3 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 (±15 minutes) minutes after administration of etrumadenant and prior to zimberelimab infusion start, and 3) 30 minutes (±15 minutes) after the end of the zimberelimab infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated.

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[k] Refer to the central laboratory manual for immunogenicity sampling timepoints.

[l] On-treatment biopsy may be obtained at Cycle 2 Day 8 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 8 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 8, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.

[m] On visit days when etrumadenant is administered together with zimberelimab, etrumadenant may be taken at least 30 minutes prior to the start of IV infusion of zimberelimab. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[n] Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (zimberelimab). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[o] Cycles 4, 5, 6, 8, 12 and 16 only.

[p] Cycles 4, 6, 8, 12 and 16 only.

[q] Cycle 4 and every 4 cycles thereafter.

16.9. Dose Modification and Safety Management Guidelines

The safety plan for participants in the etrumadenant and zimberelimab treatment arm may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and zimberelimab or other anti-PD-1 antibodies (ie, class effects), respectively. The combination of etrumadenant + zimberelimab may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and zimberelimab.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

16.9.1. Dose Modifications for Etrumadenant + Zimberelimab

Dose Modifications for Etrumadenant

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outlined in Table 31. 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.

Table 31: Recommended Dose Reductions for Etrumadenant

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant	150 mg	100 mg	75 mg

Dose Modifications for Zimberelimab

There will be no dose modifications for zimberelimab in this study

16.9.2. Study Treatment Interruptions for Etrumadenant + Zimberelimab

Treatment interruptions of etrumadenant and zimberelimab are allowed throughout the study for no more than 42 days. Holding of one agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + zimberelimab, then both drugs should be held.

If etrumadenant, zimberelimab, or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

16.9.3. Management Guidelines for Adverse Events: Etrumadenant + Zimberelimab

Guidelines for the management of participants who experience specific AEs are provided below in Table 32. Guidelines for the management of dermatologic toxicity associated with zimberelimab and etrumadenant are provided in Table 33 and Table 34, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 32: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant in Combination with 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected <u>non</u>immune-mediated transaminase elevations:** Withhold etrumadenant and zimberelimab for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction (Table 31) and resume zimberelimab.[1,2,4] If not, permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] **For suspected immune-mediated transaminase elevations:** Permanently discontinue zimberelimab. Withhold etrumadenant for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant with a 1-level dose reduction.[1,2,4] If not, permanently discontinue etrumadenant and contact medical monitor.[3,5]	
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and contact medical monitor.[3] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	Permanently discontinue zimberelimab and contact medical monitor.[5] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,5] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. <u>Exception</u>: Participants 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]

Table 32: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant in Combination with Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[2] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated.[4,5] Refer to the NCCN 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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 42 days, resume etrumadenant at the same dose level.[1] **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.[3,5] Refer participant 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.	

Table 32: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant in Combination with Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken
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 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]

[1] Etrumadenant may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.

[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[4] Zimberelimab may be withheld for a longer period (ie, >42 days after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[5] Resumption of zimberelimab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with zimberelimab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 33: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab	Topical emollient Oral antihistamine for pruitus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab with intensified antipruritic therapy Consider holding in select cases	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold zimberelimab	Treatment with high potency topical steroids to affected areas ▪Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Consider resuming after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4 [c]	Total body skin exam, including mucosa ▪ Assess for history of prior inflammatory dermatologic diseases ▪ Consider biopsy if unusual features	Permanently discontinue zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy ▪Consider inpatient care.	Do not resume

Table 33: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 34: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 34: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (e.g. pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (e.g. pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

16.10. Collection of Pregnancy Information

16.10.1. Collection of Pregnancy Information for Etrumadenant + Zimberelimab

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant or 90 days after the last dose of zimberelimab, whichever is longer.

17. ETRUMADENANT + ZIMBERELIMAB + AB680 TREATMENT ARM

17.1. Introduction

This treatment arm combines 3 investigational agents in development by Arcus Biosciences: etrumadenant, zimberelimab, and AB680.

17.1.1. Background for Etrumadenant + Zimberelimab + AB680

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

Zimberelimab, a fully human immunoglobulin G4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated PK, pharmacodynamics including receptor occupancy, efficacy, and safety that is consistent with currently approved anti-PD-1 therapies. Arcus in-licensed zimberelimab to enable development of precision combination regimens with full line-of-sight to the commercialization of innovative therapies for all patients who may benefit. The most advanced study with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic NSCLC, evaluating zimberelimab in combination with 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.

AB680 is the first clinic-stage small molecule, reversible and high potency inhibitor of the ectonucleotidase CD73. In preclinical studies, AB680 was shown to selectively prevent the generation of adenosine from AMP and reverse the immunosuppressive effects caused by high concentrations of AMP/adenosine, without causing any immune activation effects on its own. These data suggest that treatment with AB680 may be associated with inhibition of adenosine-mediated immunosuppression within the tumor microenvironment. In healthy volunteers, single ascending intravenous doses of AB680 were well tolerated across all dose levels evaluated and exhibited PK supportive of a repeat-dose infusion frequency once every 2 weeks in patient studies. AB680 is currently being evaluated in combination with zimberelimab

and gemcitabine/nab-paclitaxel in a Phase 1 trial for previously untreated metastatic pancreatic cancer.

Refer to the investigator brochures for etrumadenant, zimberelimab, and AB680 for complete discussion of the agents and additional information on preclinical and clinical studies.

17.1.2. Rationale for Combining Etrumadenant + Zimberelimab + AB680

The opportunity to combine etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 study in participants with advanced solid tumors (NCT03846310). Emerging data show that etrumadenant administered together with zimberelimab is well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months (Powderly et al., 2019), in heavily pretreated participants across multiple disease indications.

Active cohorts in mCRPC and advanced clear cell RCC are currently under study. This investigational doublet regimen is also the base for other anticancer combinations with chemotherapy in current and planned studies in NSCLC, colorectal cancer, and head and neck cancers, as well as the backbone for numerous cohorts in this platform trial in mCRPC. The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents. Moreover, the addition of AB680 to an etrumadenant + zimberelimab backbone provides an opportunity to combine 3 agents with nonoverlapping but complementary mechanisms of action for the purpose of maximizing antagonism of adenosine-mediated immunosuppression. This study represents the first clinical investigation of the safety and clinical activity of AB680 administered in combination with etrumadenant + zimberelimab.

Recent clinical data from KEYNOTE-199 has shown minimal response activity but potential survival advantage for NHA and taxane experienced mCRPC participants treated with the anti-PD-1 antibody pembrolizumab (Antonarakis et al., 2019). This, coupled with the early activity signal seen when AZD4635, an adenosine $A_{2a}R$ antagonist, was combined with the anti-PD-L1 antibody durvalumab in late-line mCRPC (Bendell et al., 2019), help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and supports the evaluation of etrumadenant and zimberelimab together with AB680 in this study. Specifically, mCPRC participants treated with AZD4635 with or without durvalumab showed radiographic and PSA responses. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

Standard of care treatment options for mCRPC that has progressed following NHA therapy and docetaxel (ie, third and subsequent lines) include an NHA not previously administered, chemotherapy (either cabazitaxel or docetaxel re-challenge), Radium-223 (limited to treatment of symptomatic bone metastases in the absence of visceral disease), pembrolizumab (limited to treatment of microsatellite instability-high or deficient mismatch repair disease), an investigational agent, or best supportive care. Novel therapies for late-line mCRPC, most notably tolerable ones that are efficacious for both bony and visceral metastases, are greatly needed, hence the evaluation of AB680 together with etrumadenant and zimberelimab in this platform study.

17.1.3. Risk/Benefit Assessment for Etrumadenant + Zimberelimab + AB680

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

Zimberelimab is currently being evaluated for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

Nonclinical data supports its binding to both PD-L1 and PD-L2 and release of the immunosuppressive inhibition of the T-cell effector function after 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 and every 3 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. However, the risks associated with this drug class given experience with the approved anti-PD-1 agents, nivolumab (Opdivo Package Insert, 2019) and pembrolizumab (Keytruda Package Insert, 2020), are appropriate for zimberelimab.

The combination of etrumadenant and zimberelimab has been evaluated in early-phase studies across multiple tumor types illustrating both tumor response and disease stabilization. Current and future evaluation of this combination with additional chemotherapy or investigational agents added onto this backbone are ongoing to assess efficacy in specific tumor types. This 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.

AB680 is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

In vitro, AB680 is a highly selective and effective inhibitor of CD73 activity and adenosine generation. AB680 reproducibly inhibited the generation of adenosine from AMP by inhibition of CD73 activity expressed on human CD4+ and CD8+ T cells, with the half maximal inhibitory concentration (IC50) values of 13 and 6 pM, respectively. AMP-mediated suppression of markers of inflammation, IFN-γ and granzyme B production, was alleviated by greater than 70% with the addition of AB680. That is, addition of AB680 abrogated the immunosuppressive effect of adenosine. In preclinical tumor models, co-administration of 10 mg/kg AB680 with an anti-PD-1 antibody in established B16F10 melanoma syngeneic mouse tumors significantly increased the CD8+ to regulatory T cell ratio compared with that observed with vehicle control. Consistent with the positive increases in tumor-infiltrating effector T cells, AB680 conferred a significant survival advantage in tumor-bearing mice dosed therapeutically (treatment initiated when the average tumor volume reached 50 mm^3) with an anti-PD-1 antibody (median survival of 36 days) compared with either agent alone (median survival of 26 days in the vehicle group; median survival of 28 days in the anti-PD-1 antibody group). The clinical combination including zimberelimab, therefore, is to be evaluated for potentially augmented antitumor activity.

AB680 has been evaluated in a healthy volunteer study for establishment of a starting dose in cancer patients, as well as early evidence of safety and toxicity. Study AB680CSP0001 was a first-in-human, double-blind, randomized, placebo-controlled, single- and repeat-dose study to evaluate the safety, tolerability, PK profile, and potential pharmacodynamic effects of AB680 in healthy volunteers. Preliminary safety data showed that AB680 administered at a single dose up to 25 mg and multiple doses at 8 mg are tolerated with no evidence of a tolerability concern. No early stopping rules were met in studies with healthy volunteers, and dose escalation is ongoing in cancer patients. All treatment-emergent AEs reported in single-dose cohorts (0.1 to 25mg) were mild or moderate in severity with no clear pattern of toxicity. Two out of 64 healthy volunteers did not complete the planned dosing regimen due to AEs; 1 due to an elevated liver function test and 1 due to an anomaly associated with a cardiac event. Both events returned to baseline levels. The clinical study report for AB680CSP0001 is complete and available upon request.

AB680 is currently under evaluation in AB680CSP0002 (NCT04104672), a Phase 1 study to evaluate the safety, tolerability, PK, pharmacodynamic, and clinical activity of escalating doses of AB680 (25 mg up to 125 mg) in combination with zimberelimab, nab-paclitaxel, and gemcitabine in participants with advanced pancreatic cancer. In accordance with the AB680CSP0002 protocol, members from the Sponsor and principal investigators met on December 14, 2020 to review available safety data and supporting PK/PD data from six participants who received AB680 100 mg IV every 2 weeks (Q2W). No dose-limiting toxicities were observed at 100 mg, and adequate target coverage was observed throughout the treatment interval. Based on the totality of available data at 100 mg and lower dose levels, the committee recommended AB680 100 mg IV Q2W as the recommended dose for expansion. A maximum tolerated dose (MTD) for AB680 was not identified in AB680CSP0002. As a result of data from AB680CSP0002, in this study, the dose of AB680 is 100 mg IV Q2W.

For the most up to date clinical data, please refer to the current AB680 IB.

17.2. Objectives and Endpoints

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + zimberelimab + AB680 treatment arm are described in Section 3 with the exception of those that are treatment arm-specific and described below.

17.2.1. Stage 1 (Etrumadenant + Zimberelimab +AB680)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant, zimberelimab, and AB680 when administered as part of a combination regimen in Stage 1	Serum/plasma concentration and PK parameters for etrumadenant, zimberelimab, and AB680 when administered as part of a combination regimen in Stage 1

17.2.2. Stage 2 (Etrumadenant + Zimberelimab + AB680)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant, zimberelimab, and AB680 when administered as part of a combination regimen in Stage 2	Serum/plasma concentration and PK parameters for etrumadenant, zimberelimab, and AB680 when administered as part of a combination regimen in Stage 2

17.3. Investigational Plan

The etrumadenant + zimberelimab + AB680 treatment arm will be conducted as described in Section 4.

If clinical activity (> 10% radiographic response rate by PCWG3) is observed in a key subgroup of participants (eg, those with measurable disease at baseline), enrollment from that subgroup may continue up to a total of 40 participants (Stage 1 and Stage 2 combined).

17.4. Eligibility

17.4.1. Inclusion Criteria for Etrumadenant + Zimberelimab +AB680

All participants receiving AB680 in combination with etrumadenant + zimberelimab must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving AB680 in combination with etrumadenant + zimberelimab must satisfy the following:

D.1 Disease progression after prior NHA treatment (first- or second-generation nonsteroidal antiandrogens, abiraterone) and up to 2 prior lines of taxane chemotherapy, unless the physician and participant consider a taxane-containing regimen to be inappropriate (the latter must be documented in the source documents)

D.2 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of AB680, whichever is longer

17.4.2. Exclusion Criteria for Etrumadenant + Zimberelimab + AB680

All participants receiving AB680 in combination with etrumadenant + zimberelimab must not meet any of the main study exclusion criteria in Section 5.2. Participants are excluded from receiving AB680 in combination with etrumadenant + zimberelimab if any of the following criteria apply:

D.1 Prior treatment with 3 or more lines of taxane chemotherapy administered as a single agent or as part of a combination regimen

D.2 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain Barré syndrome, or multiple sclerosis with the following exceptions:

D.2.1 Patients with a history of autoimmune related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

D.2.2 Patients with controlled Type 1 diabetes mellitus who, in the judgment of the investigator, are on a stable insulin regimen are eligible for the study.

D.2.3 Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

Rash must cover < 10% of body surface area.

Disease is well controlled at baseline and requires only low potency topical corticosteroids.

D.2.4 There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency corticosteroids within the previous 12 months

D.3 History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins

D.4 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

D.4.1 Treatment with known 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.4.2 Treatment with known 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

D.4.3 Treatment with known 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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment

Refer to 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

17.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant, zimberelimab, and AB680 may be found in the respective investigator brochure.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

17.5.1. Dosage and Administration: Etrumadenant, Zimberelimab, AB680

All participants in Stage 1 and Stage 2 randomized to the etrumadenant + zimberelimab + AB680 treatment arm will receive:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (28-day cycle)
- **Zimberelimab:** 240 mg, IV, every 2 weeks (Days 1 and 15 of a 28-day cycle)
- **AB680:** 100 mg IV, Q2W (Days 1 and 15 of a 28-day cycle).

Table 35: Etrumadenant + Zimberelimab + AB680 Administration

Product Name[a]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Capsule	QD	150 mg	Oral	
AB680	Lyophilized powder for injection	Q2W	100 mg	IV	
Zimberelimab	C mg/mL solution	Q2W	240 mg	IV	

IV = intravenous; Q2W = every 2 weeks; QD = once daily
Product names are listed in order of administration.

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of AB680. AB680 should be administered prior to zimberelimab. Zimberelimab should be administered at least 30 minutes after completion of the AB680 infusion. Participants will be administered zimberelimab, AB680, and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

On study visit days when PK samples are collected, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant, zimberelimab, and AB680 is described in the study pharmacy manual.

For all participants receiving AB680 in combination with etrumadenant + zimberelimab, guidelines for dose modification and safety management guidelines are provided in Section 17.9.

17.6. Method of Treatment Assignment

Beginning in Stage 1 and continuing into Stage 2, participants may be randomized 1:1:1 to 1 of 3 treatment arms:

- Etrumadenant + zimberelimab (Section 16)
- Etrumadenant + zimberelimab + AB680
- Etrumadenant + AB680 (Section 18)

A permuted block randomization method will be employed with stratification based on the presence of measurable disease at baseline.

17.7. Concomitant Medications

17.7.1. Permitted Therapy for Etrumadenant + Zimberelimab + AB680

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 17.7.2.

- For applicable participants, continued ADT will be allowed for the duration of the study.
- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including INR, according to institutional guidelines.
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

17.7.2. Prohibited Therapy for Etrumadenant + Zimberelimab + AB680

Use of the following concomitant therapies while receiving etrumadenant in combination with zimberelimab + AB680 is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.
- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; acute, low dose (≤ 10 mg/day prednisone or

equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.

- Co-administration of:
  - 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 inhibitors of BCRP and P-gp
  - 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)
  - Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4.
  - Sensitive substrates of BSEP, MATE1 and OCT2.

Use of the following concomitant therapies with caution while receiving etrumadenant:

- Investigators should use caution when administering etrumadenant concomitantly with strong inhibitors or inducers of CYP2C8.

Refer to 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

17.8. Schedule of Activities

17.8.1. Screening Procedures for Etrumadenant + Zimberelimab + AB680

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving AB680 in combination with etrumadenant + zimberelimab.

17.8.2. Treatment Procedures for Etrumadenant + Zimberelimab + AB680

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for participants receiving AB680 in combination with etrumadenant + zimberelimab.

Refer to Table 36 for the schedule of activities during the treatment period for participants receiving AB680 in combination with etrumadenant + zimberelimab.

Table 36: Schedule of Activities / TREATMENT PERIOD for AB680 in Combination with Etrumadenant + Zimberelimab

Procedure[h]	Cycle 1[n]					Cycle 2[n]					Cycle ≥3[n] (all odd cycles)		Cycle ≥4[n] (all even cycles)	
	D1[a]	D2	D4	D8 (±1)	D15 (±1)	D1	D2	D4	D8 (±1)	D15 (±1)	D1	D15 (±2)	D1	D15 (±2)
Administrative Procedures														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments														
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X				X	X				X	X		X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X				X	X				X				
ECOG performance status	X					X					X		X	
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]														
Hematology[g]	X	X	X	X	X	X			X	X	X	X	X	X
Clinical chemistry[g]	X	X	X	X	X	X			X	X	X	X	X	X
Thyroid tests[g]	X										X			
PSA	X					X					X		X	
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]														
PK for etrumadenant[i]	X	X		X	X	X	X				X		X[o]	
PK for zimberelimab[i]	X	X	X	X	X	X					X		X[o]	
PK for AB680[i]	X	X	X	X	X	X	X	X	X	X	X		X[o]	
Pharmacodynamics[j]	X	X		X	X	X				X	X		Cycle 4	
Immunogenicity[k]	X				X	X					X		X[o]	
Tumor biopsy[l]						X								
Efficacy Measurements														
Disease assessment	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.													
Investigational Product Administration														
Etrumadenant administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Zimberelimab administration[m]	X				X	X				X	X	X	X	X
AB680 administration[m]	X				X	X				X	X	X	X	X
Medication diary review	X					X					X		X	

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to AB680 infusion start), every 20 minutes (± 5 minutes) from the start of the infusion until infusion end (AB680 and zimberelimab infusions), and thereafter as clinically indicated until the participant completes all planned study visit assessments. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of study treatment infusions (AB680 and zimberelimab), and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with oral study treatment.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion Days 1 and 15 for applicable participants, 4 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to AB680 infusion start, 3) at the end of the AB680 infusion and prior to zimberelimab infusion start (±15 minutes), and 4) 30 minutes (±15 minutes) at the end of the zimberelimab infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated.

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[k] Refer to the central laboratory manual for immunogenicity sampling timepoints.

[l] On-treatment biopsy may be obtained at Cycle 2 Day 1 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 1 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 1, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.

[m] On infusion days, etrumadenant will be given at least 30 minutes prior to the start of IV administration of AB680. AB680 should be administered prior to zimberelimab. Zimberelimab should be administered at least 30 minutes after completion of the AB680 infusion. Participants will be administered zimberelimab, AB680, and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[n] Assessments are based on the start of a new 4-week combination treatment cycle. New 4-week cycles of combination treatment will begin on the day IV therapy is administered. In the absence of any dose delays, 1 experimental treatment cycle will be 28 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 28 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[o] Cycles 4, 6, 8, 12, and 16 only.

17.9. Dose Modification and Safety Management Guidelines

The safety plan for participants in the etrumadenant + zimberelimab + AB680 treatment arm may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists, zimberelimab or other anti-PD-1 antibodies (ie, class effects), and AB680. The combination of etrumadenant + zimberelimab + AB680 may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant, zimberelimab, and AB680.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

17.9.1. Dose Modifications for Etrumadenant + Zimberelimab + AB680

Dose Modifications for Etrumadenant

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outlined in Table 37. 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.

Table 37: Recommended Dose Reductions for Etrumadenant

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant	150 mg	100 mg	75 mg

Dose Modifications for Zimberelimab

There will be no dose modifications for zimberelimab in this study.

Dose Modifications for AB680

For management of drug-related toxicities, the dose of AB680 may be reduced up to 2 times as outlined in Table 38. If further dose reduction below the recommended starting dose is indicated, AB680 should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

Table 38: Recommended Dose Reductions for AB680

	Initial Dose[a]	First Dose Reduction	Second Dose Reduction
AB680	100 mg	75 mg	50 mg

[a] As defined in Section 17.5.1.

17.9.2. Study Treatment Interruptions for Etrumadenant + Zimberelimab + AB680

Treatment interruptions of etrumadenant, zimberelimab, and AB680 are allowed throughout the study for no more than 42 days. Holding of one 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 treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + zimberelimab + AB680, then all drugs should be held.

If etrumadenant, zimberelimab, AB680 or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

17.9.3. Management Guidelines for Adverse Events: Etrumadenant + Zimberelimab + AB680

Guidelines for the management of participants who experience specific AEs are provided below in Table 39. Guidelines for the management of dermatologic toxicity associated with zimberelimab, etrumadenant, or AB680 are provided in Table 40, Table 41, and Table 42, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 39: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	AB680 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Institute symptom-directed supportive care according to institutional guidelines. **Grade 2 events:** Consider AB680 infusion interruption as clinically indicated.
	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.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	**Grade 3 events:** Interrupt AB680 infusion and institute symptom-directed supportive care according to institutional guidelines. If event resolves to Grade 1 or better within 42 days, resume AB680 with a 1 dose-level reduction (Table 38).[6,7] If not, permanently discontinue AB680 and contact medical monitor.[8] **Grade 4 events:** Permanently discontinue AB680 and contact medical monitor[8]
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue AB680 at the same dose level at the investigator's discretion. Monitor LFTs more frequently until return to < 3 × ULN or baseline.
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected <u>non</u>immune-mediated transaminase elevations:** Withhold etrumadenant, zimberelimab, and AB680 for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant and AB680, each with a 1-level dose reduction (Table 37 and Table 38 respectively).[1,2,6,7] Resume zimberelimab.[4] If not, permanently discontinue etrumadenant, zimberelimab, and AB680 and contact medical monitor.[3,5,8] **For suspected immune-mediated transaminase elevations:** Permanently discontinue zimberelimab.[5] Withhold etrumadenant and AB680 for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant and AB680, each with a 1-level dose reduction (Table 37 and Table 38 respectively).[1,2,6,7] If not, permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,8]		
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3] For	Permanently discontinue zimberelimab and contact medical monitor.[5] For	Permanently discontinue AB680 and contact medical monitor.[8] For suspected

Table 39: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	AB680 Action to be Taken
	ALT/AST > 20 × ULN	suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	immune-mediated transaminase elevations, follow Grade 3 management guidelines.
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,5,8] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. Exception: Participants 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue AB680 at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[2] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.	Consider AB680 dose modification as clinically indicated, otherwise continue at the same dose.[7] Institute symptom-directed supportive care according to institutional guidelines.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue AB680 at the same dose level. Initiate symptomatic treatment and monitor closely. Endoscopy is recommended if symptoms persist > 7 days.

Table 39: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	AB680 Action to be Taken
	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 42 days, resume etrumadenant at the same dose level.[1] **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation of is permitted at the investigator's discretion.		Consider AB680 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 AB680 was withheld and event resolves to Grade 1 or better within 42 days, resume AB680 at the same dose level.[6] **Recurrent or persistent events:** If AB680 was withheld and event resolves to Grade 1 or better within 42 days, resume AB680 with a 1-level dose reduction.[6,7] If not, permanently discontinue AB680 and contact medical monitor.[8] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.		Withhold AB680 for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.

Table 39: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	AB680 Action to be Taken
	Grade 4	Permanently discontinue etrumadenant, zimberelimab, and AB680 and contact medical monitor.[3,5,8] Refer participant 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.	Consider AB680 dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.	Withhold AB680 for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume AB680 with a 1-level dose reduction.[6,7] If not, permanently discontinue AB680 and contact medical monitor.[8] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]	Permanently discontinue AB680 and contact medical monitor.[8]
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Continue AB680 at the same dose level.

Table 39: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant + Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken	AB680 Action to be Taken
	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]	Consider AB680 dose modification as clinically indicated, otherwise continue at the same dose. Initiate symptomatic treatment. If AB680 was withheld and event resolves to Grade 1 or better within 42 days, resume AB680 with a 1-level dose reduction.[6,7] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]	Permanently discontinue AB680 and contact medical monitor.[8]
AB680-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.	Consider AB680 dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.	Withhold AB680 for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume AB680 with a 1-level dose reduction.[6,7] If not, permanently discontinue AB680 and contact medical monitor.[8] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]	Permanently discontinue AB680 and contact medical monitor.[8]

[1] Etrumadenant may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.
[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.
[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.
[4] Zimberelimab may be withheld for a longer period (ie, >42 days after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.
[5] Resumption of zimberelimab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with zimberelimab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.
[6] AB680 may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.
[7] The dose of AB680 may be reduced up to 2 times from the starting dose level in accordance with Table 38 for management of drug-related toxicities. Additional dose reductions are not allowed. If third dose reduction is indicated, then that participant should discontinue AB680.
[8] Resumption of AB680 may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with AB680 only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 40: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab	Topical emollient Oral antihistamine for pruitus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab with intensified antipruritic therapy Consider holding in select cases	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Consider resuming after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic	Grade 3	Urgent dermatology consultation: if	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until	Do not resume

Table 40: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
epidermal necrolysis (TEN) [d]		unavailable, consider skin biopsy		symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 41: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 41: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (e.g. pruritis, burning, tightness)
[b] Macules/papules covering 10-30% BSA with or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental ADLs
[c] Macules/papules covering >30% BSA with or without symptoms (e.g. pruritis, burning, tightness) limiting ADLs
[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 42: Guidelines for Management of Participants who Experience Dermatologic Toxicity While Receiving AB680

Event	Severity	AB680 Action to be Taken
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis)	**Grade 1**	Continue AB680 at the same dose level. Immediately institute supportive care measures for symptomatic relief.
	Grade 2	Consider AB680 dose modification as clinically indicated; otherwise continue at the same dose. **For suspected AB680-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 AB680 at the same dose or with a 1-level dose reduction (Table 38). AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 3	Withhold AB680 for at least 7 days until toxicity resolves to Grade 1 or better. **For suspected AB680-related events:** Immediately institute supportive measures. If event resolves to Grade 1 or better within 42 days, resume AB680 with a 1-level dose reduction (Table 38).[1,2] If not, permanently discontinue AB680 and contact medical monitor.[3] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue AB680 and contact medical monitor[3]

[1] AB680 may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.
[2] The dose of AB680 may be reduced up to 2 times from the starting dose level in accordance with Table 38 for management of drug-related toxicities. Additional dose reductions are not allowed. If third dose reduction is indicated, then that participant should discontinue AB680.
[3]Resumption of AB680 may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with AB680 only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

17.10. Collection of Pregnancy Information

17.10.1. Collection of Pregnancy Information for Etrumadenant + Zimberelimab + AB680

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, or 90 days after the last dose of AB680, whichever is longer.

18. ETRUMADENANT + AB680 TREATMENT ARM

18.1. Introduction

This treatment arm combines 2 investigational agents in development by Arcus Biosciences: etrumadenant and AB680.

18.1.1. Background for Etrumadenant + AB680

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

AB680 is the first clinic-stage small molecule, reversible and high potency inhibitor of the ectonucleotidase CD73. In preclinical studies, AB680 was shown to selectively prevent the generation of adenosine from AMP and reverse the immunosuppressive effects caused by high concentrations of AMP/adenosine, without causing any immune activation effects on its own. These data suggest that treatment with AB680 may be associated with inhibition of adenosine-mediated immunosuppression within the tumor microenvironment. In healthy volunteers, single ascending intravenous doses of AB680 were well tolerated across all dose levels evaluated and exhibited PK supportive of a repeat-dose infusion frequency once every 2 weeks in patient studies. AB680 is currently being evaluated in combination with zimberelimab and gemcitabine/nab-paclitaxel in a Phase 1 trial for previously untreated metastatic pancreatic cancer.

Refer to the investigator brochures for etrumadenant and AB680 for complete discussion of the agents and additional information on preclinical and clinical studies.

18.1.2. Rationale for Combining Etrumadenant + AB680

The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents. The doublet regimen of etrumadenant administered with AB680 provides an opportunity to combine 2 investigational agents with nonoverlapping but complementary mechanisms of action; this represents a dual-targeted approach to reverse the effects of adenosine-mediated immunosuppression. This study represents the first clinical

investigation of the safety and clinical activity of AB680 administered in combination with etrumadenant.

Recent clinical data showed that treatment of late-line mCRPC patients with AZD4635, an adenosine $A_{2a}R$ antagonist, with or without the anti-PD-L1 antibody durvalumab was associated with radiographic and PSA responses (Bendell et al., 2019). These data help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and support evaluation of etrumadenant + AB680 combination therapy in this study. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

Standard of care treatment options for mCRPC that has progressed following NHA therapy and docetaxel (ie, third and subsequent lines) include an NHA not previously administered, chemotherapy (either cabazitaxel or docetaxel re-challenge), Radium-223 (limited to treatment of symptomatic bone metastases in the absence of visceral disease), pembrolizumab (limited to treatment of microsatellite instability-high or deficient mismatch repair disease), an investigational agent, or best supportive care. Novel therapies for late-line mCRPC, most notably tolerable ones that are efficacious for both bony and visceral metastases, are greatly needed, hence the evaluation of AB680 together with etrumadenant in this platform study.

18.1.3. Risk/Benefit Assessment for Etrumadenant + AB680

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

AB680 is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

In vitro, AB680 is a highly selective and effective inhibitor of CD73 activity and adenosine generation. AB680 reproducibly inhibited the generation of adenosine from AMP by inhibition of CD73 activity expressed on human CD4+ and CD8+ T cells, with IC50 values of 13 and

6 pM, respectively. AMP-mediated suppression of markers of inflammation, IFN-γ and granzyme B production, was alleviated by greater than 70% with the addition of AB680. That is, addition of AB680 abrogated the immunosuppressive effect of adenosine. In preclinical tumor models, co-administration of 10 mg/kg AB680 with an anti-PD-1 antibody in established B16F10 melanoma syngeneic mouse tumors significantly increased the CD8+ to regulatory T cell ratio compared with that observed with vehicle control. Consistent with the positive increases in tumor-infiltrating effector T cells, AB680 conferred a significant survival advantage in tumor-bearing mice dosed therapeutically (treatment initiated when the average tumor volume reached 50 mm^3) with an anti-PD-1 antibody (median survival of 36 days) compared with either agent alone (median survival of 26 days in the vehicle group; median survival of 28 days in the anti-PD-1 antibody group).

AB680 has been evaluated in a healthy volunteer study for establishment of a starting dose in cancer patients, as well as early evidence of safety and toxicity. Study AB680CSP0001 was a first-in-human, double-blind, randomized, placebo-controlled, single- and repeat-dose study to evaluate the safety, tolerability, PK profile, and potential pharmacodynamic effects of AB680 in healthy volunteers. Preliminary safety data showed that AB680 administered at a single dose up to 25 mg and multiple doses at 8 mg are tolerated with no evidence of a tolerability concern. No early stopping rules were met in studies with healthy volunteers, and dose escalation is ongoing in cancer patients. All treatment-emergent AEs reported in single-dose cohorts (0.1 to 25mg) were mild or moderate in severity with no clear pattern of toxicity. Two out of 64 healthy volunteers did not complete the planned dosing regimen due to AEs; 1 due to an elevated liver function test and 1 due to an anomaly associated with a cardiac event. Both events returned to baseline levels. The clinical study report for AB680CSP0001 is complete and available upon request.

AB680 is currently under evaluation in AB680CSP002 (NCT04104672), a Phase 1 study to evaluate the safety, tolerability, PK, pharmacodynamic, and clinical activity of escalating doses of AB680 (25 mg up to 125 mg) in combination with zimberelimab, nab-paclitaxel, and gemcitabine in participants with advanced pancreatic cancer. In accordance with the AB680CSP0002 protocol, members from the Sponsor and principal investigators met on December 14, 2020 to review available safety data and supporting PK/PD data from six participants who received AB680 100 mg IV every 2 weeks (Q2W). No dose-limiting toxicities were observed at 100 mg, and adequate target coverage was observed throughout the treatment interval. Based on the totality of available data at 100 mg and lower dose levels, the committee recommended AB680 100 mg IV Q2W as the recommended dose for expansion. A maximum tolerated dose (MTD) for AB680 was not identified in AB680CSP0002. As a result of data from AB680CSP0002, in this study, the dose of AB680 is 100 mg IV Q2W.

For the most up to date clinical data, please refer to the current AB680 IB.

18.2. Objectives and Endpoints

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + AB680 treatment arm are described in Section 3 with the exception of those that are treatment arm-specific and described below.

18.2.1. Stage 1 (Etrumadenant + AB680)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and AB680 when administered as part of a combination regimen in Stage 1	Serum/plasma concentration and PK parameters for etrumadenant and AB680 when administered as part of a combination regimen in Stage 1

18.2.2. Stage 2 (Etrumadenant + AB680)

Secondary Objectives	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate of at least 4 months
To determine the PK profile for etrumadenant and AB680 when administered as part of a combination regimen in Stage 2	Serum/plasma concentration and PK parameters for etrumadenant and AB680 when administered as part of a combination regimen in Stage 2

18.3. Investigational Plan

The etrumadenant + AB680 treatment arm will be conducted as described in Section 4.

If clinical activity (> 10% radiographic response rate by PCWG3) is observed in a key subgroup of participants (eg, those with measurable disease at baseline), enrollment from that subgroup may continue up to a total of 40 participants (Stage 1 and Stage 2 combined).

18.4. Eligibility

18.4.1. Inclusion Criteria for Etrumadenant + AB680

All participants receiving AB680 in combination with etrumadenant must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving AB680 in combination with etrumadenant must satisfy the following:

E.1 Disease progression after prior NHA treatment (first- or second-generation nonsteroidal antiandrogens, abiraterone) and up to 2 prior lines of taxane chemotherapy, unless the physician and participant consider a taxane-containing regimen to be inappropriate (the latter must be documented in the source documents)

E.2 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant or 90 days after the last dose of AB680, whichever is longer

18.4.2. Exclusion Criteria for Etrumadenant + AB680

All participants receiving AB680 in combination with etrumadenant must not meet any of the main study exclusion criteria in Section 5.2. Participants are excluded from receiving AB680 in combination with etrumadenant if any of the following criteria apply:

E.1 Prior treatment with 3 or more lines of taxane chemotherapy administered as a single agent or as part of a combination regimen

E.2 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

E.2.1 Treatment with known 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

E.2.2 Treatment with known 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

E.2.3 Treatment with known 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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment

Refer to 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

18.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant and AB680 may be found in the respective investigator brochure.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

18.5.1. Dosage and Administration: Etrumadenant + AB680

All participants in Stage 1 and Stage 2 randomized to the etrumadenant + AB680 treatment arm will receive:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (28-day cycle)
- **AB680:** 100 mg, IV, Q2W (Days 1 and 15 of a 28-day cycle).

Table 43: Etrumadenant + AB680 Administration

Product Name[a]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Capsule	QD	150 mg	Oral	[redacted]
AB680	Lyophilized powder for injection	Q2W	100 mg	IV	

IV = intravenous; Q2W = every 2 weeks; QD = once daily

[a] Product names are listed in order of administration.

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of AB680. Participants will be administered AB680 and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

On study visit days when PK samples are collected, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant and AB680 is described in the study pharmacy manual.

For all participants receiving AB680 in combination with etrumadenant, guidelines for dose modification and safety management guidelines are provided in Section 18.9.

18.6. Method of Treatment Assignment

Beginning in Stage 1 and continuing into Stage 2, participants may be randomized 1:1:1 to 1 of 3 treatment arms:

- Etrumadenant + zimberelimab (Section 16)
- Etrumadenant + zimberelimab + AB680 (Section 17)
- Etrumadenant + AB680

A permuted block randomization method will be employed with stratification based on the presence of measurable disease at baseline.

18.7. Concomitant Medications

18.7.1. Permitted Therapy for Etrumadenant + AB680

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 18.7.2.

- For applicable participants, continued ADT will be allowed for the duration of the study.
- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including INR, according to institutional guidelines.
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

18.7.2. Prohibited Therapy for Etrumadenant + AB680

Use of the following concomitant therapies while receiving etrumadenant in combination with AB680 is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.
- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; acute, low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.
- Co-administration of:
  - 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 inhibitors of BCRP and P-gp
  - 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)

- Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4.
- Sensitive substrates of BSEP, MATE1 and OCT2.

Use of the following concomitant therapies with caution while receiving etrumadenant:

- Investigators should use caution when administering etrumadenant concomitantly with strong inhibitors or inducers of CYP2C8.

Refer to 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

18.8. Schedule of Activities

18.8.1. Screening Procedures for Etrumadenant + AB680

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving AB680 in combination with etrumadenant.

18.8.2. Treatment Procedures for Etrumadenant + AB680

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for participants receiving AB680 in combination with etrumadenant.

Refer to Table 44 for the schedule of activities during the treatment period for participants receiving AB680 in combination with etrumadenant.

Table 44: Schedule of Activities / TREATMENT PERIOD for AB680 in Combination with Etrumadenant

Procedure[h]	Cycle 1[m]					Cycle 2[m]					Cycle ≥3[m] (all odd cycles)		Cycle ≥4[m] (all even cycles)	
	D1[a]	D2	D4	D8 (±1)	D15 (±1)	D1	D2	D4	D8 (±1)	D15 (±1)	D1	D15 (±2)	D1	D15 (±2)
Administrative Procedures														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments														
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X				X	X				X	X		X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X				X	X				X				
ECOG performance status	X					X					X		X	
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]														
Hematology[g]	X	X	X	X	X	X			X	X	X	X	X	X
Clinical chemistry[g]	X	X	X	X	X	X			X	X	X	X	X	X
PSA	X					X					X		X	
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]														
PK for etrumadenant[i]	X	X		X	X	X	X				X		X[n]	
PK for AB680[i]	X	X	X	X	X	X	X	X	X	X	X		X[n]	
Pharmacodynamics[j]	X	X		X	X	X				X	X		Cycle 4	
Tumor biopsy[k]						X								
Efficacy Measurements														
Disease assessment	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.													

Investigational Product Administration														
Etrumadenant administration[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AB680 administration[l]	X				X	X				X	X	X	X	X
Medication diary review	X					X					X		X	

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to AB680 infusion start), every 20 minutes (± 5 minutes) from the start of the AB680 infusion until infusion end, and thereafter as clinically indicated until the participant completes all planned study visit assessments. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of AB680 infusion, and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with oral study treatment.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion Days 1 and 15 for applicable participants, 3 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to AB680 infusion start, and 3) 30 minutes (±15 minutes) after the end of the AB680 infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[k] On-treatment biopsy may be obtained at Cycle 2 Day 1 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 1 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 1, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.

[l] On infusion days, etrumadenant will be given at least 30 minutes prior to the start of IV administration of AB680. Participants will be administered AB680 and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[m] Assessments are based on the start of a new 4-week combination treatment cycle. New 4-week cycles of combination treatment will begin on the day IV therapy is administered. In the absence of any dose delays, 1 experimental treatment cycle will be 28 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 28 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[n] Cycles 4, 6, 8, 12, and 16 only.

18.9. Dose Modification and Safety Management Guidelines

The safety plan for participants in the etrumadenant + AB680 treatment arm may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and AB680. The combination of etrumadenant + AB680 may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and AB680.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

18.9.1. Dose Modifications for Etrumadenant + AB680

Dose Modifications for Etrumadenant

For management of drug-related toxicities, the dose of etrumadenant may be reduced up to 2 times as outlined in Table 45. 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.

Table 45: Recommended Dose Reductions for Etrumadenant

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant	150 mg	100 mg	75 mg

Dose Modifications for AB680

For management of drug-related toxicities, the dose of AB680 may be reduced up to 2 times as outlined in Table 46. If further dose reduction below the recommended starting dose is indicated, AB680 should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

Table 46: Recommended Dose Reductions for AB680

	Initial Dose[a]	First Dose Reduction	Second Dose Reduction
AB680	100 mg	75 mg	50 mg

[a] As defined in Section 18.5.1.

18.9.2. Study Treatment Interruptions for Etrumadenant + AB680

Treatment interruptions of etrumadenant and AB680 are allowed throughout the study for no more than 42 days. Holding of one 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 treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If,

in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + AB680, then all drugs should be held.

If etrumadenant, AB680 or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor

18.9.3. Management Guidelines for Adverse Events: Etrumadenant + AB680

Guidelines for the management of participants who experience specific AEs are provided below in Table 47. Guidelines for the management of dermatologic toxicity associated with etrumadenant and AB680 are provided in Table 48 and Table 49, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 47: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant

Event	Severity	Etrumadenant Action to be Taken	AB680 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.	Institute symptom-directed supportive care according to institutional guidelines. **Grade 2 events:** Consider AB680 infusion interruption as clinically indicated.
	Grade 3	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.	**Grade 3 events:** Interrupt AB680 infusion and institute symptom-directed supportive care according to institutional guidelines. If event resolves to Grade 1 or better within 42 days, resume AB680 with a 1 dose-level reduction (Table 38).[4,5] If not, permanently discontinue AB680 and etrumadenant and contact medical monitor.[6]
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor[3]	Permanently discontinue AB680 and contact medical monitor[6]
Hepatic toxicity (including elevations in transaminases and/or bilirubin)	**Grade 1-2** ALT/AST ≤ 5 × ULN	Continue etrumadenant and AB680 at the same dose level at the investigator's discretion. Monitor LFTs more frequently until return to < 3 × ULN or baseline.	
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected <u>non</u>immune-mediated transaminase elevations:** Withhold etrumadenant and AB680 for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant and AB680, each with a 1-level dose reduction (Table 45 and Table 46).[1,2,4,5] If not, permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6] **For suspected immune-mediated transaminase elevations:** Withhold etrumadenant and AB680 for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant and AB680, each with a 1-level dose reduction (Table 45 and Table 46).[1,2,4,5] If not, permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6]	
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,6] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. <u>Exception</u>: Participants 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 and AB680 at the same dose level. Institute symptom-directed supportive care according to institutional guidelines.	
	Grade 3-4	Consider etrumadenant and AB680 dose modification as clinically indicated, otherwise continue at the same dose.[2,5]	

Table 47: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant

Event	Severity	Etrumadenant Action to be Taken	AB680 Action to be Taken
		Institute symptom-directed supportive care according to institutional guidelines.	
Gastrointestinal toxicity (including but not limited to diarrhea and colitis)	**Grade 1**	Continue etrumadenant and AB680 at the same dose level. Initiate symptomatic treatment and monitor closely. Endoscopy is recommended if symptoms persist > 7 days.	
	Grade 2	Consider etrumadenant and AB680 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 and AB680 were withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant and AB680 at the same dose level.[1,4] **Recurrent or persistent events:** If etrumadenant and AB680 were withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant and AB680, each with a 1-level dose reduction.[1,2,4,5] If not, permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6] Etrumadenant and AB680 dose re-escalation of is permitted at the investigator's discretion.	
	Grade 3	Withhold etrumadenant and AB680 for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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 AB680 and contact medical monitor.[3,6]	

Table 47: Guidelines for Management of Participants who Experience Adverse Events While Receiving AB680 in Combination with Etrumadenant

Event	Severity	Etrumadenant Action to be Taken	AB680 Action to be Taken
Etrumadenant- or AB680-related toxicities not described above	**Grade 1-2**	Consider etrumadenant and AB680 dose modification as clinically indicated, otherwise continue at the same dose. Institute symptom-directed supportive care according to institutional guidelines.	
	Grade 3	Withhold etrumadenant and AB680 for up to 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant and AB680, each with a 1-level dose reduction.[1,2,4,5] If not, permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6] Etrumadenant and AB680 dose re-escalation is permitted at the investigator's discretion.	
	Grade 4	Permanently discontinue etrumadenant and AB680 and contact medical monitor.[3,6]	

[1] Etrumadenant may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.

[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[4] AB680 may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[5] The dose of AB680 may be reduced up to 2 times from the starting dose level in accordance with Table 46 for management of drug-related toxicities. Additional dose reductions are not allowed. If third dose reduction is indicated, then that participant should discontinue AB680.

[6] Resumption of AB680 may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with AB680 only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 48: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases ▪ Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 48: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4. 2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (e.g. pruritis, burning, tightness)
[b] Macules/papules covering 10-30% BSA with or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental ADLs
[c] Macules/papules covering >30% BSA with or without symptoms (e.g. pruritis, burning, tightness) limiting ADLs
[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 49: Guidelines for Management of Participants who Experience Dermatologic Toxicity While Receiving AB680

Event	Severity	AB680 Action to be Taken
Dermatologic toxicity (including but not limited to rash, maculopapular rash, and pruritis)	**Grade 1**	Continue AB680 at the same dose level. Immediately institute supportive care measures for symptomatic relief.
	Grade 2	Consider AB680 dose modification as clinically indicated; otherwise continue at the same dose. **For suspected AB680-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 AB680 at the same dose or with a 1-level dose reduction (Table 38). AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 3	Withhold AB680 for at least 7 days until toxicity resolves to Grade 1 or better. **For suspected AB680-related events:** Immediately institute supportive measures. If event resolves to Grade 1 or better within 42 days, resume AB680 with a 1-level dose reduction (Table 38).[1,2] If not, permanently discontinue AB680 and contact medical monitor.[3] AB680 dose re-escalation is permitted at the investigator's discretion.
	Grade 4	Permanently discontinue AB680 and contact medical monitor[3]

[1] AB680 may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.
[2] The dose of AB680 may be reduced up to 2 times from the starting dose level in accordance with Table 38 for management of drug-related toxicities. Additional dose reductions are not allowed. If third dose reduction is indicated, then that participant should discontinue AB680.
[3] Resumption of AB680 may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with AB680 only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

18.10. Collection of Pregnancy Information

18.10.1. Collection of Pregnancy Information for Etrumadenant + AB680

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant or 90 days after the last dose of AB680, whichever is longer.

19. ETRUMADENANT + ZIMBERELIMAB TREATMENT ARM: PHARMACOKINETICS SUBSTUDY

19.1. Introduction

This treatment arm combines 2 investigational agents in development by Arcus Biosciences: etrumadenant and zimberelimab.

19.1.1. Background for Etrumadenant + Zimberelimab

Refer to Section 16.1.1 for a summary of the background on the investigational agents etrumadenant and zimberelimab.

19.1.2. Rationale for Combining Etrumadenant + Zimberelimab

The scientific and clinical rationale for evaluating an investigational regimen that combines etrumadenant with zimberelimab for the potential treatment of mCRPC is described in Section 16.1.2.

19.1.3. Risk/Benefit Assessment for Etrumadenant + Zimberelimab

Refer to Section 16.1.3 for a risk/benefit summary of etrumadenant + zimberelimab in mCRPC.

19.2. Objectives and Endpoints: PK Substudy

Primary Objectives	Corresponding Endpoints
To assess the relative bioavailability of etrumadenant tablets and etrumadenant capsules	Serum/plasma concentration and PK parameters for etrumadenant tablets and etrumadenant capsules
To assess the effect of food on the bioavailability of etrumadenant tablets	Serum/plasma concentration and PK parameters for etrumadenant tablets administered in the fed and fasted states
Secondary Objectives	**Corresponding Endpoints**
To evaluate the safety of etrumadenant tablets and etrumadenant capsules in combination with zimberelimab	Incidence and severity of AEs and SAEs
To evaluate the antitumor activity of etrumadenant tablets and etrumadenant capsules in combination with zimberelimab	ORR, defined as the composite proportion of participants with a PSA and/or radiographic complete or partial response determined by the investigator according PCWG3 criteria
To evaluate PSA response rate	Proportion of participants with a PSA CR or PR as defined by PCWG3
To evaluate radiographic response rate	Proportion of participants with radiographic CR or PR as defined by PCWG3
To evaluate clinical efficacy	DCR of at least 4 months
To assess immunogenicity of zimberelimab	Number and percentage of participants who develop ADAs to zimberelimab

Exploratory Objectives
To characterize the relationship between tumor tissue/blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy
To use tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy for treatment of the disease under study

19.3. Investigational Plan: PK Substudy

The PK substudy will use a substudy specific ICF and will be conducted in parallel to the etrumadenant + zimberelimab non-substudy treatment arm based on availability of etrumadenant as a tablet formulation.

At least 1 and up to 2 etrumadenant tablet dose levels may be evaluated: 150 mg and 225 mg. Initially, 3 participants will receive etrumadenant 150 mg once daily. Following review of the available PK data by the sponsor, the total number of participants at the etrumadenant 150-mg dose level may be increased, and/or an initial 3 to 6 participants may be enrolled at the etrumadenant 225-mg once daily dose level. The maximum planned duration of tablet use is 14 days; thereafter, participants will transition to capsules for the remainder of study treatment.

Regardless of tablet dose level, participants in the PK substudy will receive etrumadenant as follows:

- **Days 1 through 7:** etrumadenant tablets under fasted conditions
- **Days 8 through 14:** etrumadenant tablets under fed conditions
- **Day 15 and onward until one or more of the treatment discontinuation criteria defined in Section 7.4.1 are met:** etrumadenant capsules under fasted conditions

Dose modifications for etrumadenant (tablet and capsule formulations) are permitted throughout study treatment as clinically indicated. However, only PK data from participants who complete the planned etrumadenant treatment schedule in Cycle 1 are evaluable for relative bioavailability assessment. Therefore, participants who require etrumadenant treatment interruption or dose reduction in Cycle 1 will be replaced as well as excluded from primary endpoint analyses for the PK substudy. The number of participants enrolled in the PK substudy may be adjusted beyond the planned sample size to account for participant replacement.

19.4. Eligibility

19.4.1. PK Substudy Inclusion Criteria

All participants in the PK substudy must meet the main study inclusion criteria in Section 5.1 as well as those specified in Section 16.4.1 for participants receiving etrumadenant in combination with zimberelimab.

19.4.2. PK Substudy Exclusion Criteria

All participants in the PK substudy must not satisfy any of the main study exclusion criteria in Section 5.2 and must not meet any of those specified in Section 16.4.2 for participants receiving etrumadenant in combination with zimberelimab.

19.5. Study Treatment

On visit days where study treatment 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.

Formulation information for etrumadenant capsules and zimberelimab may be found in the respective investigator brochure. Formulation information for etrumadenant tablets may be found in the study pharmacy manual.

Additional information on the distribution, storage, preparation, handling, and destruction of study treatments is described in the study pharmacy manual.

19.5.1. Dosage and Administration: Etrumadenant and Zimberelimab

All participants in the PK substudy will receive:

- **Etrumadenant tablets:** 150 or 225 mg, oral, once daily continuous dosing on Days 1 through 14 of an initial 21-day cycle
- **Etrumadenant capsules:** 150 mg, oral once daily continuous dosing on Days 15 through 21 of an initial 21-day cycle and once daily continuous dosing for each 21-day cycle thereafter
- **Zimberelimab:** 360 mg, IV, every 3 weeks (Day 1 of a 21-day cycle)

Table 50: Etrumadenant + Zimberelimab Administration in the PK Substudy

Product Name	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	Tablet	QD	150 mg or 225 mg	Oral	
Etrumadenant	Capsule	QD	150 mg	Oral	
Zimberelimab	C mg/mL solution	Q3W	360 mg	IV	

IV = intravenous; Q3W = every 3 weeks; QD = once daily

Participants should take etrumadenant in the morning at the approximately same time each day.

On days when etrumadenant is administered under fasting conditions, no food should be consumed at least 6 hours before and 2 hours after etrumadenant administration. Participants should take etrumadenant with 240 mL (8 fluid ounces) of water. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour before and after etrumadenant administration.

On days when etrumadenant is administered under fed conditions, participants should be fasted overnight for at least 6 hours and eat a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) breakfast in 30 minutes or less. Participants should take etrumadenant 30 minutes after the start of the meal with 240 mL (8 fluid ounces) of water. Following etrumadenant administration, the participant should fast for a period of 4 hours until lunch. During fasting, no fluids are allowed except water; however, water is not allowed from 1 hour before and after etrumadenant administration.

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of zimberelimab.

On study visit days when PK samples are collected, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Additional information regarding administration of etrumadenant and zimberelimab is described in the study pharmacy manual. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

For all participants receiving etrumadenant in combination with zimberelimab, guidelines for dose modification and safety management guidelines are provided in Section 16.9.

19.6. Concomitant Medications: PK Substudy

Refer to Section 16.7.1 and Section 16.7.2, respectively, for guidance on permitted and prohibited concomitant therapies for participants in the PK substudy.

19.7. Method of Treatment Assignment

After informed consent has been obtained, screening procedures have been completed, and eligibility has been established, participants will be enrolled onto the PK substudy. Applicable treatment will be assigned and will not involve randomization.

19.8. Schedule of Activities

19.8.1. Screening Procedures: PK Substudy

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for PK substudy participants.

19.8.2. Treatment Procedures: PK Substudy

Study assessments for all participants are described in Section 7.3. There are no additional treatment procedures for PK substudy participants.

The schedule of activities during **Cycle 1 of the treatment period** for PK substudy participants receiving etrumadenant in combination with zimberelimab is provided in Table 51.

The schedule of activities during **Cycles 2 and onward of the treatment period** for PK substudy participants receiving etrumadenant in combination with zimberelimab is provided in Table 52.

Table 51: Schedule of Activities / TREATMENT PERIOD (Cycle 1 only) for Participants in the PK Substudy

Procedure[h]	**Cycle 1[m]**																				
Day	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Scheduled Clinic Visit	**Y**	**Y**		**Y**			**Y**	**Y**						**Y**	**Y**						**Y**
Visit Window	**--**	**--**		**--**				**+1**							**+1**						**-1**
Administrative Procedures																					
Concomitant medications	Continuous																				
Assessment of AEs/SAEs	Continuous																				
Clinical Procedures/Assessments																					
Physical examination[b]	X																				
Vital signs[c]	X	X		X				X													
Blood pressure[d]	X	X		X				X													
12-lead ECG[e]	X																				
ECOG performance status	X																				
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[f]																					
Hematology[g]	X	X		X				X													
Clinical chemistry[g]	X	X		X				X													
Thyroid tests[g]	X																				
PSA	X																				
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[f]																					
PK for etrumadenant [i]	X	X					X	X						X	X						X
PK for zimberelimab[i]	X	X		X				X							X						
Pharmacodynamics[j]	X							X							X						
Immunogenicity[k]	X																				
Investigational Product Administration																					
Meal status[n]	**FASTED**							**FED**							**FASTED**						
Etrumadenant TABLETS[l]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**							
Etrumadenant CAPSULES[l]															**X**	**X**	**X**	**X**	**X**	**X**	**X**
Zimberelimab administration[l]	X																				
Medication diary review	X	X		X				X							X						

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PK = pharmacokinetics; PSA = prostate-specific antigen; SAE = serious adverse event

[a] Laboratory tests on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.

[b] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.

[c] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycle 1, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and approximately 30 minutes after dosing with oral study treatment (prior to zimberelimab infusion start), every 20 minutes (± 5 minutes) from the start of the zimberelimab infusion until infusion end, and thereafter as clinically indicated until the participant completes all planned study visit assessments. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1, perform vital sign assessment prior to and at the end of the zimberelimab infusion, and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with etrumadenant.

[d] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[e] Perform as described in Section 7.3.3. On infusion days for applicable participants, 3 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to zimberelimab infusion start, and 3) 30 minutes (±15 minutes) after the end of the zimberelimab infusion.

[f] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[g] As defined in Section 7.3.8.

[h] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[i] Refer to the central laboratory manual for PK sampling timepoints.

[j] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[k] Refer to the central laboratory manual for immunogenicity sampling timepoints.

[l] On visit days when etrumadenant is administered together with zimberelimab, etrumadenant may be taken at least 30 minutes prior to the start of IV infusion of zimberelimab.

[m] Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (zimberelimab and/or docetaxel as appropriate). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[n] As defined in Section 19.5.1 for FASTED and FED.

Table 52: Schedule of Activities / TREATMENT PERIOD (Cycles 2 and onward) for Participants in the PK Substudy

Procedure[g]	Cycle 2[m]			Cycle 3[m]	Cycle ≥4[m]
	D1	D2	D8 (±1)	D1	D1
Administrative Procedures					
Concomitant medications	X	X	X	X	X
Clinical Procedures/Assessments					
Assessment of AEs/SAEs	X	X	X	X	X
Physical examination[a]	X			X	X
Vital signs[b]	X		X	X	X
Blood pressure[c]	X		X	X	X
12-lead ECG[d]	X				
ECOG performance status	X			X	X
Laboratory Procedures/Assessments (analysis performed by LOCAL laboratory)[e]					
Hematology[f]	X		X	X	X
Clinical chemistry[f]	X		X	X	X
Thyroid tests[f]					X[p]
PSA	X			X	X
Laboratory Procedures/Assessments (analysis performed by CENTRAL laboratory)[e]					
PK for etrumadenant[h]	X			X	X[n]
PK for zimberelimab[h]	X			X	X[n]
Pharmacodynamics[i]	X		X		Cycle 5
Immunogenicity[j]	X			X	X[o]
Tumor biopsy[k]			X		
Efficacy Measurements					
Disease assessment	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.				
Investigational Product Administration					
Etrumadenant administration[l]	X	X	X	X	X
Zimberelimab administration[l]	X			X	X
Medication diary review	X			X	X

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; Q3W = every 3 weeks; SAE = serious adverse event

[a] Symptom-directed exam (height, weight not required).

[b] Vital signs to be collected are temperature, pulse rate, and respiratory rate. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycle 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and approximately 30 minutes after dosing with oral study treatment (prior to zimberelimab infusion start), every 20 minutes (± 5 minutes) from the start of the zimberelimab infusion until infusion end, and thereafter as clinically indicated until the participant completes all planned study visit assessments. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of the zimberelimab infusion, and as clinically indicated thereafter until the visit is completed. On noninfusion days, collect vital signs prior to dosing with etrumadenant.

[c] Perform as described in Section 7.3.5 at the same frequency as vital sign assessments.

[d] Perform as described in Section 7.3.3. In Cycle 2 only, on infusion days for applicable participants, 3 single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to zimberelimab infusion start, and 3) 30 minutes (±15 minutes) after the end of the zimberelimab infusion. Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated.

[e] Samples for all local laboratory assessments may be collected 72 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.

[f] As defined in Section 7.3.8.

[g] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.

[h] Refer to the central laboratory manual for PK sampling timepoints.

[i] Refer to the central laboratory manual for pharmacodynamics sampling timepoints.

[j] Refer to the central laboratory manual for immunogenicity sampling timepoints.

[k] On-treatment biopsy may be obtained at Cycle 2 Day 8 (±7 days) from participants with accessible tumor. The biopsy at Cycle 2 Day 8 should be scheduled as closely as possible to the pharmacodynamic assessment at Cycle 2 Day 8, if feasible. If the biopsy is not performed, the blood sample for pharmacodynamics should still be collected.

[l] On visit days when etrumadenant is administered together with zimberelimab, etrumadenant may be taken at least 30 minutes prior to the start of IV infusion of zimberelimab. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

[m] Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (zimberelimab). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling.

[n] Cycles 4, 5, 6, 8, 12 and 16 only.

[o] Cycles 4, 6, 8, 12 and 16 only.

[p] Cycle 4 and every 4 cycles thereafter.

19.8.3. Pharmacokinetics Sampling Schedule for PK Substudy

Table 53: Schedule of Blood Sample Collection for PK Assessment

Study Visit	Time	Fed/Fasted State
Cycle 1 Day 1	Prior to study treatment 30 (± 5) minutes after etrumadenant dose 1 hour (± 5 minutes) after etrumadenant dose 1.5 hours (± 10 minutes) after etrumadenant dose 2 hours (± 10 minutes) after etrumadenant dose 3 hours (± 10 minutes) after etrumadenant dose 4 hours (± 10 minutes) after etrumadenant dose 5 hours (± 10 minutes) after etrumadenant dose 6 hours (± 10 minutes) after etrumadenant dose 8 hours (± 10 minutes) after etrumadenant dose 10 hours (± 10 minutes) after etrumadenant dose	Fasted
Cycle 1 Day 2	24 (± 1) hours after etrumadenant dose on Day 1	Fasted
Cycle 1 Day 7	Prior to study treatment 30 (± 5) minutes after etrumadenant dose 1 hour (± 5 minutes) after etrumadenant dose 1.5 hours (± 10 minutes) after etrumadenant dose 2 hours (± 10 minutes) after etrumadenant dose 3 hours (± 10 minutes) after etrumadenant dose 4 hours (± 10 minutes) after etrumadenant dose 5 hours (± 10 minutes) after etrumadenant dose 6 hours (± 10 minutes) after etrumadenant dose 8 hours (± 10 minutes) after etrumadenant dose 10 hours (± 10 minutes) after etrumadenant dose	Fasted
Cycle 1 Day 8	24 (± 1) hours after etrumadenant dose on Day 7	Fed/High-fat meal
Cycle 1 Day 14	Prior to study treatment 30 (± 5 minutes) after etrumadenant dose 1 hour (± 5 minutes) after etrumadenant dose 1.5 hours (± 10 minutes) after etrumadenant dose 2 hours (± 10 minutes) after etrumadenant dose 3 hours (± 10 minutes) after etrumadenant dose 4 hours (± 10 minutes) after etrumadenant dose 5 hours (± 10 minutes) after etrumadenant dose 6 hours (± 10 minutes) after etrumadenant dose 8 hours (± 10 minutes) after etrumadenant dose 10 hours (± 10 minutes) after etrumadenant dose	Fed/High-fat meal
Cycle 1 Day 15	24 (± 1) hours after etrumadenant dose on Day 14	Fasted
Cycle 1 Day 21	Prior to study treatment 30 (± 5) minutes after etrumadenant dose 1 hour (± 5 minutes) after etrumadenant dose 1.5 hours (± 10 minutes) after etrumadenant dose 2 hours (± 10 minutes) after etrumadenant dose 3 hours (± 10 minutes) after etrumadenant dose 4 hours (± 10 minutes) after etrumadenant dose 5 hours (± 10 minutes) after etrumadenant dose 6 hours (± 10 minutes) after etrumadenant dose 8 hours (± 10 minutes) after etrumadenant dose 10 hours (± 10 minutes) after etrumadenant dose	Fasted
Cycle 2 Day 1	24 (± 1) hours after etrumadenant dose on Day 21	Fasted

19.9. Dose Modification and Safety Management Guidelines

The safety plan for participants in the etrumadenant and zimberelimab treatment arm may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and zimberelimab or other anti-PD-1 antibodies (ie, class effects), respectively. The combination of etrumadenant + zimberelimab may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and zimberelimab.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

19.9.1. Dose Modifications for Etrumadenant + Zimberelimab

Dose modifications for etrumadenant (tablet and capsule formulations) are permitted. However, participants who require etrumadenant treatment interruption or dose reduction in Cycle 1 will be replaced as well as excluded from primary endpoint analyses for the PK substudy.

Dose Modifications for Etrumadenant/Tablet Formulation

For management of drug-related toxicities, the dose of etrumadenant tablets may be reduced once or twice, depending on the initial dose, as outlined in Table 54. If further dose reduction below 75 mg is indicated, etrumadenant tablets should be discontinued. After dose reduction, the dose may be escalated during subsequent administrations at the investigator's discretion.

Table 54: Recommended Dose Reductions for Etrumadenant Tablets

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant tablets	225 mg	150 mg	75 mg
	150 mg	75 mg	Not applicable

Dose Modifications for Etrumadenant/Capsule Formulation

For management of drug-related toxicities, the dose of etrumadenant capsules may be reduced up to 2 times as outlined in Table 55. 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.

Table 55: Recommended Dose Reductions for Etrumadenant Capsules

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant capsules	150 mg	100 mg	75 mg

Dose Modifications for Zimberelimab

There will be no dose modifications for zimberelimab in this study

19.9.2. Study Treatment Interruptions for Etrumadenant + Zimberelimab

Treatment interruptions of etrumadenant tablets, etrumadenant capsules, and zimberelimab are allowed throughout the study for no more than 42 days. Holding of one agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the combination of etrumadenant + zimberelimab, then both drugs should be held.

If etrumadenant, zimberelimab, or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single-agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

19.9.3. Management Guidelines for Adverse Events: Etrumadenant + Zimberelimab

Guidelines for the management of participants who experience specific AEs are provided in Table 16. In addition, guidelines for the management of participants who experience dermatologic toxicities associated with zimberelimab or etrumadenant are provided in Table 17 and Table 18, respectively.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

19.10. Collection of Pregnancy Information

19.10.1. Collection of Pregnancy Information for Etrumadenant + Zimberelimab

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant (tablets or capsules) or 90 days after the last dose of zimberelimab, whichever is longer.

20. SACITUZUMAB GOVITECAN CONTAINING TREATMENT ARMS

20.1. Introduction

20.1.1. Background for Investigational Products

20.1.1.1. Sacituzumab govitecan

Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) composed of the following 3 components:

- The humanized monoclonal antibody hRS7 IgG1κ, which binds to trophoblast cell-surface antigen 2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers, including triple-negative breast cancer (TNBC).
- The camptothecin-derived agent SN-38, a topoisomerase I inhibitor.
- A hydrolyzable linker, with the company designation as CL2A that links the humanized monoclonal antibody to SN-38.

Binding of Trop-2 by the parental RS7 antibody has been shown to result in internalization and processing of the antibody by the targeted cells (Shih 1994, Stein 1995). Because of its hydrolyzable linker, SG will release its SN 38 payload both intra- and extracellularly in the tumor microenvironment (Goldenberg 2015, Govindan 2013). SG delivers significantly greater amounts of SN 38 to a Trop 2-expressing tumor than conventional irinotecan chemotherapy (Sharkey 2015). The extracellular release of SN 38 from SG also allows for bystander killing of Trop 2 negative tumor cells (Lopez 2020, Perrone 2020, Zeybek 2020). Thus, SG can deliver cytotoxic chemotherapy to tumors, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.

Refer to the SG investigator brochure for complete discussion of the agent and additional information on preclinical and clinical studies.

20.1.1.2. Etrumadenant

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} and A_{2b} receptors on immune cells, resulting in an ineffective antitumor immune response. Extracellular adenosine is primarily produced by the enzyme CD73. In prostate cancer, $A_{2b}R$ is upregulated and the activity of PAP produces additional adenosine, suggesting this tumor type may be more susceptible than others to adenosine-mediated immunosuppression. Etrumadenant is the first clinic-stage small molecule dual antagonist of both $A_{2a}R$ and$A_{2b}R$ and was designed to maximally inhibit the adenosine-driven impairment of tumor-infiltrating lymphocytes (mainly through $A_{2a}R$ on CD8+ T cells and NK cells) and myeloid cells (through $A_{2b}R$ 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 nonspecific protein binding. As a result, etrumadenant is hypothesized to

uniquely block adenosine's immunosuppressive and cancer cell-intrinsic effects. Etrumadenant exhibits PK/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.

Refer to the etrumadenant investigator brochure for complete discussion of the agent and additional information on preclinical and clinical studies.

20.1.1.3. Zimberelimab

Zimberelimab is a fully human immunoglobulin G4 monoclonal antibody targeting the human PD-1 immune checkpoint. In preclinical and clinical evaluations, zimberelimab has demonstrated PK, pharmacodynamics including receptor occupancy, efficacy, and safety that is consistent with currently approved anti-PD-1 therapies. Arcus in-licensed zimberelimab to enable development of precision combination regimens with full line-of-sight to the commercialization of innovative therapies for all patients who may benefit. The most advanced study with zimberelimab is entering Phase 2 development for the treatment of first-line metastatic NSCLC, evaluating zimberelimab in combination with 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.

Refer to the zimberelimab investigator brochure for complete discussion of the agent and additional information on preclinical and clinical studies.

20.1.2. Rationale for Sacituzumab Govitecan + Etrumadenant with or without Zimberelimab Combination Therapy

The potency of etrumadenant and favorable safety profile make it an apt component for combination therapy with multiple agents. The opportunity to combine etrumadenant and zimberelimab is currently being evaluated in an ongoing Phase 1 study in participants with advanced solid tumors (NCT03846310). Emerging data show that etrumadenant administered together with zimberelimab is well tolerated and demonstrated evidence of clinical benefit, including antitumor response and disease stabilization > 6 months (Powderly et al., 2019), in heavily pretreated participants across multiple disease indications. Preliminary data from Stage 1 of the combination of etrumadenant, zimberelimab and docetaxel in this study demonstrated a tolerable safety profile and promising clinical activity with radiographic and PSA responses in participants previously treated with a new hormonal agent in chemotherapy-naïve mCRPC (Subudhi et al., 2021).

Recent clinical data from KEYNOTE-199 has shown minimal response activity but potential survival advantage for NHA and taxane experienced mCRPC participants treated with the anti-PD-1 antibody pembrolizumab (Antonarakis et al., 2020). This, coupled with the early activity signal seen when AZD4635, an adenosine A2aR antagonist, was combined with the anti-PD-L1 antibody durvalumab in late-line mCRPC (Bendell et al., 2019), help provide validation for the adenosine pathway as a relevant therapeutic target in mCRPC and supports the evaluation of etrumadenant and zimberelimab in this study. Specifically, mCPRC participants treated with AZD4635 with or without durvalumab showed radiographic and PSA responses. Additional description of these clinical data and the biological rationale for the inhibition of the adenosine pathway in mCRPC are found in Section 2.2.

In prostate cancer, Trop-2 expression is upregulated and elevated compared to normal prostatic tissue which has suggested prognostic significance. Trop-2 expression increases in localized, organ confined prostate cancer and peaks in advanced mCRPC with extracapsular extension (Shen et al, 2021). High levels of Trop-2 expression have also been found to be predictive of prostate cancer recurrence (Shen et al, 2021).

The Phase 1/2 basket study IMMU-132-01 demonstrated encouraging activity of SG in multiple types of cancer with an ORR of 17% and a median overall survival (mOS) of 9.5 months in Trop-2 unselected patients. Of the eleven patients with CRPC there was one CR and a clinical benefit rate of 27% (Bardia et al, 2021).

To further evaluate SG in mCRPC there is an ongoing investigator-sponsored trial of SG in participants with mCRPC who have progressed on second generation AR-Directed therapy (NCT03725761). Preliminary data have shown disease stabilization with a 6-month radiographic progression-free survival of 45% in the initial 20 participants enrolled.

The antitumor effects of cytotoxic chemotherapy have historically been associated with direct tumor cell killing and more recently, mCRPC clinical trials have demonstrated that clinical activity of cytotoxic agents may be enhanced with the addition of immunotherapy such as anti-PD-1/L1 antibodies (Appleman et al, 2021; Bardia et al, 2021; Fizazi et al, 2021). It is hypothesized that Sacituzumab govitecan may demonstrate antitumor effects similar to other cytotoxic agents.

As adenosine is highly immunosuppressive, SG alone may not be as effective in adenosine-rich tumors such as prostate cancer. Therefore, the addition of an adenosine receptor antagonist to combination cytotoxic therapy with or without immunotherapy may result in enhanced antitumor activity. To test this hypothesis, the safety and efficacy of etrumadenant in combination with Sacituzumab govitecan, with or without zimberelimab, will be evaluated in this treatment arm.

Results from in-vitro human microsomal assays suggest that etrumadenant is a weak inhibitor of UGT1A1 with predicted minor increase in exposure of a sensitive UGT1A1 substrate. Given the variability in free SN-38 (payload of SG) exposure with Sacituzumab govitecan administration, impact of weak UGT1A1 inhibition on exposure of free SN-38 is expected to be not clinically relevant. This is further supported by the results from the population PK analyses of data from Phase 1/2 study in participants with advanced epithelial cancers (IMMU-132-01), and Phase 3 study in participants with locally advanced or metastatic (TNBC). In these analyses, UGT1A1 genotype was not identified as a significant covariate for SG or free SN-38 exposure, including in subjects with *28/*28 genotype known to have 70% reduced UGT1A1 transcriptional activity, as supported by finding that free SN-38 and SG exposures were similar across UGT1A1 genotypes including the wild type.

Exposures of free SN-38 and SG in the presence of etrumadenant will be further characterized in relevant cohort(s), and subjects will be closely monitored for adverse reactions.

Despite advances in the treatment of mCRPC, many patients either remain refractory to currently available therapy, or relapse following a response to available therapy, resulting in a need for the development of novel agents and combinations of agents for the treatment of mCRPC.

20.1.3. Risk/Benefit Assessment for Etrumadenant + Sacituzumab with or without Zimberelimab

Etrumadenant is currently being evaluated for use in cancer patients as a potential therapy in combination with approved agents or other experimental treatments.

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 anticancer agents as defined by objective responses or prolonged stabilization of disease. 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. This 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.

Zimberelimab is currently being evaluated for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

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

Clinical data from monotherapy treatment in heavily pretreated patients with various advanced solid tumors have established tolerable and pharmacokinetically stable dosing regimens of zimberelimab intravenously every 2 and every 3 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. However, the risks associated with this drug class given experience with the approved anti-PD-1 agents, nivolumab (Opdivo Package Insert, 2019) and pembrolizumab (Keytruda Package Insert, 2020), are appropriate for zimberelimab.

Sacituzumab govitecan is currently being evaluated for use in cancer patients in both monotherapy and combination studies with approved agents or other experimental regimens.

Nonclinical data demonstrate Sacituzumab govitecan has antitumor activity and significant inhibition of tumor growth in various epithelial cancer xenograft models compared to controls; Sacituzumab govitecan also demonstrated low cytotoxicity in multiple cell lines representative of different epithelial tumors (IC50 values ranged from 1.95 nM to 23.14 nM). Nonclinical studies confirmed that the majority of SN 38 administered as Sacituzumab govitecan remains bound to the ADC in the serum and is not circulating as the free cytotoxic payload.

For the most up-to-date clinical data, refer to the current version of the etrumadenant, zimberelimab, and sacituzumab govitecan Investigator's Brochure.

The combination of etrumadenant and zimberelimab has been evaluated in early-phase studies across multiple tumor types illustrating both tumor response and disease stabilization. The high Trop-2 expression in mCRPC and the preliminary activity of SG monotherapy in prostate cancer supports a favorable benefit/risk assessment and provides justification for continued clinical development of this investigational therapy combination of SG with etrumadenant with and without zimberelimab.

In summary, the safety and early activity of the combination of etrumadenant and zimberelimab with or without existing standard of care in cancer patients supports its evaluation in this study as part of regimen with SG. Considering the activity signals seen with similar mechanistic combinatory regimens in mCRPC and other PD-1 resistant tumor types with etrumadenant and zimberelimab, it is hypothesized that treatment with etrumadenant and SG, with or without zimberelimab, has promising therapeutic potential in mCRPC.

20.2. Objectives and Endpoints for Sacituzumab Govitecan Containing Treatment Arms

Primary, secondary, and exploratory objectives along with corresponding endpoints for the etrumadenant + SG with or without zimberelimab treatment arms are described in Section 3. In addition, the following objectives and endpoints are specific to etrumadenant + SG with or without zimberelimab treatment arms based on stage.

20.2.1. Stage 1

Secondary Objective	Corresponding Endpoints
To evaluate clinical efficacy in Stage 1	Disease control rate (DCR) of at least 6 months

20.2.2. Stage 2

Secondary Objective	Corresponding Endpoints
To evaluate clinical efficacy in Stage 2	Disease control rate (DCR) of at least 6 months
Exploratory Objective	
To assess and compare efficacy by tumor expression of Trop-2 and evaluate the role of Trop-2 expression as a biomarker for response to SG combination therapy	

20.3. Investigational Plan

Sacituzumab govitecan-containing treatment arms will be conducted as described in Section 4, with additional information described below. Two treatment arms are planned to enroll as follows:

- Etrumadenant + SG: Etrumadenant 150 mg QD + Sacituzumab govitecan 10 mg/kg on Days 1 and 8 of a 21-day cycle.

- Etrumadenant + zimberelimab + SG: Etrumadenant 150 mg QD + zimberelimab 360 mg Q3W + Sacituzumab govitecan 10 mg/kg on Days 1 and 8 of a 21-day cycle.

Enrollment will begin initially with etrumadenant + SG. If no excess toxicity (defined in Section 20.12.1) is observed in the first 6 participants in Stage 1, enrollment will continue as described in Section 4. Based on the safety evaluation of etrumadenant + Sacituzumab govitecan, at the sponsor's discretion, one of the following scenarios may occur:

6. Stop etrumadenant + SG enrollment; or
7. Continue enrollment into etrumadenant + SG only; or
8. Continue enrollment into etrumadenant + SG, and open enrollment of etrumadenant + zimberelimab + SG.

Depending on the treatment arm and stage, enrollment may or may not involve randomization with 1:1 allocation. The decision to begin randomized enrollment will be made by the sponsor for each SG combination therapy.

As noted above, this study is designed with flexibility to add or remove treatment arms based on emerging data. Any additional SG-containing treatment arms will be added via protocol amendment and will follow the same design as described above.

20.4. Eligibility

20.4.1. Inclusion Criteria

All participants receiving etrumadenant in combination with SG with or without zimberelimab must meet the main study inclusion criteria in Section 5.1. In addition, participants receiving etrumadenant in combination with SG must satisfy the following:

F.1 Disease progression after prior NHA treatment (first- or second-generation nonsteroidal antiandrogens, abiraterone).

F.2 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures with female partners of reproductive potential, and agreement to refrain from donating sperm, for 30 days after the last dose of etrumadenant, 90 days after the last dose of zimberelimab, and 6 months after the last dose of SG, whichever is longer.

F.3 No growth factor support within 2 weeks of study drug initiation.

F.4 Participants with 2 or more measurable lesions will be requested to consent to provide baseline tumor tissue sample (either archival or fresh tumor biopsy). If archived specimen (within 24 months of screening) is unavailable for these patients, a fresh tumor biopsy in a lesion not previously irradiated is required (tumors progressing in a prior site of radiation may be considered after sponsor consultation). The biopsy must not put participants at undue risk and the procedure must not be more invasive than a core biopsy as documented in the medical record by the investigator.

Participants with non-measurable disease at baseline will be asked to provide archival tissue (<24 months old) where it is available. Participants with non-measurable disease at baseline without available archival tissue will not be requested to provide fresh biopsy.

20.4.2. Exclusion Criteria

All participants receiving etrumadenant in combination with SG with or without zimberelimab must not meet any of the main study exclusion criteria in Section 5.2. Additionally, participants are excluded from receiving etrumadenant in combination with SG if any of the following criteria apply:

F.1 Prior treatment with docetaxel, cabazitaxel, topoisomerase 1 inhibitors, or other taxane chemotherapy administered as a single agent or as part of a combination regimen.

F.2 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain Barré syndrome, or multiple sclerosis with the following exceptions:

F.2.1 Patients with a history of autoimmune related hypothyroidism who are on thyroid replacement hormone are eligible for the study.

F.2.2 Patients with controlled Type 1 diabetes mellitus who, in the judgment of the investigator, are on a stable insulin regimen are eligible for the study.

F.2.3 Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis are excluded) are eligible for the study provided all following conditions are met:

Rash must cover < 10% of body surface area.

Disease is well controlled at baseline and requires only low potency topical corticosteroids.

F.2.4 There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency corticosteroids within the previous 12 months.

F.3 History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins.

F.4 Due to the potential risk for drug-drug interactions with etrumadenant, participants must not have had:

F.4.1 Treatment with known 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.

F.4.2 Treatment with known 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.

F.4.3 Treatment with known 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) within 4 weeks or 5 half-lives of the drug (whichever is shorter) prior to initiation of study treatment.

Refer to 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

F.5 No history of gastrointestinal perforation within 6 months of enrollment.

20.5. Study Treatment

20.5.1. Dosage and Administration: Etrumadenant, Sacituzumab govitecan, and Zimberelimab

Participants will receive etrumadenant + sacituzumab govitecan, with or without zimbelimab, as follows:

- **Etrumadenant:** 150 mg, oral, once daily continuous dosing (21-day cycle)
- **Zimberelimab:** 360 mg, IV, every 3 weeks (Day 1 of each 21-day cycle)
- **Sacituzumab govitecan:** 10 mg/kg, IV, on Days 1 and 8 of a 21-day cycle

Table 56 provides study intervention details.

Table 56: Etrumadenant + Sacituzumab Govitecan with or without Zimberelimab

Product Name [a,b]	Dosage Formulation	Dose Frequency	Dosage Level	Route of Administration	CCI
Etrumadenant	25 mg Capsule	QD	150 mg	Oral	
Etrumadenant	75 mg Tablet	QD	150 mg	Oral	
Etrumadenant [c]	50 mg Tablet	QD	100 mg	Oral	
Zimberelimab	C mg/mL solution	Q3W	360 mg	IV	
Sacituzumab govitecan	Supplied as 180 mg vials and reconstituted to a 10 mg/mL solution	Days 1 and 8 per 21-day cycle	10 mg/kg	IV	

IV = intravenous; Q3W = every 3 weeks; QD = once daily

[a] Product names are listed in order of administration.
[b] A participant may receive etrumadenant as a capsule or tablet but cannot receive both formulations.
[c] Etrumadenant 50 mg tablet dose strength will be used only for dose reduction to 100 mg, for applicable participants.

The dose of SG will be calculated based on actual weight at randomization (using weight obtained either at screening or on Cycle 1 Day 1) and remains constant throughout the study, unless there is a > 10% change in body weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

Sacituzumab govitecan is administered via IV infusion as described below with additional information available in the current version of the Pharmacy Manual. Sacituzumab govitecan should not be administered as an IV push or bolus. Sacituzumab govitecan is a cytotoxic drug and applicable special handling and disposal procedures should be followed.

Sacituzumab govitecan will be administered in 21-day cycles on Days 1 and 8; the next cycle should start a minimum 14 days after the Day 8 dose (ie, the Day 8 infusion will be counted as the first day of that 14-day period). On in-clinic study visit days, participants should take their etrumadenant dose in the clinic when directed by study personnel.

To assess participant compliance with self-administration of etrumadenant, participants will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Participants will be instructed to bring all unused study medication and their medication diary at specified study visits for assessments of compliance.

Etrumadenant + SG Administration

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of SG. Sacituzumab govitecan is administered via IV infusion as described below.

- Administer the first infusion over 3 hours. Subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated. Monitor the patient during, and for at least 30 minutes after infusion.
- An infusion pump may be used.

- IV bag types: Polyvinyl Chloride, Polypropylene / Polyethylene, Polyolefin, and Ethylene Vinyl Acetate can be used for infusion; protect infusion bags from light
- In-line filters and other ancillary infusion equipment are not recommended for use.
- Do not mix SG, or administer as an infusion, with other medicinal products.

Upon completion of the infusion, flush the IV line with 20 mL 0.9% Sodium Chloride Injection, USP.

Additional information regarding administration of etrumadenant and SG is described in the current version of the study pharmacy manual. Participants will be administered etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

Etrumadenant + Zimberelimab + SG

On infusion days, participants will hold etrumadenant administration until directed by study personnel. Etrumadenant should be taken at least 30 minutes prior to the start of IV infusion of zimberelimab. Administer zimberelimab IV infusion followed by a 30-minute observation (+15 min) interval. Following the zimberelimab observation period, sacituzumab govitecan should be administered as described above.

Additional information regarding administration of etrumadenant, Sacituzumab govitecan, and zimberelimab is described in the current version of the study pharmacy manual. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

20.6. Method of Treatment Assignment

Depending on the results of the safety and futility evaluations, approximately 40 participants per arm may be enrolled and/or randomized to one of the two arms below:

Etrumadenant + Sacituzumab govitecan

Etrumadenant + zimberelimab + Sacituzumab govitecan

If randomization is involved, a permuted block randomization method will be employed with stratification based on the presence of measurable disease at baseline.

20.7. Concomitant Medications

20.7.1. Permitted Therapy for Etrumadenant + Sacituzumab Govitecan with or without Zimberelimab

Concomitant medications or treatments may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as prohibited in Section 20.7.2.

- For applicable participants, continued ADT will be allowed for the duration of the study.
- Growth factor support for the management of treatment-emergent hematological toxicity as recommended according to the National Comprehensive Cancer Network/European Organization for Research and Treatment of Cancer guidelines.

- Anticoagulant therapy, including low-molecular-weight heparins, are allowed as clinically indicated. Applicable participants should undergo routine monitoring of coagulation parameters, including INR, according to institutional guidelines.
- In states and regions where marijuana is legal in a medical or recreational context, concomitant use for study participants may default to the investigator's judgment.

20.7.1.1. Premedication for Treatment with SG

Premedication is permitted for treatment with SG. Guidance for premedication for prevention of toxicities associated with SG is presented in Table 57.

Table 57: Guidance for Premedication and Prophylaxis for Toxicities Associated with Sacituzumab Govitecan

Potential Reaction	Premedication and Prophylaxis Guidance
Infusion-related reaction	Antipyretics and H1/H2 blockers should be administered before each SG infusion. Corticosteroids (hydrocortisone 50 mg or equivalent PO or IV) may be administered prior to infusions.
Nausea and vomiting	Premedication with a 2-drug antiemetic regimen is recommended. If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV). Anticipatory nausea can be treated with olanzapine.
Neutropenia	Complete blood counts must be obtained prior to each SG infusion and treatment should be administered if ANC meets the following criteria: Day 1: ANC $\geq$ 1500/mm^3 Day 8: ANC $\geq$ 1000/mm^3 The routine prophylactic use of growth factors is not required; however, prophylactic administration should comply with current NCCN/EORTC guidelines for use of growth factors.

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology, IV = intravenous; PO = orally; SG = Sacituzumab govitecan

20.7.2. Prohibited Therapy for Etrumadenant + Sacituzumab Govitecan with or without Zimberelimab

Use of the following concomitant therapies while receiving etrumadenant in combination with SG with or without zimberelimab is prohibited. The sponsor must be notified as soon as possible of any instances in which prohibited therapies are administered.

- Concurrent experimental or investigational therapy.

- Concurrent therapy intended for the treatment of cancer (including but not limited to chemotherapy, immunotherapy, and radiotherapy for reasons other than palliative care); however, supportive care agents, including denosumab, bisphosphonates, and hormonal agents are allowed.
- Systemic immunostimulatory agents (including but not limited to interferons and interleukin-2).
- Systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α agents) administered at > 10 mg/day prednisone or equivalent on a long-term basis; acute, low dose (≤ 10 mg/day prednisone or equivalent) systemic immunosuppressant medications for management of AEs are allowed after medical monitor approval has been obtained.
- Co-administration of:
  - 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, osaconazole, telithromycin, and voriconazole)

Use the following concomitant therapies with caution while receiving etrumadenant:

  - Strong inhibitors of UDP-glucuronosyltransferases (UGTs) of UGT1A1, 1A4, 1A9 and 2B4
  - Sensitive substrates of BSEP, MATE1 and OCT2
- Strong inhibitors or inducers of CYP2C8

Inhibitors or inducers of UGT1A1 should be avoided while receiving SG:

- SN-38 (the active metabolite of sacituzumab govitecan) is metabolized via human UGT1A1. Because of the potential to either increase (inhibitors) or decrease (inducers) the exposure to SN-38, concomitant administration of inhibitors or inducers of UGT1A1, with sacituzumab govitecan, should be avoided unless relevant in-vitro or in-vivo data suggest a lack of clinically significant impact on free SN-38 exposure or there are no therapeutic alternatives. Examples of UGT1A1 inhibitors and inducers are provided in the list below.

Inducers of UGT1A1	Inhibitors of UGT1A1	
Carbamazepine	Amitriptyline	Ketoconazole
Efavirenz	Atazanavir	Nilotinib
Ethinylestradiol	Dacomitinib	Ombitasvir
Lamotrigine	Dasabuvir	Paritaprevir
Phenobarbital	Deferasirox	Pazopanib
Phenytoin	Eltrombopag	Pexidartinib
Primidone	Enasidenib	Pibrentasvir
Rifampicin	Erlotinib	Probenecid
Ritonavir	Flunitrazepam	Propofol
Tipranavir	Flurbiprofen	Regorafenib
	Fostamatinib	Rucaparib
	Gemfibrozil	Silibinin
	Glecaprevir	Sorafenib
	Indinavir	Valproic acid
	Indomethacin	

Refer to 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.

20.8. Schedule of Activities

20.8.1. Screening Activities

Screening procedures for all participants are described in Section 7.1. There are no additional screening procedures for participants receiving etrumadenant + sacituzumab govitecan with or without zimberelimab.

20.8.2. On-Treatment Activities

The schedule of on-treatment activities is provided in Table 58.

Table 58: Schedule of Activities / TREATMENT PERIOD for Sacituzumab Govitecan-Containing Treatment Arms

	C1		C2				C3		C≥4	
Procedure [a]	**D1 [b]**	**D8 (±1)**	**D1**	**D2**	**D4**	**D8 (±1)**	**D1**	**D8 (±1)**	**D1**	**D8 (±1)**
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Physical examination [c]	X		X				X		X	
Vital signs [d]	X	X	X	X	X	X	X	X	X	X
12-lead ECG [e]	X		X							
ECOG performance status	X		X				X		X	
Hematology [f]	X	X	X			X	X	X	X	X
Clinical chemistry [f]	X	X	X			X	X	X	X	X
Thyroid tests [g]	X								X	
PSA	X		X				X		X	
Pharmacokinetics and Immunogenicity										
PK for etrumadenant [h]	Refer to Table 59 for blood collection time points for etrumadenant PK.									
PK for zimberelimab [h]	Refer to Table 59 for blood collection time points for zimberelimab PK.									
PK for SG [h]	Refer to Table 59 for blood collection time points for SG PK.									
Immunogenicity for zimberelimab [h]	Refer to Table 59 for blood collection time points for zimberelimab immunogenicity									
Immunogenicity for SG [h]	Refer to Table 59 for blood collection time points for SG immunogenicity									
UGT1A1 genotype [i]	X									
Pharmacodynamics and Exploratory Biomarkers										
Pharmacodynamics [j]	Refer to Table 60 for blood collection timepoint for pharmacodynamics assessments.									
Disease Response Evaluation										
Disease assessment	Includes CT scan, bone scan, MRI as applicable Perform every 12 weeks (±7 days) from the start of study treatment until disease progression (regardless of whether the participant is still receiving treatment), the start of new anticancer therapy, withdrawal of consent, death, or the end of the study.									
Study Treatment Administration										
Etrumadenant administration [k]	X	X	X	X	X	X	X	X	X	X
Zimberelimab administration [k]	X		X				X		X	
SG administration [k]	X	X	X			X	X	X	X	X
Medication diary review	X		X				X		X	

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenously; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSA = prostate-specific antigen; SAE = serious adverse event; SG=Sacituzumab govitecan

[a] Assessments on dosing days must be done prior to administration of study treatment unless otherwise specified. Preliminary assessment results should be available and reviewed by the investigator prior to initiation of the next study treatment cycle.
[b] Laboratory tests performed on Cycle 1 Day 1 need not to be repeated from the screening visit if they were performed within the previous 72 hours.
[c] Full physical examination including height and weight to be performed on Cycle 1 Day 1; thereafter, perform a symptom-directed exam.
[d] Vital signs to be collected are temperature, pulse rate, respiratory rate, and blood pressure. Refer to Section 7.3.4. On visit days where multiple assessments are planned at the same nominal time point, vital signs should be performed first followed by ECG(s) and then blood draws. On infusion days in Cycles 1 and 2, collect vital signs as follows: within 30 minutes prior to dosing with oral study treatment and 30 minutes (±5 minutes) after dosing with oral study treatment (prior to zimberelimab/SG infusion start), every 20 minutes (± 5 minutes) from the start of the zimberelimab/SG infusions until infusion end, and thereafter as clinically indicated until visit completion. For participants who experience an infusion-related or other hypersensitivity reaction in Cycle 1 or 2, the same vital sign collection frequency should be followed in subsequent cycles. In the absence of infusion-related or other hypersensitivity reaction in Cycle 1 or 2, perform vital sign assessment prior to and at the end of study treatment infusion (SG with or without zimberelimab), and as clinically indicated thereafter until the visit is completed. On non-infusion days, collect vital signs prior to dosing with etrumadenant.
[e] Perform as described in Section 7.3.3. For Cycles 1 and 2 only, on infusion days for applicable participants, single ECGs should be collected (unless clinically relevant abnormalities are noted): 1) within 30 minutes prior to administration of etrumadenant, 2) 30 minutes (±15 minutes) after administration of etrumadenant and prior to zimberelimab/SG infusion start, 3) 30 minutes (±15 minutes) after the end of the zimberelimab/SG infusion, and 4) for the etrumadenant +zimberelimab and SG cohort only 30 minutes (±15 minutes) after the end of the SG infusion . Beginning with Cycle 3, ECGs during the treatment period will be completed only if clinically indicated.
[f] Samples for all local laboratory assessments may be collected 24 hours prior to dosing, and samples for all central laboratory assessments must be collected at the designated times listed in the central laboratory manual.
[g] As defined in Section 7.3.8. Thyroid tests during study treatment are only applicable to participants who receive etrumadenant + zimberelimab + SG. Thyroid tests will occur on Day 1 of Cycles 1, 4 and then Day 1 of every 4 cycles thereafter.
[h] Blood for PK analysis will be assessed at the central lab. Refer to the central laboratory manual for additional details.
[i] Blood collected for UGT1A1 genotype testing will be assessed by the central lab.
[j] Blood will be collected for pharmacodynamics assessments as described in Table 60. Refer to the central laboratory manual for additional details.
[k] Refer to Section 20.5.1 regarding dosing instructions for etrumadenant + SG with or without zimberelimab. Assessments are based on the start of a new 3-week combination treatment cycle. New 3-week cycles of combination treatment will begin on the day IV therapy is administered (SG with or without zimberelimab as appropriate). In the absence of any dose delays, 1 experimental treatment cycle will be 21 days in duration. If the initiation of a new cycle is delayed in response to toxicity, 1 experimental treatment cycle may last more than 21 days but should not exceed a maximum of 42 days in duration. This window may also be applied to accommodate flexibility and ease of participant scheduling. Participants will be administered zimberelimab and etrumadenant for a maximum of 2 years following Cycle 1 Day 1.

20.8.3. Follow-Up Activities

Follow up activities will follow what is detailed in Section 7.2.

20.9. Study Procedure Descriptions for Sacituzumab Govitecan-Containing Treatment Arms

All study procedure descriptions should follow what is detailed in Section 7.3 with the exception of the following:

20.9.1. Pharmacokinetics

Whole blood samples will be collected for measurement of concentrations of etrumadenant, sacituzumab govitecan, and zimberelimab on study days detailed in Table 59. Timepoints (and the associated sampling windows) for blood collection for participants receiving etrumadenant + SG or etrumadenant + zimberelimab + SG can be found in Table 59. For SG PK assessments, the following analytes will be measured at the specified time points: free SN 38, total SN 38, and total antibody.

Based on emergent data, plasma/serum/whole blood/urine samples for PK and ADA analysis may be added or removed or the timing of sampling may be altered at the discretion of the sponsor and will be conveyed to investigators via an administrative letter. Additionally, ad hoc samples may be collected at any time if there is a suspected safety issue.

Instructions for the collection and handling of biological samples will be provided by the sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample for PK analysis must be recorded.

Blood collection for PK analysis will stop if a participant starts a new anticancer therapy.

Blood samples remaining after the bioanalyses may be analyzed for exploratory analyses, such as drug metabolism, and/or protein binding and/or other PK/pharmacodynamics work, as deemed appropriate by the Sponsor. The results of such exploratory work may only be included in the clinical study report (CSR) if deemed appropriate by the Sponsor or may be reported in a separate exploratory report.

Table 59: Blood Sampling Schedule for Etrumadenant, Zimberelimab, and Sacituzumab Govitecan Pharmacokinetics and Immunogenicity

Cycle	Day	Nominal Time	Collection Window	Etruma PK	Zim PK	SG PK	UGT1A1 Genotype	Zim Immunogenicity	SG Immunogenicity
Cycle 1	Day 1	Pre-dose[a]		X	X	X	X	X	X
		Zim EOI	+30 min		X				
		SG EOI	+30 min	X		X			
	Day 8 (±1)	Pre-dose [a]		X		X			
		SG EOI	+30 min	X		X			
Cycle 2	Day 1	Pre-dose [a]	-30 min	X	X	X		X	X
		Zim EOI	+30 min		X				
		SG EOI	+30 min	X		X			
		3 hrs after SG EOI	±20 min	X[b]		X[b]			
	Day 2	24 hrs after SG EOI	±2 hrs	X[b]		X[b]			
	Day 4	72 hrs after SG EOI	±2 hrs	X[b]		X[b]			

Table 59: Blood Sampling Schedule for Etrumadenant, Zimberelimab, and Sacituzumab Govitecan Pharmacokinetics and Immunogenicity

Cycle	Day	Nominal Time	Collection Window	Etruma PK	Zim PK	SG PK	UGT1A1 Genotype	Zim Immunogenicity	SG Immunogenicity
	Day 8 (±1)	Pre-dose [a]	-30 min	X		X			
		SG EOI	+30 min	X		X			
Cycle 6	Day 1	Pre-dose [a]	-30 min	X	X	X		X	X
		Zim EOI	+30 min		X				
	Day 8 (±1)	Pre-dose [a]	-30 mins	X		X			
		SG EOI	+30 min	X		X			
Cycle 10	Day 1	Pre-dose [a]	-30 min	X	X	X		X	X
		Zim EOI	+30 min		X				
	Day 8 (±1)	SG EOI	+30 min	X		X			
Cycle 18	Day 1	Pre-dose [a]	-30 min	X				X	X
		Zim EOI	+30 min		X				
	Day 8 (±1)	SG EOI	+30 min	X		X			
Cycle 26 [c]	Day 1	Pre-dose [a]	-30 min	X				X	X
		Zim EOI	+30 min		X				

Table 59: Blood Sampling Schedule for Etrumadenant, Zimberelimab, and Sacituzumab Govitecan Pharmacokinetics and Immunogenicity

Cycle	Day	Nominal Time	Collection Window	Etruma PK	Zim PK	SG PK	UGT1A1 Genotype	Zim Immunogenicity	SG Immunogenicity
	Day 8 (±1)	SG EOI	+30 min	X		X			
EOT		One sample drawn any time during visit		X	X	X		X	X

EOI=end of infusion; EOT=end of treatment; PK=pharmacokinetics; Zim=zimberelimab

[a] The pre-dose blood sample will be taken prior to etrumadenant dosing and will be used as the pre-dose timepoint sample for etrumadenant, zimberelimab, and SG.

[b] Applies only to participants receiving etrumadenant + SG without zimberelimab. For etrumadenant and SG PK analysis, evaluable blood sample from up to 12 participants are needed. Once a sufficient number of participants provide samples for etrumadenant and SG PK, further blood collection for PK will cease.

[c] Blood will be collected for PK and immunogenicity analysis every 8th cycle from Cycle 26 onwards. Blood sample collection for immunogenicity analysis may be stopped 2 years post first dose.

20.9.2. Immunogenicity

Antibodies to Sacituzumab govitecan and zimberelimab will be evaluated in blood samples collected from applicable participants at the timepoints outlined in the schedule of activities (Section 7.1, Section 7.2, and Section 20.8.2) and Table 59. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

Serum samples will be assessed using a validated assay by the sponsor or central laboratory designee for antibodies binding to SG and zimberelimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of SG and zimberelimab and evaluate neutralization activity. Anti-SG and -zimberelimab immune response analysis may also be conducted on PK samples collected at other timepoints noted in Section 7.1, Section 7.2; Section 20.8.2, and Table 59 based on emerging data.

20.9.3. Pharmacodynamics/Biomarker Assessments

Pharmacodynamic biomarkers will be collected from all participants at the timepoints outlined in the schedule of activities (Section 7.1, Section 7.2, and Section 20.8.2) and in Table 60. The exact dates and times of biomarker sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

As SG is a CCI directed ADC, the expression of CCI in tumors may be associated with response to SG. Measuring of CCI and correlating the expression with clinical response will help determine if patient selection may be beneficial in prostate cancer. Availability of tumor tissue from a site not previously irradiated will be required as part of the study eligibility evaluation (Section 5.1). It is expected that pretreatment tumor samples (baseline fresh [preferred] or archival [within 24 months of screening] will be obtained from all participants with measurable disease (at least 2 lesions; Section 20.4.1) within a given treatment arm at the timepoints outlined in the schedule of activities (Section 7.1, Section 7.2, and Section 20.8.2). The exact dates of sampling must be recorded on the laboratory requisition form. Refer to the central laboratory manual for sample collection and processing requirements. Collected samples must be stored and shipped under specified controlled conditions at the temperatures indicated in the central laboratory manual.

The biomarker objectives of this study are exploratory. Evaluation of baseline levels and/or changes with study treatment may be performed on peripheral blood samples and tumor tissue to determine association with clinical outcomes, including clinical response and resistance, and to inform development of diagnostic tests related to use of etrumadenant-based combination therapy for the disease under study. Biomarker scope may include but is not limited to assessment of:

- DNA
- RNA

- Protein (eg, enzymes, cytokines, antibodies, and/or markers associated with immune characteristics and activation or cancer)
- Immune cell profiling (eg, immune cell phenotyping, enumerations, and/or activation state)

Details regarding sample collection, storage, and analysis, data protection, and consent and withdrawal of consent to future use of samples is provided in Section 7.3.11.

Table 60: Blood Collection Schedule for Etrumadenant, Zimberelimab and SG Pharmacodynamics

Cycle	Day	Nominal Time	PD*
Cycle 1	Day 1	Pre-dose[a]	X
Cycle 2	Day 1	Pre-dose[a]	X
	Day 8 (±1)	Pre-dose[a]	X
Cycle 3	Day 1	Pre-dose[a]	X
Cycle 4	Day 1	Pre-dose[a]	X
Cycle 5	Day 1	Pre-dose[a]	X
EOT			X

PD=pharmacodynamics
[a] Pre-dose of Etrumadenant

Refer to the central laboratory manual for additional details.

20.10. Dose Modification and Safety Management

The safety plan for participants in an etrumadenant and zimberelimab treatment arm may be predicted based on the single-agent pharmacodynamic mechanism of action as well as results from nonclinical studies and clinical trials with etrumadenant or other adenosine receptor antagonists and zimberelimab or other anti-PD-1 antibodies (ie, class effects), respectively. The combination of etrumadenant + zimberelimab may exacerbate the frequency and/or severity of AEs reported with either agent alone or may result in nonoverlapping toxicity. The anticipated important safety risks are outlined below. Refer to the investigator brochure for detailed safety information from the ongoing clinical programs of etrumadenant and zimberelimab.

Dose/dosage adjustment should be overseen by the investigator. All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgment in the management of toxicities and dose modifications.

20.10.1. Dose Modifications for Etrumadenant, SG, and Zimberelimab

20.10.1.1. Dose Modifications for Etrumadenant

Dose modifications for etrumadenant are permitted. However, participants who require etrumadenant treatment interruption or dose reduction in Cycle 1 will be replaced.

For management of drug-related toxicities, the dose of etrumadenant capsules may be reduced up to 2 times as outlined in Table 61 and 2 times for tablets, as outlined in Table 62. 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.

Table 61: Recommended Dose Reductions for Etrumadenant Capsules

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant capsules	150 mg	100 mg	75 mg

Table 62: Recommended Dose Reductions for Etrumadenant Tablets

	Initial Dose	First Dose Reduction	Second Dose Reduction
Etrumadenant tablets	150 mg	100 mg	75 mg

20.10.1.2. Dose Modifications for SG

Table 63 summarizes recommendations for SG dose reductions and discontinuations for treatment-related toxicities.

Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity. Leukopenia or lymphopenia in the absence of neutropenia does not require dose modification. The SG dose must not be re-escalated following a dose reduction.

Table 63: Recommended Dose Modification Schedule for Sacituzumab Govitecan

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days, OR Grade 3 to Grade 4 febrile neutropenia, OR At time of scheduled treatment, Grade 3 or Grade 4 neutropenia that delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer G-CSF
	Second	50% dose reduction
	Third	Discontinue treatment
At time of scheduled treatment, Grade 3 or Grade 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR Any Grade 3 or Grade 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grade 3 or Grade 4 nonhematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or Grade 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose by 2 or 3 weeks for recovery to ≤ Grade1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3 or Grade 4 nonneutropenic hematologic or nonhematologic toxicity that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-related toxicities		
Grade 2 or Grade 3 infusion-related reaction despite optimal management	Recurrent	Discontinue treatment
Grade 4 infusion-related reaction	First	Discontinue treatment

G-CSF = granulocyte colony stimulating factor; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

Refer to Section 8.1.4 for the NCI-CTCAE severity grading details.

20.10.1.3. Dose Modifications for Zimberelimab

There will be no dose modifications allowed for zimberelimab in this study.

20.10.2. Study Treatment Interruptions for Etrumadenant, Zimberelimab, and SG

Treatment interruptions of etrumadenant, zimberelimab and SG are allowed throughout the study for no more than 42 days. Holding of one 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 treatments. Appropriate documentation is required regarding the drug to which the investigator is attributing the AE. If, in the opinion of the investigator, the toxicity is related to the entire combination of etrumadenant + SG with or without zimberelimab, then all drugs should be held.

If etrumadenant, zimberelimab, SG, or the combination has been withheld > 42 days, then all study treatment should be permanently discontinued unless the participant is likely to derive clinical benefit from single agent or combination therapy use, as determined by the investigator after discussion with the medical monitor.

SG may be interrupted based on ANC as described in Table 57.

Treatment interruptions for reasons other than resolution of toxicities/procedures are not permitted outside of the permitted visit windows.

20.10.3. Management Guidelines for Adverse Events from Treatment with Etrumadenant, Zimberelimab, or SG

Guidelines for the management of participants who experience specific AEs are provided in Table 64 for participants receiving etrumadenant and zimberelimab. In addition, guidelines for the management of participants who experience dermatologic toxicities associated with zimberelimab or etrumadenant are provided in Table 65 and Table 66, respectively.

The major toxicities of SG are expected to be gastrointestinal symptoms and neutropenia. Premedication and prophylaxis for the prevention of SG-associated toxicities is described in Section 20.7.1.1. Management of toxicities should be in accordance with best clinical practices, standard institutional guidelines, and current ASCO/ESMO guidelines. SG administration should be withheld for Grade 3 nausea or Grade 3 or Grade 4 diarrhea or vomiting at the time of the scheduled treatment administration and resume SG when resolved to ≤ Grade 1. For toxicities not specifically addressed in Table 64, dosing may be delayed for > Grade 2 toxicities for a maximum of 3 weeks per investigator assessment. If the toxicity has improved to ≤ Grade 2, the dose should be administered at that time. For a toxicity that delays Day 8 dosing, if dosing is delayed for more than 1 week, dosing should resume as Day 1 of next cycle to minimize treatment gap. Regardless of whether the Day 8 dose is delayed for toxicity, there should be a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

All patients will be closely monitored over the course of their treatment and aggressively medically managed, including dose reduction and interruption, to prevent the need for treatment discontinuation and serious complications of these toxicities. All efforts to avoid dose reduction should be taken to address toxicity prior to initiation of dose reduction.

Instructions for dose modification and discontinuation of SG for treatment related toxicities are provided in Section 20.10.1.2 and instructions for treatment delays are provided in Section 20.10.2.

For AEs in which management guidelines are not provided, participants should be managed, and study treatment should be modified as deemed appropriate by the investigator according to best medical judgment.

Table 64: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant with or without 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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.[4,5] Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care.
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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	Grade 3 ALT/AST > 5 × ULN but ≤ 20 × ULN	**For suspected <u>non</u>immune-mediated transaminase elevations:** Withhold etrumadenant and zimberelimab for up to 42 days. Monitor LFTs at least weekly for a minimum of 4 weeks until transaminases return to < 3 × ULN or baseline. Consider participant referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction (Table 31) and resume zimberelimab.[1,2,4] If not, permanently discontinue etrumadenant and zimberelimab and contact medical monitor.[3,5] **For suspected immune-mediated transaminase elevations:** Permanently discontinue zimberelimab. Withhold etrumadenant for up to 42 days. Consider participant 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 42 days, taper corticosteroids over ≥ 1 month and resume etrumadenant with a 1-level dose reduction.[1,2,4] If not, permanently discontinue etrumadenant and contact medical monitor.[3,5]	
	Grade 4 ALT/AST > 20 × ULN	Permanently discontinue etrumadenant and contact medical monitor.[3] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.	Permanently discontinue zimberelimab and contact medical monitor.[5] For suspected immune-mediated transaminase elevations, follow Grade 3 management guidelines.
	ALT/AST > 3 × ULN with concurrent bilirubin > 2 × ULN	Permanently discontinue all study treatment and contact medical monitor.[3,5] Monitor liver function at least weekly until values return to baseline. Investigate causes for elevated bilirubin and initiate treatment according to institutional guidelines. <u>Exception</u>: Participants 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]

Table 64: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant with or without Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken
	Grade 3-4	Consider etrumadenant dose modification as clinically indicated, otherwise continue at the same dose.[2] Institute symptom-directed supportive care according to institutional guidelines.	Consider zimberelimab treatment interruption or permanent discontinuation as clinically indicated.[4,5] Refer to the NCCN 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 Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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 42 days, resume etrumadenant at the same dose level.[1] **Recurrent or persistent events:** If etrumadenant was withheld and event resolves to Grade 1 or better within 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	
	Grade 3	Withhold etrumadenant for up to 42 days after event onset. **For suspected immune-mediated events (including colitis):** Refer participant 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.[3,5] Refer participant 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.	

Table 64: Guidelines for Management of Participants who Experience Adverse Events While Receiving Etrumadenant with or without Zimberelimab

Event	Severity	Etrumadenant Action to be Taken	Zimberelimab Action to be Taken
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 42 days after event onset. If event resolves to Grade 1 or better within 42 days resume etrumadenant with a 1-level dose reduction.[1,2] If not, permanently discontinue etrumadenant and contact medical monitor.[3] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Continue zimberelimab at the investigator's discretion.
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Withhold zimberelimab for up to 42 days after event onset.[4] If event improves and medical monitor agrees that zimberelimab should be continued, resume zimberelimab; otherwise, permanently discontinue zimberelimab.[5]
Zimberelimab-related toxicities not described above	**Grade 1-2**	Continue etrumadenant at the same dose level.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	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 42 days, resume etrumadenant with a 1-level dose reduction.[1,2] Etrumadenant dose re-escalation is permitted at the investigator's discretion.	Refer to the NCCN Guidelines for the Management of Immune CPI-Related Toxicities for symptom-directed supportive care. Zimberelimab, if interrupted, may be withheld for up to 42 days after event onset.[4]
	Grade 4	Permanently discontinue etrumadenant and contact medical monitor.[3]	Permanently discontinue zimberelimab and contact medical monitor.[5]

[1] Etrumadenant may be withheld for a longer period (ie, >42 days after event onset). The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[2] The dose of etrumadenant can be reduced from 150 mg to 100 mg (ie, 1 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 participant receiving the 75-mg dose of etrumadenant, then that participant should discontinue etrumadenant.

[3] Resumption of etrumadenant may be considered in participants who are deriving benefit and who have fully recovered (to baseline or Grade ≤1) from the toxicity. Participants can be re-challenged with etrumadenant only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

[4] Zimberelimab may be withheld for a longer period (ie, >42 days after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be agreed upon by the investigator and the medical monitor.

[5] Resumption of zimberelimab may be considered in participants who are deriving benefit and have fully recovered from the event. Participants can be re-challenged with zimberelimab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 65: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1[a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue zimberelimab with intensified antipruritic therapy Consider holding in select cases	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For the select cases where treatment is held, consider resuming after symptoms have resolved to ≤ Grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Consider resuming after symptoms have resolved to ≤ Grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue zimberelimab	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume

Table 65: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Zimberelimab

Adverse Event	Severity	Assessment	Action Taken with Zimberelimab	AE Management	Resumption
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ Grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue zimberelimab	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ Grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

Table 66: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
Dermatologic Toxicity (including but not limited to rash, maculo-papular rash, and pruritus)	Grade 1 [a]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant	Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas	N/A
	Grade 2 [b]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Continue etrumadenant with intensified antipruritic therapy Cases of worsening rash, etrumadenant should be held for at least 7 days.	Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day	For worsening rash where treatment is held, hold for at least 7 days and resume only after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).
	Grade 3 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Hold etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Hold for at least 7 days and resume only after symptoms have resolved to ≤ Grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated).

Table 66: Guidelines for Management of Participants who Experience Dermatologic Adverse Events While Receiving Etrumadenant

Adverse Event	Severity	Assessment	Action Taken with Etrumadenant	AE Management	Resumption
	Grade 4 [c]	Total body skin exam, including mucosa Assess for history of prior inflammatory dermatologic diseases Consider biopsy if unusual features	Permanently discontinue etrumadenant	Treatment with high potency topical steroids to affected areas Prednisone 0.5-1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care.	Do not resume
Dermatologic Toxicity: Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) [d]	Grade 3	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume
	Grade 4	Urgent dermatology consultation: if unavailable, consider skin biopsy	Permanently discontinue etrumadenant	Prednisone or methylprednisolone 1-2 mg/kg/day (treat until symptoms improve to ≤ grade 1 then taper over 4-6 weeks). Consider IVIG (1g/kg/day in divided doses per package insert for 3-4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation	Do not resume

Note: Guidelines are referenced from the National Comprehensive Cancer Network (NCCN) Management of Immunotherapy-Related Toxicities version 4.2021 – September 27, 2021

[a] Macules/papules covering <10% BSA with or without symptoms (eg, pruritis, burning, tightness)

[b] Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritis, burning, tightness); limiting instrumental ADLs

[c] Macules/papules covering >30% BSA with or without symptoms (eg, pruritis, burning, tightness) limiting ADLs

[d] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10-30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and mucous membranes.

20.11. Collection of Pregnancy Information

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancies in female partners of male participants will be collected from the first dose of study treatment until 30 days after the last dose of etrumadenant, or 90 days after the last dose of zimberelimab or SG, whichever is longer.

20.12. Statistical Considerations and Analysis Plan

Unless otherwise specified, please refer to Section 9.

20.12.1. Sample Size Determination

This study is not designed with explicit Type I error and power considerations in mind. Unless otherwise specified, assessment of efficacy will focus primarily on measures of direct antitumor activity per RECIST v1.1 and/or PCWG3 criteria.

During Stage 1, approximately 15 participants will be enrolled into each SG-containing treatment arm. A safety evaluation in each treatment arm will be performed for approximately 6 participants treated with at least 1 dose of treatment based on their assigned study intervention, and completed safety follow-up assessments of at least 1 full treatment cycle. A rate of toxicity of <33% will be targeted, with toxicity being defined as the occurrence of either a treatment-related Grade 4 AE or a treatment-related Grade 3 AE that is not responsive to supportive care during Cycle 1. If 2 or more such events are observed, enrollment in that arm may not continue.

During Stage 1, a futility evaluation will be conducted in each treatment arm in order to guide continuation of enrollment from Stage 1 into Stage 2 for an additional enrollment of approximately 25 participants. To be evaluable for the futility evaluation, participants must have at least 1 post-baseline radiographic disease evaluation or at least 2 consecutive post-baseline PSA assessments measured at least 3 to 4 weeks apart to be considered evaluable for futility analysis. Futility gates for SG-containing arms will be anchored to existing standard of care historical control information for use in a beta-binomial Bayesian decision-making framework (Thall and Simon, 1994; Thall et al., 1995). Futility criteria will be assessed based on RECIST v1.1 and/or PCWG3. Additional details will be outlined in a separate IMC charter for internal data monitoring review.

20.12.2. Populations for Analysis

Please refer to Section 9.2.

20.12.3. Statistical Analyses

Please refer to Section 9.3.

20.12.4. Internal Monitoring Committee

Safety and futility evaluations of each SG-containing arm will be reviewed and conducted by an IMC that will meet to review accumulating safety and efficacy data and to make

recommendations regarding the conduct of the trial on an ongoing basis as part of data monitoring. Detailed safety and futility gating criteria will be outlined in a separate IMC charter for internal data monitoring review. The IMC will be composed of members from the sponsor or delegate, including, at a minimum, a clinician independent of the study team, the medical monitor, a safety representative, and a biostatistician. The IMC may bring in other internal or external scientific and clinical expertise as needed. Details of the IMC, including membership, timing, scope, and communication of committee recommendations are further described in the IMC charter as well.

21. PROTOCOL VERSION CHRONOLOGY

21.1. Version 1.0 (27 February 2020)

Original version.

21.2. Version 2.0 (09 March 2020)

Version 2.0 is applicable to all study sites.

The primary purpose of this amendment is:

- Clarify a typographical error for the secondary study endpoint related to pharmacokinetic objectives in Stage 1.

Text revisions resulting from this amendment are incorporated as follows:

- Protocol Synopsis (Section 1)
- Objectives and Endpoints (Section 3)

21.3. Version 3.0 (24 April 2020)

Version 3.0 is applicable to all study sites.

The primary purpose of this amendment is:

- Incorporate US FDA recommendations provided during initial review of IND 147652:
  - Due to the potential risk for drug-drug interactions with AB928, concomitant use of strong CYP3A4 inhibitors/inducers as well as transporter substrates (ie, BCRP and P-gp substrates with narrow therapeutic index) is now prohibited in all treatment arms both prior to and throughout study therapy
- Update safety follow-up time for the outcome of any pregnancy that occurs in female partners of study participants to align with sponsor standard practice
- Extend the window for collection and reporting of local laboratory assessments from 24 to 72 hours prior to dosing for greater flexibility and ease of participant scheduling
- Clarify that blood samples for PK and immunogenicity assessment are not applicable and therefore not required to be collected for participants in Stage 2 who receive study treatment with either enzalutamide or docetaxel monotherapy
- Evidence for CYP3A4 inducers to result in clinically relevant changes in docetaxel exposure is limited and suggests that the drug-drug interaction potential between AB928 and docetaxel is low (Goey et al., 2014). However, should emerging data from participants who receive AB928 + zimberelimab in combination with docetaxel suggest the potential for clinically relevant drug-drug interactions, this amendment clarifies that blood samples for AB928 PK assessment may also be used for docetaxel PK evaluation at the sponsor's discretion.

Text revisions resulting from this amendment are incorporated as follows:

- Prohibited Therapy for AB928 + Zimberelimab + Enzalutamide (Section 14.7.2)
- Prohibited Therapy for AB928 + Zimberelimab + Docetaxel (Section 15.7.2)
- Prohibited Therapy for AB928 + Zimberelimab (Section 16.7.2)
- Prohibited Therapy for AB928 + Zimberelimab + AB680 (Section 17.7.2)
- Prohibited Therapy for AB928 + AB680 (Section 18.7.2)
- Treatment Procedures for AB982 + Zimberelimab + Enzalutamide (Section 14.8.2)
- Treatment Procedures for AB928 + Zimberelimab + Docetaxel (Section 15.8.2)
- Collection of Pregnancy Information (Section 8.2.8)

21.4. Version 4.0 (13 November 2020)

Version 4.0 is applicable to all study sites.

The primary purpose of this amendment is:

Comply with the US FDA request provided during initial review of IND 147652 to identify an AB680 dose for use in combination with AB928 with or without zimberelimab. Emerging data safety, PK, pharmacodynamics, and clinical activity data from the ongoing study AB680CSP0002 have been included as supportive rationale.

Text revisions resulting from this purpose are incorporated as follows:

- Protocol Synopsis, Treatment Arms and Regimens (Section 1)
- Investigational Plan/Stage 1 (Section 4.1)
- Risk/Benefit Assessment for Etrumadenant + Zimberelimab + AB680 (Section 17.1.3)
- Dosage and Administration: Etrumadenant, Zimberelimab, AB680 (Section 17.5.1) including Table 27, footnote “b”
- Dose Modifications for Etrumadenant + Zimberelimab + AB680 (Section 17.9.1) including Table 30, footnote “a”
- Risk/Benefit Assessment for Etrumadenant + AB680 (Section 18.1.3)
- Dosage and Administration: Etrumadenant + AB680 (Section 18.5.1) including Table 32, footnote “b”
- Dose Modifications for Etrumadenant + AB680 (Section 18.9.1) including Table 35, footnote “a”

Other changes were made throughout the text to add explanatory language or to clarify some typographical errors as follows:

- Clarify that adenocarcinoma of the prostate must be confirmed by histology (Item # 4) in the general inclusion criteria for all participants.

- Specify that serum testosterone levels correspond to "total" levels of testosterone (Item #4) in the general inclusion criteria for all participants.
- Add serum (total) testosterone as a laboratory procedure to the schedule of activities for the screening period to confirm the general inclusion criterion #4.
- The acronym ASI (androgen synthesis inhibitor) was replaced by the acronym NHA (new hormonal agent) for the clarification of prior use of hormonal agents as part of inclusion/exclusion criteria specific to study treatment regimens.
- Clarify thyroid hormone testing is intended for "free" rather than albumin-bound T3 and T4.
- Clarify the screening window, "within Day -28 to -Day 1 prior to enrollment," instead of, "within 28 days" for the schedule of activities.
- To ensure the requisite data are available for Stage 2 decision gating, text was added to define participant eligibility for this interim analysis.
- Clarify the discontinuation from study treatment to exclude progression by PSA alone as per PCWG3 criteria, and to include symptomatic deterioration (eg, clinical progression) based on the treating physician's assessment.
- Clarification of the window time for the collection of PK samples on C1D8, C1D15 and C1D21 in the PK substudy.
- Clarify baseline as from the start of study treatment for the 12-week period for the postbaseline radiographic evaluations for disease and response assessments.
- Clarify the time reporting period for the collection of AEs and SAEs for AB680-containing regimens.
- Clarify that, in case of pregnancy, monitoring of the mother should continue until conclusion of the pregnancy and that the newborn should be monitored for up to 12 weeks for a healthy newborn or at least 1 year for a newborn with complications.
- Delete the blood collection for immunogenicity in the etrumadenant + AB680 treatment arm.
- Clarify the window for Day 1 of all cycles that is applicable to accommodate flexibility and ease of participant scheduling in all treatment arms.
- Modify the window from the previous 48 to 72 hours for laboratory tests on C1D1 that need not to be repeated from the screening visit, in footnote "a" of the schedule of activities (treatment period) of all treatment arms to be consistent with footnote "f."
- Clarify that the formulation information for etrumadenant tablets (for the PK substudy) may be found in the study pharmacy manual.
- Clarify that the AB680 dose mentioned in footnote "a" of the corresponding recommended dose reduction tables for AB680-containing treatment arms refers directly to the respective dosage and administration section that describes the AB680 dose.

- Clarify the number of ECGs to perform during the treatment phase (ie, single ECGs at each timepoint and triplicates only as indicated if abnormalities) in footnote “d” or “e” of the schedule of activities table for all treatment arms.

Text revisions resulting from these other changes are incorporated as follows:

- Note added to Figure 1 for Study Schema (Section 1.1)
- Table 1 in Stage 2 (Section 4.2)
- Inclusion Criteria (Section 5.1), Item #4
- Table 2 in schedule of activities/SCREENING (Section 7.1)
- Table 4 in Laboratory Assessments (Section 7.3.8)
- Disease and Response Assessment (Section 7.3.12)
- Discontinuation from Study Treatment (Section 7.4.1)
- Table 8 in Adverse Event Reporting Period (Section 8.2.1)
- Collection of Pregnancy Information (Section 8.2.8)
- Sample Size Determination (Section 9.1)
- Exclusion Criteria for Etrumadenant + Zimberelimab + Enzalutamide (Section 14.4.2)
- Table 13 in Treatment Procedures for Enzalutamide with or without Etrumadenant + Zimberelimab (Section 14.8.2)
- Crossover Procedures following Enzalutamide Monotherapy (Section 14.8.3)
- Inclusion Criteria for Etrumadenant + Zimberelimab + Docetaxel (Section 15.4.1)
- Table 19 in Treatment Procedures for Docetaxel with or without Etrumadenant+ Zimberelimab (Section 15.8.2)
- Crossover Procedures following Docetaxel Monotherapy (Section 15.8.3)
- Inclusion Criteria for Etrumadenant + Zimberelimab (Section 16.4.1)
- Table 24 in Treatment Procedures for Etrumadenant + Zimberelimab (Section 16.8.2)
- Inclusion Criteria for Etrumadenant + Zimberelimab + AB680 (Section 17.4.1)
- Table 28 in Treatment Procedures for Etrumadenant + Zimberelimab + AB680 (Section 17.8.2)
- Table 30 in Dose Modifications for Etrumadenant + Zimberelimab +AB680 (Section 17.9.1)
- Inclusion Criteria for Etrumadenant + AB680 (Section 18.4.1)
- Table 33 in Treatment Procedures for Etrumadenant + AB680 (Section 18.8.2)
- Table 35 in Dose Modifications for Etrumadenant and AB680 (Section 18.9.1)
- Study Treatment for the PK Substudy (Section 19.5)

- Table 38 in Treatment Procedures for the PK Substudy (Section 19.8.2)
- Table 39 in Treatment Procedures for the PK Substudy (Section 19.8.2)
- Footnote “a” in Table 13 (Section 14.8.2), Table 19 (Section 15.8.3), Table 24 (Section 16.8.2), Table 28 (Section 17.8.2), Table 33 (Section 18.8.2), Table 38 (Section 19.8.2).

In addition, the use of the generic name “etrumadenant” to replace “AB928” after International Nonproprietary Name (INN) implementation was inserted throughout the document, as applicable.

21.5. Version 5.0 (22 November 2021)

The primary purpose of this amendment was to update the toxicity management guidelines for treatment with zimberelimab and etrumadenant in response to a recent event of Steven’s-Johnson Syndrome. In addition, other corrections, updates, and clarifications were made.

Only major changes are reflected in this summary.

General:

- The sponsor’s medical monitor was updated.
- The dose of AB680 was confirmed as 100 mg (from data from study AB680CSP0002), where applicable.

Section 7.1**:** Schedule of Activities: Screening

- Table 2 footnote ‘d’ was corrected to include a window of Day -28 to Day -1.

Section 7.4.1**:** Discontinuation from Study Treatment

- An additional criterion was added for when participants should be discontinued from study treatment which included symptomatic deterioration based on investigator judgement.

Schedule of Activities:

- For all schedule of activities, where applicable, windows for ECG assessments were added and the frequency of ECGs was reduced from Cycle 3 on.
- For all schedule of activities, where applicable, windows for vital signs were clarified.
- For the SoAs for AB680 containing treatment arms only, a specification was made that ECGs must be collected on both Days 1 and 15 of the first 2 cycles.

Exclusion Criteria:

- Sections 14.4.2, 15.4.2, 16.4.2, 17.4.2, and 18.4.2: Clarification that potential DDI components must not have been used withing the prespecified timeframe (whichever is “shorter”).

Toxicity Management with Zimberelimab and Etrumdenant:

- Sections 14.9.3, 15.9.3, 16.9.3, 17.9.3, and 18.9.3 were updated to include the toxicity management of dermatologic toxicity, including SJS, associated with zimberelimab and etrumadenant administration.

Concomitant Medication (Prohibited Therapy for Etrumadenant):

- Sections 14.7.2, 15.7.2, 16.7.2, 17.7.2, and 18.7.2 were updated to include the prohibition of additional therapeutics when in combination with etrumadenant.

21.6. Version 6.0 (11 May 2022)

The primary purpose of this amendment is to add additional 2 treatment arms to the study as follows:

- Etrumadenant + SG, and
- Etrumadenant + zimberelimab + SG

Major updates are described below. All changes made in the body of the protocol are reflected in the protocol synopsis, where applicable.

The following sections were updated to include mention of the 2 new treatment arms:

- Section 4.1: Stage 1
- Section 4.2: Stage 2
- Section 5.1: Inclusion Criteria
  - In addition, Criterion #6 was updated to clarify that the criterion excludes the new SG-containing treatment arms.
- Section 5.2: Exclusion Criteria

In addition, the following changes were made:

Section 7.1 Schedule of Activities

- Table 2 footnote “e” was updated to reference Sections pertaining to biopsy requirements for inclusion in the study for SG-containing treatment arms.

Section 7.3.9: Pharmacokinetics

- A clarification was made detailing that blood remaining from PK analysis may be used for exploratory analyses.

Section 8.2: Reporting

- Table 8 was updated to include reporting requirements for treatment arms containing SG.

Updates to enable inclusion of 2 new treatment arms are captured in Section 20 which includes the following new sections specific to SG-containing treatment arms.

Section 20.1: Introduction

Section 20.2: Objective and Endpoints for Sacituzumab Containing Treatment Arms

Section 20.3: Investigational Plan

Section 20.4: Eligibility

Section 20.5: Study Treatment

Section 20.6: Method of Treatment Assignment

Section 20.7: Concomitant Medication

Section 20.8: Schedule of Activities

Section 20.9: Study Procedure Descriptions for Sacituzumab Containing Treatment Arms

Section 20.10: Dose Modification and Safety Management

Section 20.11: Collection of Pregnancy Information

Section 20.12: Statistical Considerations and Analysis Plan

21.7. Version 7.0 (11 Aug 2022)

The primary purpose of this amendment was to correct general eligibility criteria #9 that was inadvertently changed during Version 6.0 authoring. In addition, minor corrections/administrative changes were made which are not detailed below. All changes made in the body are reflected in the synopsis, as applicable.

Section 5.1: Inclusion Criteria

- Inclusion criteria #9 sub-criteria “f”, “g”, “h”, “h ‘i’”, and “j” were corrected by changing the sign from “≥” to “≤” when discussing the ULN threshold.

Section 5.4.1: Contraception Requirements

- The words “which include condom use” was removed from the contraception guidelines due to the fact that condom use does not meet criteria as a highly effective measure of contraception for male participants.

21.8. Version 8.0 (17 May 2024)

The primary purpose of this amendment was to include a maximum treatment duration of 2 years after Cycle 1 Day 1. The affected sections are listed below. In addition, minor administrative changes were made which are not detailed below. All changes made in the body are reflected in the synopsis, as applicable.

Section 2.2.4: Rationale for the 2-year Maximum Duration of Treatment for Resistant Castration Resistant Prostate Cancer

Section 4.2: Stage 2

Updates to remove ‘long term follow-up’ language included the following sections:

- Table 3 (Section 7.2) removal of the last column and footnotes ‘c’ and ‘d
- Removed Section 7.3.15

Section 7.4.1: Discontinuation from Study Treatment

Section 13: References

- Added references Antonarakis, Fizazi, Petrylak, and Yu

Section 14.5.1: Dosage and Administration: Etrumadenant, Zimberelimab, Enzalutamide

Section 15.5.1: Dosage and Administration: Etrumadenant, Zimberelimab, Docetaxel

Footnotes ‘m’ and ‘r’ in Table 13 (Section 14.8.2), footnote ‘m’ in Table 30 (Section 16.8.2), footnote ‘m’ in Table 36 (Section 17.8.2), footnote ‘l’ in Table 44 (Section 18.8.2), footnote ‘l’ in Table 52 (Section 19.8.2), and footnote ‘k’ in Table 58 (Section 20.8.2)

Section 14.8.3: Crossover Procedures following Enzalutamide Monotherapy

Section 16.5.1: Dosage and Administration: Etrumadenant and Zimberelimab

Section 17.5.1: Dosage and Administration: Etrumadenant, Zimberelimab, AB680

Section 18.5.1: Dosage and Administration: Etrumadenant + AB680

Section 19.5.1: Dosage and Administration: Etrumadenant and Zimberelimab

Section 20.5.1: Dosage and Administration: Etrumadenant, Sacituzumab govitecan, and Zimberelimab

Protocol ARC-6 Version 7.0
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