CLINICAL STUDY PROTOCOL: CP-MGC018-03
PROTOCOL AMENDMENT 5

Study Title:	A Phase 2, Open-Label Study of Vobramitamab Duocarmazine in Participants with Metastatic Castration-Resistant Prostate Cancer and Other Solid Tumors (TAMARACK)
Study Number:	CP-MGC018-03
Study Phase:	Phase 2
Product Name:	Vobramitamab duocarmazine (also known as MGC018)
NCT Number:	NCT05551117
EU CT Number:	2022-501078-20
Indication:	Advanced solid tumors
Coordinating Principal Investigator:	To be determined
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 USA +1 (301) 251-5172
Sponsor's Study Physician:	Refer to study contact list for current details

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Study Number: CP-MGC018-03

This clinical study protocol has been approved by the sponsor:

Signed: ***See Appended Electronic Signature Page*** Date: _____

Study Physician
MacroGenics, Inc.

Signed: ***See Appended Electronic Signature Page*** Date: _____

Study Biostatistician
MacroGenics, Inc.

LIST OF ABBREVIATIONS

The list of abbreviations of specialist terms does not include general scientific abbreviations of temperature, weight, and volume.

ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARAT	androgen receptor axis-targeted therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_t	area under the concentration-time curve until time t
AUC_{tau}	area under the concentration-time curve for a dosing interval
BID	twice daily
BOR	best overall response
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	coronavirus disease-2019
CR	complete response
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DCR	disease control rate
DoR	duration of response
eCRF	electronic case report form
EDC	electronic data capture
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EOTV	end of treatment visit
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HBV	hepatitis B virus
HCV	hepatitis C virus
HFS	hand-foot syndrome
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IRB	Institutional Review Board
IRR	infusion related reaction
IRT	interactive response technology
ITT	intention to treat
IV	intravenous(ly)
LTFU	lost to follow up
LVEF	left ventricular ejection fraction
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease

PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (oral)
PPE	palmar-plantar erythrodysesthesia
PPK	population pharmacokinetic(s)
PQC	product quality complaint
PR	partial response
PSA	prostate-specific antigen
PT	preferred term
Q3W	once every 3 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
Q12W	once every 12 weeks
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SD	stable disease
SOC	system organ class
SPP	statistical programming plan
SSE	symptomatic skeletal event
SUSAR	suspected unexpected serious adverse reaction
TBSE	total body skin examination
T_{max}	time to maximal concentration
ULN	upper limit of normal
US	United States
v	version
vc-*seco*-DUBA	valine-citrulline-seco-DUocarmycin hydroxyBenzamide-Azaindole (SYD980)

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**EU CT Number:** 2022-501078-20
Name of Product: Vobramitamab duocarmazine (MGC018)	
Study Title: A Phase 2, Open-Label Study of Vobramitamab Duocarmazine in Participants with Metastatic Castration-Resistant Prostate Cancer and Other Solid Tumors (TAMARACK)	
Study Number: CP-MGC018-03	
Study Phase: Phase 2	
Investigator(s)/Centers: The study will be conducted at approximately 70 centers in approximately 9 countries.	
Primary Objectives: **Part 1:** To evaluate the efficacy of vobramitamab duocarmazine in metastatic castration-resistant prostate cancer (mCRPC) at two dose levels as measured by radiographic progression-free survival (rPFS) by investigator assessment using Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. **Part 2:** To evaluate the efficacy of vobramitamab duocarmazine in select solid tumors as measured by investigator assessment of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.	
Secondary Objectives: Both Parts: • To characterize the frequency and severity of adverse events (AE) and overall tolerability observed with vobramitamab duocarmazine. Part 1 Only: • To evaluate the efficacy of vobramitamab duocarmazine as measured by prostate-specific antigen (PSA). • To evaluate the efficacy of vobramitamab duocarmazine in participants with RECIST-evaluable disease as measured by ORR and duration of response (DoR) by investigator assessment using PCWG3 criteria. • To evaluate the effect of vobramitamab duocarmazine on symptomatic skeletal events (SSEs). Part 2 Only: • To evaluate the efficacy of vobramitamab duocarmazine in participants with select solid tumors as measured by DoR and progression-free survival (PFS) by investigator assessment using RECIST v1.1.	
Study Treatments: Part 1: *Experimental Arm A* • Vobramitamab duocarmazine 2.0 mg/kg IV every 4 weeks (Q4W) *Experimental Arm B* • Vobramitamab duocarmazine 2.7 mg/kg IV Q4W Part 2: Vobramitamab duocarmazine 2.7 mg/kg IV Q4W (before 22Jul2024); now 2.0 mg/kg IV Q4W for 6 cycles	

Study Design:

Study CP-MGC018-03 is an open-label, two-part, Phase 2 study assessing the efficacy, safety, and tolerability of vobramitamab duocarmazine.

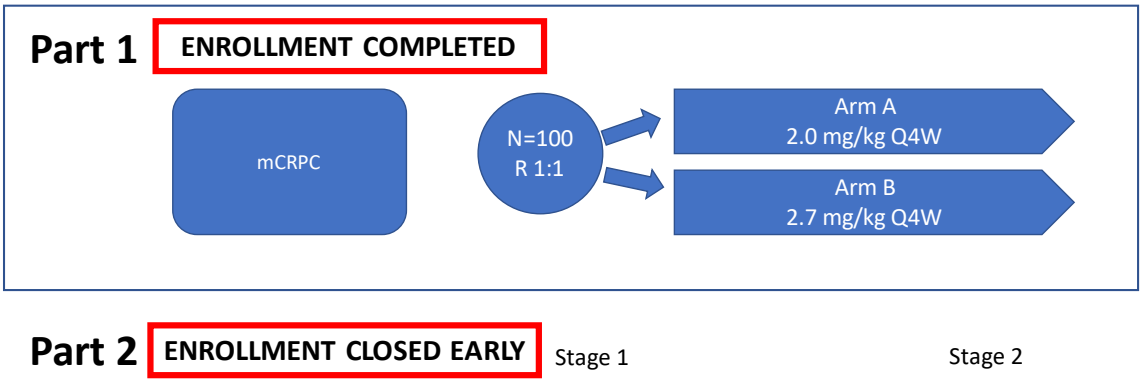
In Part 1 of the study, approximately 100 participants will be randomized 1:1 to one of two dose levels of vobramitamab duocarmazine (2.0 mg/kg Q4W and 2.7 mg/kg Q4W). Part 1 will enroll participants with metastatic castration-resistant prostate cancer (mCRPC) previously treated with one prior ARAT (abiraterone, enzalutamide, or apalutamide) for prostate cancer in either the metastatic or non-metastatic, castration-sensitive or castration-resistant setting. Participants may also have received up to one prior docetaxel-containing regimen for prostate cancer, and up to 3 total prior lines of therapy for mCRPC. Enrollment will use a central randomization scheme with stratified permuted blocks. Randomization will be stratified based on 1) presence of visceral disease (yes vs no), 2) prior taxane (yes vs no) and 3) region (United States/Canada vs other).

Per the Dear Investigator Letter, dated 22 July 2024, participants on treatment in Part 1 will discontinue vobramitamab duocarmazine, complete an EOTV, and enter the follow-up period.

Part 2 of the study consists of participants with unresectable, locally advanced or metastatic squamous carcinoma of the anal canal (anal SCC), head and neck squamous cell carcinoma (HNSCC), melanoma, squamous non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) whose disease has progressed following at least one prior line of standard systemic therapy for advanced or metastatic disease. Participants initially received vobramitamab duocarmazine 2.7 mg/kg Q4W. Per the Dear Investigator Letter, dated 22 July 2024, participants in Part 2 who were receiving 2.7 mg/kg must lower their dose to 2.0 mg/kg Q4W and will receive a maximum of 6 cycles of treatment. Each disease-specific cohort planned to use a Simon's 2-stage design and enroll up to approximately 40 participants if both stages were conducted (see schema below). Part 2 of the study was closed to enrollment prior to reaching the Stage 1 enrollment target(s).

An Independent Data Monitoring Committee (IDMC) will provide study oversight and evaluate cumulative clinical data at regular intervals.

The study treatment schema is presented below.



Number of Participants Enrolled:

In Part 1, the study planned to enroll up to approximately 50 participants on each arm. Total enrollment in Part 1 was planned to be up to approximately 120 participants to account for participants originally enrolled on the control arm under Amendment 1 (see full protocol for details). Due to unexpected rapid enrollment in Part 1, this part of the study enrolled a total of 182 participants.

Part 2 planned to enroll up to approximately 40 participants in each of 5 disease-specific cohorts for a total enrollment in Part 2 of up to approximately 200 participants. Part 2 of the study was closed to enrollment prior to reaching the Stage 1 enrollment target(s) due to feasibility reasons.

Planned total enrollment on the study was to be up to approximately 382 participants.

Study Population:

The study population consists of adult participants with confirmed, relapsed or refractory, unresectable, locally advanced or metastatic solid tumors.

Part 1: participants with mCRPC who progressed during or after receiving one prior ARAT (enzalutamide, abiraterone, or apalutamide) for prostate cancer in either metastatic or non-metastatic, castration-sensitive or castration-resistant setting. Participants may also have received up to one prior docetaxel regimen, but no other prior chemotherapy agents.

In Part 1, prior treatment with first generation anti-androgens (e.g., nilutamide, bicalutamide), oral ketoconazole, PARP inhibitor, immunotherapy (e.g., checkpoint inhibitor, sipuleucel-T), or radiopharmaceutical (e.g., radium-223 dichloride, lutetium-177 vipivotide tetraxetan) is permitted but not required. Participants with a known history of documented BRCA mutation (germline or somatic) are not eligible unless they received prior treatment with a PARP inhibitor where such treatment is available, indicated, and tolerated. Participants must have received ≤ 3 total prior lines of therapy for mCRPC.

Part 2: participants with locally advanced or metastatic anal SCC, HNSCC, melanoma, squamous NSCLC, or SCLC who have been intolerant to or progressed after at least one prior line of systemic therapy for advanced or metastatic disease.

Participants must have good performance status, adequate organ function, and no underlying medical or psychiatric condition impairing the participant's ability to receive, tolerate, or comply with planned study treatment dosing or study procedures.

Duration of Treatment and Study Duration:

Duration of Treatment

Study treatment will continue until protocol-specified progressive disease (PD), adverse event (AE) requiring discontinuation, physician decision, withdrawal of consent, allowed treatment duration is reached, or other treatment discontinuation criteria are met per protocol.

Per the Dear Investigator Letter, dated 22 July 2024, study treatment will not be administered for more than 6 cycles. Previously, study treatment was generally not to be administered for more than 26 cycles or longer than 2 years.

Study Duration and End of Study Definition

Study accrual was anticipated to occur over approximately 3 years. Due to unexpected rapid enrollment in Part 1 and closure of Part 2 to further enrollment, study accrual was less than 2 years. With a 6-month treatment duration and post-treatment follow up of approximately 6 months, the overall study duration is estimated to be approximately 3 years.

The end of the overall study is defined as date of last participant last visit.

Criteria for Evaluation:

Safety Assessments:

The safety assessment is based on AEs occurring from the first administration of study treatment until 30 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever comes first. Events that occur during the follow-up period will be captured and followed if they are considered by the investigator to be treatment related. The safety assessment is based on signs, symptoms, physical examination findings, and laboratory test results.

PD or events related to PD are considered efficacy endpoints, and not reported as AEs or SAEs. AEs and SAEs will be reported if it is unclear whether the event is due to PD.

Tumor Response Assessments:

Tumor response assessments will be determined using computed tomography (CT) and/or magnetic resonance imaging (MRI). Bone scans will be obtained, in addition to CT and/or MRI, to evaluate bone metastasis.

Target and non-target lesions will be designated per PCWG3 criteria (Part 1) or RECIST v1.1 (Part 2) at screening and evaluated approximately every 8 weeks for the first 24 weeks and every 12 weeks thereafter (or as clinically indicated) until PD, death, initiation of another anticancer therapy, withdrawal of consent, lost to follow up (LTFU), or end of study, whichever occurs first. After receipt of the last dose of study treatment, participants will enter a post-treatment follow-up period.

At each tumor response assessment time point, the overall tumor response status will be determined by investigators based on assessment of target and non-target lesions as well as appearance of any new lesions per PCWG3 criteria (Part 1) or RECIST v1.1 (Part 2).

Survival Assessments:

Survival status is assessed approximately every 12 weeks (± 14 days) for up to 6 months from last dose of study treatment or until withdrawal of consent, LTFU, death, or end of the study, whichever occurs first. Updated survival status may be requested by the sponsor at any time during the study.

PSA Assessment (Part 1 only):

PSA is assessed at baseline and Day 1 of each cycle (Q4W) while on study treatment. During the follow-up period, PSA is assessed approximately every 12 weeks (± 14 days) from the last tumor response assessment for up to 6 months from last dose of study treatment until PD, death, initiation of another anticancer therapy, withdrawal of consent, LTFU, or end of study, whichever occurs first.

Pharmacokinetic Assessments:

Serum concentrations of vobramitamab duocarmazine (conjugated and total antibody) will be measured using validated bioanalytical methods. Plasma concentrations of the payload, SYD986, will be measured using a liquid chromatography-tandem mass spectrometry assay. Analysis of concentration data will be used to estimate PK parameters for vobramitamab duocarmazine (conjugated and total antibody) and SYD986 (and metabolites if appropriate) in participants with sufficient concentration data to calculate PK parameters.

Immunogenicity Assessments:

Anti-drug antibodies (ADAs) against vobramitamab duocarmazine will be detected using validated assay methods. Samples positive for ADA will be saved for future evaluation of neutralizing antibody activity.

Biomarker Assessments:

Exploratory biomarker assessments are described in the protocol.

Statistical Methods:

A separate statistical analysis plan (SAP) and statistical programming plan (SPP) will further describe the details regarding statistical methods and govern the statistical analysis.

Sample Size Determination:

In Part 1, approximately 100 participants as planned per Amendment 2 will be randomized in a 1:1 ratio to each of the two vobramitamab duocarmazine arms. Randomization will be stratified by 3 stratification factors: 1) visceral disease (yes vs no), 2) prior taxane (yes vs no), and 3) region (United States/Canada vs other). The historic benchmarks for each vobramitamab duocarmazine arm to compare with are 25% PSA response rate and 8 months median rPFS.

Since the goal of Part 1 is to select one of two vobramitamab duocarmazine doses for further study in mCRPC, Simon's randomized Phase 2 selection design was used to determine the sample size for each treatment arm. The planned sample size of 50 per arm would provide 76% probability of correctly selecting the best dose assuming 66% and 59% rPFS rates at 6 months (equivalent to 10 vs 8 months median rPFS) for the two vobramitamab duocarmazine arms, respectively. For PSA response rate, the planned sample size of 50 per arm would provide 84% power to reject 25% null rate at 1-sided 0.1 alpha level for each vobramitamab duocarmazine arm at an alternative rate of 40%.

Part 2 of the study was closed to enrollment prior to completing the Stage 1 enrollment target(s). Part 2 originally planned to enroll approximately 200 response-evaluable participants, consisting of approximately 40 participants for each of 5 tumor-specific cohorts. For each cohort, Simon's 2-stage design is used to test null hypothesis H_0: $p \leq p_0$ vs alternative hypothesis H_1: $p = p_1$ at 1-sided significance level ≤ 0.1 (alpha) with the power of approximately 80%, where p_0 is the benchmark response rate representing a lack of tumor response and p_1 is the target response rate representing evidence of sufficient tumor response worthy of further development. Simon's 2-stage design parameters for each tumor-specific cohort are provided herein.

Analysis Populations:

Study analyses will be performed on the following populations:

- **Safety Population:** All participants who received any dose of study treatment. This population will be used to summarize safety data. Participants will be analyzed according to the actual study treatment received. This population will also be used to summarize baseline data for biomarker and immunogenicity analyses and for supplementary analyses of rPFS, PFS, and OS.
- **Intent-to-Treat (ITT) Population**: All participants*. Participants will be analyzed according to the study treatment assigned. This population will be used for summary of baseline data and analyses of rPFS, OS, and other efficacy endpoints where applicable.
- **Tumor Response Evaluable Population**: All participants* who received at least one dose of study treatment and had RECIST-evaluable disease per PCWG3 (Part 1) or RECIST v1.1 (Part 2) at baseline (i.e., participants with bone-only disease are excluded from this population). This population will be used for efficacy analyses related to tumor response and will be analyzed according to the study treatment assigned.
- **PSA Response Evaluable Population**: All participants in Part 1* who received at least one dose of study treatment, with a baseline PSA $\geq$ 2 ng/mL and at least one post-baseline PSA measurement. This population will be used to calculate and summarize PSA response rates according to the study treatment assigned.
- **PK Evaluable Population**: All participants who received at least one dose of study treatment, date and time of dose administration and relative PK sample collection are known, and have sufficient concentration data to derive at least one PK parameter. Participant data may be excluded from PK analysis at the discretion of the pharmacokineticist.
- **ADA Evaluable Population**: All participants who received at least one dose of vobramitamab duocarmazine and have at least one ADA sample.

* Note: participants in Part 1 who were assigned to the control arm prior to its removal in Amendment 2 and who were re-randomized to a vobramitamab duocarmazine arm will be analyzed as a separate cohort for safety and efficacy endpoints.

Efficacy:

Primary Efficacy Endpoint and Analysis

Part 1:

The primary efficacy endpoint of Part 1 is rPFS determined by the investigator. The rPFS is defined as the time from the date of randomization to the date of first documented PD per PCWG3 or death from any cause, whichever occurs first. For participants without an event of PD or death at the time of data cutoff for rPFS analysis, the rPFS will be censored at the date of the last tumor assessment.

The Kaplan-Meier method will be used to generate rPFS curves and estimate the median rPFS along with 95% confidence intervals (CIs) for each study treatment arm. The method of Brookmeyer and Crowley will be used to construct 95% CI for median rPFS. The 95% CIs for rPFS rates at 6, 8, and 12 months will be calculated by normal approximation after log(-log) transformation. A sensitivity analysis will be performed that includes documented PD or death as a rPFS event regardless of when it occurs during the study.

The analysis of rPFS will occur when all participants on Part 1 have been followed for rPFS for at least 6 months. The 2.0 mg/kg Q4W dose of vobramitamab duocarmazine will be selected for further study in mCRPC if it demonstrates promising efficacy, unless there is compelling additional activity at the higher dose and it has an acceptable safety and tolerability profile. Efficacy, safety, and exposure-response variables will inform the selection decision.

Part 2:

The primary efficacy endpoint of Part 2 is ORR as determined by the investigator per RECIST v1.1. ORR is estimated as the proportion of participants in the Tumor Response Evaluable Population who achieve a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). ORR and the 2-sided 95% exact binomial CI will be calculated for each disease-specific cohort.

Secondary Efficacy Endpoints and Analyses

Part 1:

PSA response is defined as a ≥ 50% decline in PSA from baseline with PSA confirmation ≥ 3 weeks after the first documented reduction in PSA of ≥ 50%. The PSA response rate will be calculated as the proportion of participants with a PSA response in the PSA response-evaluable population. PSA response rates at 8 weeks, 12 weeks, and at any time will be summarized. The 2-sided 95% exact binomial CI for PSA response rate will be calculated. The best PSA percent change from baseline will be presented by waterfall plot.

Number and percent of participants with their best overall response (BOR) will be summarized. ORR is estimated as the proportion of participants in the Tumor Response Evaluable Population who achieve a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) without prior confirmed bone progression per PCWG3. ORR and the 2-sided 95% exact binomial CI will be calculated for each treatment arm. DoR will be estimated using the Kaplan-Meier method.

Part 2:

DoR will be estimated using the Kaplan-Meier method. PFS is defined as the time from first dose date to the date of first documented PD per RECIST v1.1 or death from any cause, whichever occurs first. For participants without an event of PD or death at the time of data cutoff for PFS analysis, PFS will be censored at the date of the last tumor assessment. The Kaplan-Meier method will be used to generate PFS curves and estimate the median PFS, and PFS rates at 6, 8 and 12 months. The method of Brookmeyer and Crowley will be used to construct 95% CI for median PFS. The 95% CIs for PFS rate will be calculated by normal approximation after log(-log) transformation.

Safety:

Treatment-emergent AEs will be summarized in tables and listings. Tables will display the number and percent of participants that experience the given AE. AEs prior to the first dose of study treatment (e.g., due to study-related procedures) will be presented in listings only. AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded to the Medical Dictionary for

Regulatory Activities (MedDRA) dictionary. AEs will be summarized by system organ class (SOC) and preferred term (PT), relationship to study treatment, and highest severity.

Interim Analysis:

In Part 1, one futility analysis will be performed on each vobramitamab duocarmazine arm based on PSA response rate at 8 weeks on the first 20 PSA evaluable participants in each vobramitamab duocarmazine arm. At the futility analysis, if the probability of true PSA response rate for a vobramitamab duocarmazine arm greater than or equal to 40% is <10%, that is, if ≤ 25% (5/20) PSA response rate is observed, enrollment to that arm may stop unless other data warrant continuing enrollment.

2 BACKGROUND INFORMATION

2.1 Disease Background

2.1.1 Prostate Cancer

With an estimated almost 1.4 million new cases and 375,000 deaths worldwide, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020 (1). Incidence rates are 3-fold higher in developed than in developing countries (37.5 and 11.3 per 100,000, respectively), whereas mortality rates are less variable (8.1 and 5.9 per 100,000, respectively). The highest incidence rates are observed in Northern and Western Europe, the Caribbean, Australia/New Zealand, Northern America, and Southern Africa, with the lowest incidence rates in Asia and Northern Africa (1).

In the United States (US), prostate cancer is the most commonly diagnosed cancer in men and the second-leading cause of cancer-related death (2). An estimated 288,300 men will be diagnosed with prostate cancer in 2023, and 34,700 deaths will occur secondary to prostate cancer in the US. Among 3.1 million new cases of prostate cancer in the US during 2003–2017, localized, regional, distant, and unknown stage prostate cancer accounted for 77%, 11%, 5%, and 7% of cases, respectively (3).

Advanced prostate cancer is commonly treated with androgen deprivation therapy (ADT) to achieve castrate levels of testosterone (4). Treatment with ADT can cause remission of metastatic prostate cancer, as evidenced by PSA suppression in about 90% of patients. After a mean time of 2–3 years on ADT, however, the disease progresses despite continuous ADT. Metastatic prostate cancer has a 5-year survival rate of 29.3% (5).

2.1.1.1 Standard of Care in Metastatic Castration-Resistant Prostate Cancer

The therapeutic landscape for metastatic castration-resistant prostate cancer (mCRPC) has shifted toward use of newer approved treatments with life-extending therapies during earlier stages of advanced castration-sensitive prostate cancer. These newer approved therapies include abiraterone acetate (hereinafter referred to as abiraterone), enzalutamide, apalutamide, and darolutamide, which block androgen synthesis or block the androgen receptor, in combination with ADT, e.g., gonadotropin-releasing hormone (GnRH) receptor modulators. Despite the efficacy of these therapies, tumors progress to castration-resistant prostate cancer (CRPC).

The CRPC state is defined as disease progression despite castrate testosterone levels (serum testosterone ≤ 50 ng/dL or 1.7 nmol/L). Despite castrate levels of androgens, the androgen receptor remains active and other biologic pathways drive progression in CRPC. Progression of CRPC can present as either a continuous rise in serum PSA levels, progression of pre-existing disease, and/or the appearance of new metastases as defined by Prostate Cancer Working Group 3 (PCWG3) criteria. The median overall survival (OS) of CRPC from first line therapy is approximately 3 years (6).

This limited OS has led to the development of agents aimed at tumor reduction through cytotoxicity or further decreasing androgen production or blocking androgen receptor function. NCCN (Prostate Cancer Version 3.2022) preferred options for management of mCRPC include the FDA-approved taxanes (docetaxel and cabazitaxel), mitoxantrone, androgen receptor axis-targeted therapy (ARAT; abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and a radioligand (radium-223 dichloride). Additional FDA-approved products for specific targeted indications that occur in a small percentage of patients include pembrolizumab for microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR), or tumor mutational burden (TMB) ≥ 10 mutations per megabase, olaparib for homologous recombination repair (HRR) mutation, and rucaparib for BRCA mutation (**7**, **8**). The FDA also recently approved lutetium-177 vipivotide tetraxetan, a targeted radioligand, for treatment of patients with prostate-specific membrane antigen (PSMA)-positive mCRPC.

Although patients with mCRPC have treatment options, none of these options are curative. In the first-line setting, 15% receive docetaxel and 65% receive ARAT. There is no agreement on the optimal sequencing for these therapies with 54% of patients receiving an ARAT in the second line and 15% in the third line setting (**9**). Abiraterone and enzalutamide are commonly used back-to-back (e.g., abiraterone followed by enzalutamide, or enzalutamide followed by abiraterone). However, this approach is typically reserved for patients with few treatment options, given reported cross-resistance and limited clinical benefit with short duration of response (**9**). Median progression-free survival (PFS) and OS for mCRPC after approved first-line therapy ranges from only 2.8–8.0 and 11–15 months, respectively (**10**).

In the randomized, open-label, Phase 3 study of cabazitaxel versus ARAT (abiraterone or enzalutamide) in mCRPC patients previously treated with docetaxel and the alternative ARAT, median PFS was 4.4 months with cabazitaxel and 2.7 months with ARAT therapy [CARD study; NCT02485691; (**11**)]. Median OS was 13.6 months with cabazitaxel and 11.0 months with ARAT. Cabazitaxel is approved only after failure of a docetaxel-containing treatment regimen, and only 1–11% of patients receive cabazitaxel during the course of their disease (**9**), as many patients with mCRPC prefer to avoid additional chemotherapy.

Sipuleucel-T and radium-223 are alternative available therapies for patients with mCRPC, but have low real-world usage (**9**). Use of sipuleucel-T and radium-223 is either limited regionally (sipuleucel-T in the US) and/or restricted to certain indications such as patients with asymptomatic/minimally symptomatic disease (sipuleucel-T) or those with bone-only disease and symptoms (radium-223). Lutetium-177 vipivotide tetraxetan, a targeted radioligand therapy, plus best standard of care demonstrated significant improvement in OS compared to that of standard of care alone in patients with progressive PSMA-positive mCRPC who had received prior ARAT and taxane-based chemotherapy regimens (see PLUVICTO™ US prescribing information). Prior use of any of these agents is permitted in participants on this study.

Published retrospective studies indicate a median PFS of 2.7–4.6 months and median OS of 4.8–15.8 months for patients who received third-line therapy (**12**). With this limited impact on tumor outcomes there continues to be an unmet need for the treatment of advanced mCRPC.

2.1.2 Anal Carcinoma

Cancers of the anus, anal canal, and anorectum are relatively uncommon, accounting for < 1% of all new cancer diagnoses in the US and globally (**1**, **2**). An estimated 9760 new cases of anal cancer occurred in the USA in 2023, with 1870 deaths due to the disease (**2**). Incidence of these cancers has increased in recent years, with a 2.7% increase per year from 2001 to 2015 according to the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database (**13**). Similar trends have been observed in Western Europe, Australia, and South America (**14**). Approximately 90% of anal cancer cases are associated with HPV infection, with rising HPV infection rates contributing to the increased incidence of anal cancer (**14**).

Metastatic anal cancer is an incurable malignancy that has limited therapeutic options. NCCN guidelines recommend carboplatin and paclitaxel or other platinum-based chemotherapy regimens as first-line therapy. Nivolumab or pembrolizumab are recommended as second-line therapy, although neither has FDA approval for this indication (National Comprehensive Cancer Network [NCCN] Guidelines Anal Carcinoma version 3.203). NCCN guidelines make no recommendations for subsequent lines of therapy as no other regimens have been shown to be effective. Thus, there is a significant unmet medical need in this population.

2.1.3 HNSCC

Squamous cell carcinoma of the head and neck accounts for about 4% of cancers in the US. In 2023, an estimated 66,920 patients will be diagnosed annually in the US with approximately 15,400 deaths secondary to head and neck cancer (**2**). Globally, over 500,000 patients are diagnosed with this disease annually (**15**). Head and neck cancers are predominately of squamous histology (> 90%) (**16**). Infection with human papillomavirus (HPV), specifically HPV-16, is a risk factor for certain head and neck cancers, particularly oropharyngeal cancers involving the tonsils or base of the tongue (**17**, **18**).

Treatment for patients with locally advanced HNSCC remains unsatisfactory. Less than 40% of patients are cured with primary treatment with combination of radiation therapy and cisplatin-based chemotherapy. Survival is less than 20% at 2 years in patients with recurrent disease following treatment with radiochemotherapy. The combination of the EGFR inhibitor cetuximab with radiotherapy showed significant improvement in outcomes for patients with locally advanced disease when compared with radiotherapy alone. However, it failed to change the rate of distant metastasis. The combination of cetuximab with radiochemotherapy failed to improve progression-free survival (PFS) and overall survival (OS) in patients with advanced stage disease (**19**). In addition, there is evidence to suggest the role of immune checkpoints that limit T cell responses to tumors in HNSCC. Pembrolizumab is approved as a single agent or in combination with chemotherapy for patients with metastatic or unresectable, recurrent HNSCC and for patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy (**20**). However, there remains a need to identify new therapeutic options for patients with HNSCC.

2.1.4 Melanoma

In 2020, an estimated 324,635 new cases of melanoma of the skin were diagnosed globally, with 57,043 deaths due to the disease (**1**). In the US, estimates for 2023 were 97,610 new cases and 7,990 deaths attributable to melanoma of the skin (**2**). Among patients with advanced melanoma, sustained long-term overall survival (OS) at 5 years was observed in a greater percentage of patients who received nivolumab plus ipilimumab or nivolumab alone than in those who received ipilimumab alone (**21**). Even with recent advancements in treatment, the median progression-free survival (PFS) for patients with advanced melanoma on pembrolizumab is limited (**22**). Other approved targeted therapies for advanced melanoma have limited duration of disease control and include agents targeting BRAF V600-activating mutations, e.g., dabrafenib/trametinib (**23**). Although current treatment options provide a survival benefit in advanced disease, a need remains for improved treatment in advanced cases.

2.1.5 NSCLC

Lung cancer accounts for approximately 12% of all cancers in adults. In 2023, approximately 238,340 patients in the US are expected to be diagnosed with lung cancer, and an estimated 127,070 will die from this disease (**2**). NSCLC represents approximately 80% to 85% of all lung cancers and can be subclassified as squamous (~30%) or non-squamous (~70%).

Although novel therapies have become available for a proportion of patients with NSCLC, the mortality related to this disease remains high. A vast majority of patients with NSCLC have advanced stage or metastatic disease (Stage IIIB/IV) at time of initial diagnosis. Systemic therapy is required for treatment of these patients. First-line systemic treatment options for Stage IIIB/IV NSCLC patients are limited, with cisplatin-based doublet chemotherapy being the basis for most first-line treatment. Patients whose tumors harbor oncogenic mutations including EGFR, KRAS, ALK, ROS1, and BRAF are treated with the respective targeted agents (**24**). Pembrolizumab has been shown to significantly improve overall and progression-free survival (PFS) compared with chemotherapy and is FDA approved for use in patients with previously untreated NSCLC and a PD-L1 tumor proportion score (TPS) of 50% or greater (**25**). Approximately 30% of patients with NSCLC have a PD-L1 TPS of 50% or higher (**26**). Pembrolizumab is also approved for the treatment of previously treated patients with advanced NSCLC with TPS ≥ 1%. Nivolumab is approved for the treatment of previously treated patients with advanced NSCLC, irrespective of their TPS (**27**–**29**). Despite these approaches, therapy for patients with advanced disease remains largely non-curative. This study will limit enrollment to participants with squamous NSCLC due to the lack of availability of other targeted therapies in this patient population compared to non-squamous NSCLC, as well as the observed activity of other B7-H3 directed ADCs (e.g., DS-7300) in this subset of patients with lung cancer.

2.1.6 SCLC

Lung cancer is the most common cancer in the world, with an estimated 2.2 million new cases in 2020 (**1**). Lung cancer is also the most common cause of death from cancer in 2020 with 1.8 million deaths globally (**1**). Similarly, lung cancer is the most lethal cancer in the US, responsible for an estimated 127,070 deaths in 2023 (**2**).

Approximately 15% of all lung cancer cases are SCLC. It is a highly aggressive neoplasm that is strongly associated with cigarette smoking. Eighty percent of patients have extensive stage disease at diagnosis and a vast majority of patients with SCLC die of their disease, despite being initially responsive to chemotherapy. Standard frontline treatment for SCLC includes platinum-etoposide doublet chemotherapy in combination with a PD-1/PD-L1 monoclonal antibody (**30**). The majority of patients will progress, and the median survival for patients with extensive stage disease is 9.5 months (**31**). New therapeutic strategies are needed to improve the prognosis.

2.2 Rationale for Study

2.2.1 Rationale for Vobramitamab Duocarmazine in Metastatic Castration-resistant Prostate Cancer (Part 1)

Antibody-drug conjugates (ADCs) have demonstrated activity and received FDA approval for several solid tumors. However, ADCs are not yet approved for management of mCRPC. Alkylating agents (e.g., estramustine) have received FDA approval for treatment of prostate cancer; thus, targeted delivery of duocarmycin, an alkylating agent, by vobramitamab duocarmazine may offer a potential therapy for patients with mCRPC.

Efficacy of ADCs is derived from the targeting of proteins expressed by tumor cells with limited expression of these target proteins in normal tissues. Vobramitamab duocarmazine is an ADC that leverages the high level of B7-H3 expression in mCRPC to control tumor growth (see **Section 2.3**). Tumor responses and disease stabilization have been observed in participants treated with vobramitamab duocarmazine in the Phase 1 cohort expansion of CP-MGC018-01 study. Vobramitamab duocarmazine is designed to maximize the therapeutic index of the cytotoxic duocarmycin and has the potential to address the unmet need and provide a novel mechanism for treatment of mCRPC with a non-overlapping toxicity profile of other available therapies.

2.2.2 Rationale for Vobramitamab Duocarmazine in Other Advanced Solid Tumors (Part 2)

B7-H3 is a member of the B7-family of immunomodulatory molecules and is overexpressed in a wide range of solid tumors, with limited expression in normal human tissues (**32**, **33**). Tumor types on which B7-H3 expression has been observed include bladder cancer (**34**, **35**), breast cancer (**33**, **36**, **37**), cervical cancer (**38**), colorectal cancer (**39**–**42**), endometrial cancer (**43**), esophageal cancer (**44**, **45**), gastric cancer (**33**, **46**), liver cancer (**47**, **48**), melanoma (**33**, **49**, **50**), osteosarcoma (**51**), ovarian cancer (**33**, **52**–**54**), pancreatic cancer (**33**, **55**–**58**), prostate cancer (**33**, **59**–**61**), renal cell carcinoma (RCC) (**33**, **62**, **63**), NSCLC (**33**, **64**–**66**), SCLC (**67**, **68**), and HNSCC (**69**–**72**). In the majority of cancers, overexpression of B7-H3 associates with adverse clinical and pathological features of disease, increased risk of recurrence, and reduced survival.

The study population for Part 2 includes participants with advanced solid tumors known to express B7-H3 and who have been intolerant of or experienced disease progression on or following standard therapy. The tumor types selected for investigation have consistent B7-H3 expression and are considered likely to be responsive to the cytotoxic payload. Objective tumor responses were observed in participants with melanoma, NSCLC, and HNSCC following

administration of vobramitamab duocarmazine in Study CP-MGC018-01 (see **MGC018 Investigator Brochure [IB]**), and other B7-H3 targeting agents have seen encouraging and durable response rates of response in SCLC (**73**).

2.3 Background on Vobramitamab Duocarmazine

Vobramitamab duocarmazine (also known as MGC018) is an ADC targeted against B7-H3. Vobramitamab duocarmazine is comprised of the cleavable linker-duocarmycin payload, valine-citrulline-*seco*-DUocarmycin hydroxyBenzamide-Azaindole (vc-*seco*-DUBA; SYD980), conjugated through reduced interchain disulfides to the anti-B7-H3 humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody MGA017 (**74**). Vobramitamab duocarmazine has an average drug-to-antibody ratio of ~2.7, and an average molecular weight of ~150 kDa.

Vobramitamab duocarmazine is designed to bind to cell-surface B7-H3, internalize into cells, and release the cytotoxic duocarmycin. Duocarmycins represent a group of antitumor antibiotics produced by *Streptomyces* that bind to the minor groove of DNA. Following binding to cell-surface B7-H3 and internalization of vobramitamab duocarmazine through endocytosis, the peptide linker is cleaved by lysosomal proteases, such as cathepsin B. Subsequently, 2 self-elimination reactions occur on the duocarmycin moiety to generate *seco*-DUBA, which then spontaneously rearranges to form the activated duocarmycin drug (also known as DUBA or SYD986) that binds and alkylates DNA. The irreversible alkylation of DNA disrupts the nucleic acid architecture, ultimately leading to cell death. Due to the nature of the "cleavable" linker/payload, the protease-cleaved, activated DUBA is membrane permeable, and when released by dying cells, can cause death of neighboring tumor cells, irrespective of B7-H3 expression (**75**). Importantly, the bystander cytotoxic effect of the vc-*seco*-DUBA linker/payload may afford vobramitamab duocarmazine therapeutic benefit toward tumors with heterogeneous overexpression of B7-H3.

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the **MGC018 IB**.

The clinical development program for vobramitamab duocarmazine includes two ongoing MacroGenics-sponsored clinical studies (Study CP-MGC018-01 and Study CP-MGC018-02). Study CP-MGC018-01 is a Phase 1/2, first-in-human, open-label, dose escalation and cohort expansion study of vobramitamab duocarmazine monotherapy in participants with advanced solid tumors. Study CP-MGC018-02 is a Phase 1/1b, open-label, dose escalation and cohort expansion study of vobramitamab duocarmazine in combination with lorigerlimab in participants with advanced solid tumors. Please refer to the **MGC018 IB** for further details on the clinical experience with vobramitamab duocarmazine.

2.4 Dose Selection

2.4.1 Dose Selection for Part 1

Clinical pharmacokinetics (PK) of vobramitamab duocarmazine were evaluated after single and multiple dose administration at doses ranging from 0.5 mg/kg to 4.0 mg/kg in Study CP-MGC018-01. The PK of vobramitamab duocarmazine and its primary metabolite, SYD986,

were estimated using noncompartmental and population pharmacokinetic (PPK) methods. Dose proportionality and steady state PK were characterized based on data from Study CP-MGC018-01. A preliminary PPK model was developed and used for preliminary exposure-response analyses to support doses selected for evaluation in Study CP-MGC018-03.

As of 06-Dec-2021, safety data in Study CP-MGC018-01 Phase 1 dose escalation did not demonstrate significant differences in the incidence or severity of adverse events (AEs) across doses ranging from 2.0 mg/kg to 4.0 mg/kg. No maximum tolerated dose (MTD) was defined. As no dose level met the per protocol criteria for MTD, i.e., ≥ 2 dose-limiting toxicities, the maximum administered dose was 4.0 mg/kg, and 3.0 mg/kg was determined as the recommended Phase 2 dose (RP2D). The RP2D was evaluated in 5 different tumor types in the Study CP-MGC018-01 cohort expansion. On average, the incidence of AEs was higher for mCRPC than the other 4 tumor types enrolled in cohort expansion.

Antitumor activity was observed at vobramitamab duocarmazine doses ranging from 2.0 mg/kg to 4.0 mg/kg. As of 06-Dec-2021, two participants, one with non-small cell lung cancer and one with mCRPC, had a reduction in target lesion sum of over 20% at the 2.0 mg/kg dose level. At the 3.0 mg/kg dose level, there were ≥ 50% PSA reductions and stabilization of disease in mCRPC. One participant with melanoma had a partial response (PR) at the 4.0 mg/kg dose level. Efficacy, safety, and PK data supported the RP2D of 3.0 mg/kg administered intravenously (IV) once every 3 weeks (Q3W) in cohort expansion of Study CP-MGC018-01.

While efficacy was demonstrated between 2.0 mg/kg to 4.0 mg/kg vobramitamab duocarmazine administered Q3W, the safety assessment in mCRPC participants demonstrated a higher incidence and severity of AEs at the RP2D resulting in 73.2% of mCRPC participants having had at least one dose reduction and the actual mean dose administered was 2.5 mg/kg every 4 weeks (Q4W) during cohort expansion. The probability of dose modification increased with increased vobramitamab duocarmazine exposure, although there was considerable overlap in exposure between participants who did not and did have a dose modification. The incidence of toxicities, particularly palmar-plantar erythrodysesthesia (PPE)/hand-foot syndrome (HFS), may have a significant impact in participants with mCRPC due to the effect of PPE/HFS on activities of daily living (ADL). The probability of a participant experiencing PPE/HFS as well as severity of PPE/HFS at exposures corresponding to 2.0 mg/kg Q4W and 2.7 mg/kg Q4W are markedly reduced. Collectively, these data suggest the number of dose modifications will decrease along with a lower incidence and severity of toxicity at the predicted area under the concentration-time curve (AUC) corresponding to 2.0 mg/kg Q4W (approximately 100 µg/mL*day) and 2.7 mg/kg Q4W (approximately 140 µg/mL*day), which are in the range of target exposure (AUC = 62–188 µg/mL*day) associated with antitumor activity in tumor-bearing mice. Increasing the dosing interval from 3 weeks to 4 weeks should allow participants sufficient time to recover from toxicities. In summary, lower doses of vobramitamab duocarmazine and an increased dosing interval may delay the onset, incidence, and severity of AEs while maintaining antitumor activity with fewer dose modifications.

The vobramitamab duocarmazine doses and schedule selected, 2.0 and 2.7 mg/kg Q4W, are based on the observed safety and efficacy profile of vobramitamab duocarmazine at all doses tested to date and the predictable PK characteristics in the ongoing Phase 1 study.

2.4.2 Dose Selection for Part 2

Part 1 of this study is ongoing, and the optimal dose for participants with mCRPC has not yet been selected. However, preliminary data suggest that both 2.0 and 2.7 mg/kg Q4W are better tolerated than the 3.0 mg/kg Q3W regimen. As of 30-Aug-2023, 5 of 26 participants (19.2%) in Study CP-MGC018-03 experienced at least one AE of Grade 3 severity, regardless of causality, including leukopenia, neutropenia, atrial fibrillation, abdominal pain, asthenia, gastrointestinal infection, and cerebrovascular accident (1 participant each; 3.8%). Additionally, data from the expansion phase of Study CP-MGC018-01 demonstrated that participants with other tumor types have fewer AEs with vobramitamab duocarmazine treatment than participants with mCRPC. Given the emerging safety profile of the 2.7 mg/kg IV Q4W dose in prostate cancer, the observation that participants on Study CP-MGC018-01 with other tumor types had fewer AEs with vobramitamab duocarmazine treatment than those with mCRPC, and the desire to minimize the possibility of providing participants with an ineffective dose, the higher dose of 2.7 mg/kg Q4W was chosen initially for the Part 2 cohorts in other advanced solid tumors. Following review of available safety data and per the Dear Investigator Letter, dated 22 July 2024, participants in Part 2 who were receiving 2.7 mg/kg will receive a reduced dose of 2.0 mg/kg Q4W. To mitigate potential late onset toxicity, participants may not receive more than 6 doses of vobramitamab duocarmazine.

Refer to the **MGC018 IB** for additional information on the safety profile of vobramitamab duocarmazine.

2.5 Risk Benefit Assessment

The following sections provide a brief summary of the risks and potential benefits associated with vobramitamab duocarmazine administration.

2.5.1 Risk Assessment

Refer to the **MGC018 IB** for detailed information on the risks of vobramitamab duocarmazine.

Based on the clinical and non-clinical experience to date, important identified risks include neutropenia (including neutrophil count decreased), thrombocytopenia (including platelet count decreased), pleural effusion, and pericardial effusion. Identified risks include infusion related reaction (IRR), palmar-plantar erythrodysesthesia (PPE) syndrome, skin hyperpigmentation, anemia, and pyrexia. Important potential risks include ocular toxicity.

Fatal events of pneumonitis, pleural effusion, and cardiac events have occurred in Study CP-MGC018-03. As of 03-Jul-2024, 2 of 3 fatal cardiac events developed in participants with known pre-existing cardiovascular disease. A causal association between these events and vobramitamab duocarmazine has not been established. Refer to the **MGC018 IB** for detailed information.

The sponsor will continue to mitigate and monitor potential and identified risks based on protocol-mandated prophylactic measures and management guidelines, and close surveillance for early identification of potential risks.

2.5.1.1 SARS-CoV-2 (COVID-19) Guidance

The study investigators must ensure that their institution can provide the protocol-specified safety and efficacy assessments during the coronavirus disease-2019 (COVID-19) pandemic. All procedures should continue per protocol and associated study documents. Prospective protocol waivers are not permitted, and participants will not be included in this study without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations. Enrollment and continuing participation in the study should follow any national, local, or institutional guidance related to COVID-19.

Telemedicine visits may be considered, in alignment with national and local guidance, to monitor AEs and any other medical issues as necessary (see **Section 9**).

The risk of treatment delays associated with the COVID-19 pandemic is not increased by participation in the clinical trial. If participants are unable to receive study treatments at the enrolling site, continuing participation at another open site should be considered in consultation with the sponsor and in accordance with local and national guidance. Direct-to-participant shipment of oral study treatment should be considered per **Section 6.5.2**.

Remote monitoring of clinical data using electronic medical records will follow all local and national guidelines regarding the access to and protection of identifiable medical information.

As with any infection, confirmed cases of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection or suspected infection should be reported as AEs or SAEs (if seriousness criteria are met) per **Section 12.2**. All medications and treatment administered for these respective events and corresponding unscheduled visits must be entered in the electronic data capture (EDC) system.

No increased risk to participants is anticipated as a result of receiving SARS-CoV-2 vaccines, which are permitted during the study.

2.5.2 Benefit Assessment

Refer to the **MGC018 IB** for detailed information on preliminary antitumor activity observed with vobramitamab duocarmazine. Data from Study CP-MGC018-01 has demonstrated antitumor activity with vobramitamab duocarmazine treatment at doses of 2.0 mg/kg and above as measured by objective tumor reduction in multiple tumor types.

2.5.3 Overall Assessment

Part 1 of the study will enroll participants with mCRPC previously treated with one prior ARAT. Participants may also have received up to one prior docetaxel-containing regimen, but no other prior chemotherapy agents for prostate cancer, except a taxane-containing regimen administered for < 60 days as bridging to lutetium-177 vipivotide tetraxetan. Prior PARP inhibitor, immunotherapy (e.g., checkpoint inhibitor, sipuleucel-T), radiopharmaceutical (radium-223 dichloride, and lutetium-177 vipivotide tetraxetan) are allowed, as long as the participant has received no more than 3 total lines of therapy for mCRPC. Given the relatively poor prognosis

and lack of treatment options with demonstrated clinical benefit, this population is considered appropriate for studies of novel therapies.

While docetaxel has demonstrated clinical benefit for patients with mCRPC, and cabazitaxel for patients with mCRPC after prior ARAT and docetaxel, this study does not require participants to have received either agent. First, because some participants may not be eligible for or wish to receive chemotherapy, and second, due to concerns that cumulative bone marrow toxicity from more than one prior chemotherapy regimen may result in an unacceptable risk of severe cytopenias from vobramitamab duocarmazine. For patients with mCRPC who are not eligible for or do not wish to receive docetaxel and/or cabazitaxel, participation on a clinical trial of an investigational agent with preliminary signs of activity in mCRPC such as vobramitamab duocarmazine may represent a reasonable option. Understanding the impact of prior chemotherapy on selected vobramitamab duocarmazine-related toxicities (e.g., cytopenias, pleural and pericardial effusions, and hand-foot syndrome) will be very helpful in ensuring selection of an appropriate dose and patient population for further study if warranted by the data from Study CP-MGC018-03.

Part 2 of the study will enroll participants with relapsed or refractory, unresectable, locally advanced or metastatic solid tumors who have failed at least one standard of care systemic therapy for advanced or metastatic disease. These participants also have a relatively poor prognosis and lack of available treatment options with demonstrated clinical benefit; thus, this population is considered appropriate for studies of novel therapies.

Currently available clinical and non-clinical data for vobramitamab duocarmazine indicate an acceptable benefit-risk profile that supports the conduct of this Phase 2 study.

The protocol incorporates risk mitigation measures including eligibility criteria, participant monitoring, toxicity management, dose modification, discontinuation criteria, and interim analyses of each vobramitamab duocarmazine arm (Part 1) and tumor-specific cohort (Part 2) for futility. An Independent Data Monitoring Committee (IDMC) will provide study oversight and evaluate cumulative clinical data at regular intervals.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Primary Objective

Primary Objective	Estimand Description
Part 1: To evaluate the efficacy of vobramitamab duocarmazine in mCRPC at two dose levels as measured by rPFS by investigator assessment using PCWG3 criteria.	Population: Intent-to-treat
	Variable: rPFS
	Intercurrent events: 1) Subsequent anticancer therapy prior to rPFS event: censored 2) Missing ≥ 2 consecutive scheduled tumor assessments immediately followed by documented progression or death: censored 3) Study treatment discontinuation: ignored
	Summary measure: Kaplan-Meier estimates of rPFS
Part 2: To evaluate the efficacy of vobramitamab duocarmazine in select solid tumors as measured by investigator assessment of ORR per RECIST v1.1.	Population: Response evaluable
	Variable: ORR
	Intercurrent events: 1) Subsequent anticancer therapy: while not having started subsequent anticancer therapy 2) Disease progression: while not having evidence of progression 3) Death due to any reason: while being alive 4) Study treatment discontinuation: ignored
	Summary measure: Proportion of participants who achieve a BOR of confirmed CR or PR per RECIST v1.1

Abbreviations: BOR: best overall response; CR: complete response; ORR: objective response rate; PR: partial response; PCWG3: Prostate Cancer Clinical Trials Working Group 3; RECIST: Response Evaluation Criteria in Solid Tumors; rPFS: radiographic progression-free survival.

3.2 Secondary Objectives

Secondary Objectives	Outcome or Endpoint
To characterize the frequency and severity of AEs and overall tolerability observed with vobramitamab duocarmazine.	Frequency and severity of AEs, SAEs, and AEs leading to study treatment discontinuation.
To evaluate the efficacy of vobramitamab duocarmazine as measured by PSA (Part 1 only).	PSA response rate per PCWG3 criteria; time to PSA progression per PCWG3 criteria, duration of PSA response per PCWG3 criteria. PSA percent change over time and best PSA percent change.
To evaluate the efficacy of vobramitamab duocarmazine in participants with RECIST-evaluable disease as measured by ORR and DoR by investigator assessment using PCWG3 criteria (Part 1 only).	ORR and DoR per PCWG3 criteria.

Secondary Objectives	Outcome or Endpoint
To evaluate the effect of vobramitamab duocarmazine on SSEs (Part 1 only).	Time to first SSE.
To evaluate the efficacy of vobramitamab duocarmazine in participants with select solid tumors as measured by DoR and PFS by investigator assessment using RECIST v1.1 (Part 2 only).	DoR and PFS per RECIST v1.1.

Abbreviations: AE: adverse event; ADA: anti-drug antibody; DoR: duration of response; IV: intravenous; ORR: objective response rate; PCWG3: Prostate Cancer Clinical Trials Working Group 3; PFS: progression-free survival; PK: pharmacokinetics; PSA: prostate specific antigen; Q4W: once every 4 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SSE: symptomatic skeletal event.

3.3 Exploratory Objectives

Exploratory Objectives	Outcome or Endpoint
To explore the effect of vobramitamab duocarmazine dose on OS.	OS
To explore the relationship between B7-H3 expression and efficacy.	Relationships between B7-H3 expression and tumor response and/or other endpoints.
To characterize the PK of vobramitamab duocarmazine.	Concentrations and PK parameters for vobramitamab duocarmazine (and metabolites as appropriate).
To characterize immunogenicity of vobramitamab duocarmazine.	Incidence of ADA formation against vobramitamab duocarmazine.
To evaluate the exposure-response relationship between vobramitamab duocarmazine exposure and select efficacy and safety variables.	Logistic regression curves relating vobramitamab duocarmazine indices of exposure (i.e., C_{max} and AUC) to incidence of key efficacy (e.g., rPFS) and safety (AEs).

Abbreviations: AE: adverse event; AUC: area under the concentration-time curve; C_{max}: maximum concentration; OS: overall survival; rPFS: radiographic progression-free survival.

Results of exploratory objectives may not be included in the clinical study report (CSR) or database lock unless they represent meaningful findings.

4 STUDY DESIGN

4.1 Overall Study Design

Study CP-MGC018-03 is an open-label, two-part, Phase 2 study assessing the efficacy, safety, and tolerability of vobramitamab duocarmazine.

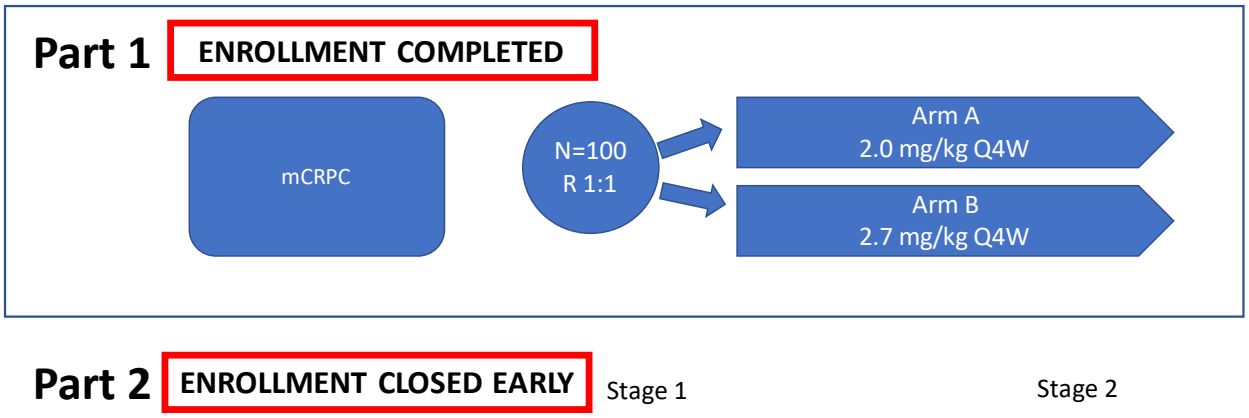
In Part 1 of the study, approximately 100 participants will be randomized 1:1 to one of two dose levels of vobramitamab duocarmazine (2.0 mg/kg Q4W and 2.7 mg/kg Q4W). Part 1 will enroll participants with mCRPC previously treated with one prior ARAT (abiraterone, enzalutamide, or apalutamide) for prostate cancer in either the metastatic or non-metastatic, castration-sensitive or castration-resistant setting. Participants may also have received up to one prior docetaxel-containing regimen for prostate cancer, and up to 3 total prior lines of therapy for mCRPC. Enrollment will use a central randomization scheme with stratified permuted blocks. Randomization will be stratified based on 1) presence of visceral disease (yes vs no), 2) prior taxane (yes vs no) and 3) region (US/Canada vs other).

Per the Dear Investigator Letter, dated 22 July 2024, participants on treatment in Part 1 will discontinue vobramitamab duocarmazine, complete an EOTV, and enter the follow-up period.

Part 2 of the study consists of participants with unresectable, locally advanced or metastatic anal SCC, HNSCC, melanoma, squamous NSCLC, or SCLC whose disease has progressed following at least one prior line of standard systemic therapy for advanced or metastatic disease. Participants initially received vobramitamab duocarmazine 2.7 mg/kg Q4W. Per the Dear Investigator Letter, dated 22 July 2024, participants in Part 2 who were receiving 2.7 mg/kg must lower their dose to 2.0 mg/kg Q4W and will receive a maximum of 6 cycles of treatment. Each disease-specific cohort planned to use a Simon's 2-stage design and enroll up to approximately 40 participants each if both stages were conducted. Part 2 of the study was closed to enrollment prior to reaching the Stage 1 enrollment target(s).

The study treatment schema is presented in **Figure 1**.

Figure 1 Study Schema



Abbreviations: HNSCC: head and neck squamous cell carcinoma; mCRPC: metastatic castration-resistant prostate cancer; NSCLC: non-small cell lung cancer; ORR: objective response rate; Q4W: once every 4 weeks; R: randomization; SCC: squamous cell carcinoma; SCLC: small cell lung cancer.

Participants will receive vobramitamab duocarmazine at their assigned dose until protocol-specified progressive disease (PD), AE requiring discontinuation, physician decision, withdrawal of consent, allowed treatment duration is reached, or other treatment discontinuation criteria are met per protocol.

Tumor assessments are performed Q8W for 24 weeks on study treatment then Q12W, regardless of dose delay, until PD. Tumor assessments are performed at the EOTV except if the prior assessment was ≤ 12 weeks of the EOTV and results are available for tumor response assessment.

Participants will be followed for safety throughout the study. Any participant who discontinues study treatment should complete an EOTV. The EOTV should be performed within 30 days following the last dose of study treatment whenever possible.

4.1.1 Part 1 Study Design

Part 1 of the study has pre-planned interim and final analyses. The interim analysis will be performed on each vobramitamab duocarmazine arm based on PSA response rate at 8 weeks when 20 PSA evaluable participants in each vobramitamab duocarmazine arm have been

enrolled and followed for at least 8 weeks. The final rPFS analysis will be conducted when all participants on Part 1 have been randomized and followed for rPFS for at least 6 months.

An IDMC will provide study oversight and evaluate cumulative clinical data at regular intervals (see **Section 14.2**). If at any time during Part 1 of the study it becomes apparent that one or both doses of vobramitamab duocarmazine have unacceptable toxicity, poor tolerability, or limited efficacy, that arm of the study may close to enrollment early while the other arm continues to enroll. If only one arm closes to enrollment, participants on that arm will stay on that arm and be analyzed according to their originally assigned arm, but be offered the opportunity to switch to the other dose.

Prior to Amendment 2, the study contained a control arm. Participants who enrolled prior to Amendment 2 and were randomized to the control arm may choose to stay on the control arm or discontinue study treatment. Participants who choose to discontinue study treatment may re-enroll on the study after implementation of Amendment 2 and be randomized to one of the vobramitamab duocarmazine arms if they meet eligibility criteria (including washout period). Participants assigned to one of the vobramitamab duocarmazine arms prior to Amendment 2 will stay on their assigned arm under Amendment 2 onwards with no changes to their study treatment.

4.1.2 Part 2 Study Design

Part 2 of the study was closed to enrollment prior to completing the Stage 1 enrollment target(s).

Part 2 planned to use Simon's 2-stage design for each tumor-specific expansion cohort. A futility assessment was to be conducted at the end of Stage 1 on a pre-specified number of response-evaluable participants in each tumor-specific expansion cohort (**Section 14.1** and **Section 14.9**). Enrollment was to be paused separately for each cohort while the analysis was conducted. Upon passing futility assessment, each cohort may have enrolled additional participants (up to a total of 37 to 42 response-evaluable participants per cohort; **Table 1**) to further evaluate antitumor activity, safety, tolerability, PK, and immunogenicity.

Table 1 Part 2 Cohort Enrollment (Closed to Enrollment)

4.2 Study Treatment Discontinuation

Participants will continue to receive study treatment as specified in the protocol until any one of the following conditions are met:

- Adverse event requiring treatment discontinuation
- Completed treatment per protocol
- Death
- Lost to follow up
- Physician decision
- Progressive disease – clinical progression
- Progressive disease – objective radiographic progression per PCWG3 criteria (Part 1) or RECIST v1.1 (Part 2)
- Protocol deviation requiring treatment discontinuation
- Study terminated by sponsor
- Participant decision to discontinue study treatment
- Participant withdrew consent from study

An isolated increase in PSA is not a condition for study treatment discontinuation for Part 1 participants. Participants with rising PSA levels only (i.e., in the absence of confirmed radiographic or clinical progression) will continue to receive study treatment per PCWG3 recommendations until radiographic PD (**76**).

The investigator must make every effort to confirm PD per PCWG3 criteria or RECIST v1.1, as appropriate. However, in instances when participants have progressive symptoms and signs of metastatic cancer for whom it is not possible or feasible to undergo radiologic assessment, investigators may discontinue study treatment due to "progressive disease – clinical progression." Use of this condition for discontinuing participants from study treatment should be restricted to cases in which it is not clinically appropriate for the participant to undergo further radiologic assessment and where there is clinical confidence for disease progression in the absence of radiographic confirmation. Special consideration should be given to ensure that other possible reasons, particularly AEs, are not a more accurate description of the reason for study treatment discontinuation in these cases.

By discontinuing from study treatment, the participant is not withdrawn from the study unless they withdraw consent to participate in any further follow up. Participants must be followed for progression (if discontinued in the absence of progression) and survival following treatment discontinuation, per the study schedule.

If a participant withdraws consent, they will be asked specifically if they are withdrawing consent for study treatment or for further participation in the study including follow up (e.g., survival follow up).

4.2.1 Lost to Follow Up

A participant is considered lost to follow up (LTFU) if the participant fails to return for scheduled visits and is non-responsive to repeated contact attempts. Site personnel are expected to make at least 2 attempts (e.g., by telephone call, text message, email, certified letter, etc.) to contact participants who fail to attend a scheduled visit or who the site is otherwise unable to follow. These contact attempts should be documented in the participant's medical record.

4.3 Participant Study Discontinuation

Participants who are no longer on treatment may continue to be followed on the study as specified in the protocol until any of the following conditions are met:

- Completed protocol-defined follow-up period (**Section 9.15**)
- Death
- Lost to follow up
- Study terminated by sponsor
- Participant withdrew consent from study

4.4 Definition of End of Study

The end of the overall study is defined as the date of last participant last visit.

Refer to **Section 16.10** for criteria related to discontinuation of the entire study.

5 ELIGIBILITY CRITERIA

Participants must meet all the inclusion criteria. Participants will be excluded from the study if they meet any exclusion criteria. No exceptions to these criteria will be granted by the sponsor.

5.1 Inclusion Criteria

1. Participant must provide signed informed consent prior to initiation of any study-related tests or procedures not part of standard of care. The participant must also be willing and able to comply with all study procedures.
2. Age ≥ 18 years old.
3. Participant must have one of the following cancer types:
    a. Part 1: Histologically confirmed adenocarcinoma of the prostate without evidence of neuroendocrine differentiation, signet cell, or small cell features.
    b. Part 2: Histologically confirmed squamous carcinoma of the anus, melanoma, HNSCC, squamous NSCLC, or SCLC.
4. Participant must meet the following criteria regarding cancer disease state:
    a. Part 1: Metastatic castration-resistant prostate cancer. Participants must have ≥ 1 metastatic (measurable or non-measurable per PCWG3) lesion that is present on magnetic resonance imaging (MRI), computed tomography (CT), or bone scan obtained ≤ 28 days prior to initiation of study treatment.
    b. Part 2: Locally advanced or metastatic, unresectable disease. Participants must have at least one measurable lesion per RECIST v1.1 that is present on MRI or CT obtained ≤ 28 days prior to initiation of study treatment. Participants with cutaneous or subcutaneous disease not assessable by imaging are eligible if the lesions are measurable with calipers. Lesions to be used as measurable disease for the purpose of response assessment must not reside in a field that has been subjected to prior radiotherapy or must have clearly progressed following radiotherapy.
5. Participant must meet the following criteria regarding recent cancer progression:
    a. Part 1: Tumor progression at study entry documented by PSA or imaging per PCWG3 criteria, defined as ≥ 1 of the following 3 criteria:
        i. Progressive disease in measurable disease.
        ii. Bone disease progression defined by the appearance of ≥ 2 new bone lesions.
        iii. PSA progression defined as ≥ 2 sequential rises in PSA obtained ≥ 1 week apart with a minimal starting value of ≥ 1 ng/mL. A PSA value ≥ 2 ng/mL is required at study entry.

b. Part 2: Tumor progression on or following their most recent systemic anti-cancer treatment as defined per RECIST v1.1. Participants who were intolerant of their most recent study treatment and did not have an objective response to that treatment are eligible even in the absence of disease progression on or following that treatment.

6. Participant must meet the following criteria regarding prior anti-cancer therapies:
    a. Part 1: Received one prior ARAT regimen (abiraterone, enzalutamide, or apalutamide) for prostate cancer. An ARAT regimen is defined as ≥ 60 days duration of therapy. ARAT regimen may have been received in either the metastatic or non-metastatic setting, and in either the castration-sensitive or castration-resistant setting. Participants who received a second ARAT regimen for < 60 days as bridging therapy while awaiting lutetium-177 vipivotide tetraxetan are also eligible. Participants who received an ARAT regimen because they were randomized to the control arm of this study under Protocol Amendment 1 and are re-enrolling on an experimental arm after implementation of Amendment 2 are also eligible regardless of the duration of that ARAT treatment.
    b. Part 2: At least one prior line of systemic therapy for unresectable or metastatic disease and no more than two prior lines of cytotoxic chemotherapy. Participants with HNSCC or melanoma must have received a prior PD-1 or PD-L1 inhibitor for advanced or metastatic disease.
7. Availability of archival or formalin-fixed paraffin-embedded (FFPE) tumor tissue sample. Participants may undergo a fresh tumor biopsy to obtain a specimen for testing if an archival tumor sample is not available. Determination of B7-H3 status is not required to be eligible. Participants with bone-only mCRPC without available tumor tissue and who are not amenable to fresh biopsy are eligible.
8. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
9. Life expectancy ≥ 24 weeks.
10. Part 1 only: Willing and able to maintain ongoing ADT with a GnRH/luteinizing hormone-releasing hormone modulator on study, or prior bilateral orchiectomy.
11. Acceptable laboratory parameters as follows:
    a. Platelet count ≥ $100 \times 10^3/\mu L$ without platelet transfusion and/or growth factors within 28 days prior to initiation of study treatment.
    b. Absolute neutrophil count ≥ $1.5 \times 10^3/\mu L$ without growth factors within 28 days prior to initiation of study treatment.
    c. Hemoglobin ≥ 9.0 g/dL without whole blood or red blood cell transfusion and/or growth factors within 28 days prior to initiation of study treatment.
    d. Alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 3.0 × upper limit of normal (ULN). For participants with hepatic tumor lesions, ALT/AST ≤ 5 × ULN.

e. Total bilirubin ≤ 1.5 × ULN except if attributed to Gilbert's syndrome. Participants with Gilbert's syndrome are eligible if conjugated bilirubin is within normal limits.

f. Creatinine clearance > 50 mL/min per Cockcroft-Gault equation.

g. Albumin ≥ 3.0 g/dL.

h. Part 1 only: Serum testosterone ≤ 50 ng/dl or ≤ 1.7 nmol/L.

12. People of childbearing potential (POCBP), defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause, and male participants with a partner who is a POCBP must agree to use highly effective methods of contraception according to **Section 8.1.3** from the time of consent through 27 weeks after last dose of study treatment. Participants must agree to abstain from sperm donation through 27 weeks after last dose of study treatment.
13. POCBP must have a negative highly sensitive urine or serum pregnancy test performed within 72 hours prior to initiation of study treatment. Participants must agree to abstain from egg donation during the study.
14. Not pregnant or breastfeeding, and must be willing to avoid initiating a pregnancy within the projected duration of the study, starting with screening visit through 27 weeks after the last dose of study treatment.

5.2 Exclusion Criteria

Clinical significance of underlying medical or psychiatric conditions is determined by the investigator. Sponsor consultation with the medical monitor is encouraged if there is a concern to clarify the exclusion criteria.

1. Any underlying medical or psychiatric condition impairing participant's ability to receive, tolerate, or comply with the planned treatment or study procedures.
2. Part 1: Prior receipt of up to one prior docetaxel-containing regimen for prostate cancer (in either the metastatic or non-metastatic, castration-sensitive or castration-resistant setting) is permitted. Participants who received an additional taxane-containing regimen (e.g., additional docetaxel or cabazitaxel) for < 60 days as bridging therapy while awaiting lutetium-177 vipivotide tetraxetan are also eligible. Other prior chemotherapy for prostate cancer is not allowed.

3. Part 1: Prior receipt of one or more of the following anticancer therapies is permitted but not required: first generation anti-androgens (e.g., nilutamide, bicalutamide), oral ketoconazole, PARP inhibitor, immunotherapy (e.g., checkpoint inhibitor, sipuleucel-T), or radiopharmaceutical (e.g., radium-223 dichloride, lutetium-177 vipivotide tetraxetan). However, participants must not have received > 3 total prior lines of therapy for mCRPC (bridging therapy followed by lutetium-177 vipivotide tetraxetan counts as one line). Participants who were randomized to the control arm of this study and are re-enrolling on an experimental arm after implementation of Amendment 2 are eligible regardless of the number of prior lines of therapy for mCRPC.
    a. Note: Participants with a known history of documented BRCA mutation (germline or somatic) are not eligible unless they received prior treatment with a PARP inhibitor where such treatment is available, indicated, and tolerated.
4. Another hematologic or solid tumor ≥ stage 1 malignancy that completed surgery, last dose of radiotherapy, or last dose of systemic anti-cancer therapy ≤ 2 years from first dose of study treatment. Participants who had curative therapy for localized malignancy are eligible.
5. Untreated, symptomatic central nervous system (CNS) metastasis. Participants with history of prior CNS metastasis must have been treated. The following criteria are exclusionary at the time of enrollment:
    a. Concurrent treatment for CNS disease (e.g., surgery, radiation, corticosteroids ≥ 10 mg prednisone/day or equivalent).
    b. Progression of CNS metastases on MRI or CT < 4 months after surgery or the last day of prior radiotherapy or systemic anti-cancer therapy for CNS metastases.
    c. Concurrent leptomeningeal disease or spinal cord compression.
6. Active viral, bacterial, or fungal infection requiring systemic treatment within 1 week of initiation of study treatment.
7. Known chronic hepatitis B virus (HBV) infection (defined by detectable HBV surface antigen and HBV DNA ≥ 500 IU/mL). **For Czech Republic and other countries where required by local authorities only**: HBV testing is required; testing should follow local clinical practice guidelines/standards.
    a. Participants with resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) are eligible.
8. Known current hepatitis C virus (HCV) infection (defined by detectable HCV RNA). Participants with a history of resolved hepatitis C with detectable HCV antibody are eligible. **For Czech Republic and other countries where required by local authorities only**: HCV testing is required; testing should follow local clinical practice guidelines/standards.

9. Known history of positive test for human immunodeficiency virus (HIV) unless all the following criteria are met:
    a. Cluster of differentiation (CD)4+ lymphocyte count ≥ 350/μL.
    b. HIV viral load (HIV RNA) < 400 copies/mL.
    c. Maintained on approved antiretroviral therapy for a minimum of 4 weeks.

    For Czech Republic and other countries where required by local authorities only: HIV testing is required; testing should follow local clinical practice guidelines/standards.
10. Prior autologous/allogeneic stem cell or tissue/solid organ transplant.
11. Known hypersensitivity to recombinant proteins, polysorbate 80, or any excipient contained in the drug formulation for vobramitamab duocarmazine or other study treatments.
12. Received one or more of the following anticancer treatments within the specified exclusionary time frame:
    a. Major surgery within 4 weeks prior to initiation of study treatment.
    b. Systemic cytotoxic anti-neoplastic therapy within 4 weeks prior to initiation of study treatment.
    c. ARAT within 4 weeks prior to initiation of study treatment.
    d. Investigational therapy within 4 weeks prior to initiation of study treatment.
    e. Small molecule targeted or kinase inhibitors within 5 half-lives prior to initiation of study treatment.
    f. Chimeric antigen receptor T-cell therapy within 4 weeks prior to initiation of study treatment.
    g. Radiopharmaceutical (e.g., radium-223 dichloride, lutetium-177 vipivotide tetraxetan) for mCRPC within 2 months prior to initiation of study treatment.
    h. Radiation therapy within 4 weeks prior to initiation of study treatment. Palliative, limited field radiation for symptom control to soft tissues or bone lesions is excluded within 2 weeks prior to initiation of study treatment.
    i. Part 1 only: Use of products that have published anti-prostate cancer activity and/or are known to decrease PSA levels (specifically, saw palmetto and pomegranate juice/extract) within 4 weeks prior to initiation of study treatment. Use of 5-alpha-reductase inhibitors is allowed as long as the participant has been on a stable dose for at least 2 months prior to study entry.
13. Prior treatment with any B7-H3 targeted agent for cancer.
14. Clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within 12 months prior to initiation of study treatment.

b. Stroke or transient ischemic attack within 12 months prior to initiation of study treatment.

c. Clinically significant cardiac arrythmia within 12 months prior to initiation of study treatment.

d. Uncontrolled hypertension: systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.

e. Congestive heart failure (New York Heart Association class II–IV).

f. Pericarditis.

g. Myocarditis.

h. Left ventricular ejection fraction (LVEF) < 50%.

i. Prolongation of corrected QT interval per Fridericia's formula (QTcF) > 480 milliseconds.

15. Clinically significant venous insufficiency (e.g., pain, skin tightness, skin changes of venous stasis, pitting edema not controlled with diuretics or compression stockings).
16. Clinically significant pulmonary compromise including pneumonia, pneumonitis, or a requirement for supplemental oxygen use to maintain adequate oxygenation, or history of ≥ Grade 3 drug-induced or radiation pneumonitis.
17. Evidence of pleural effusion. Asymptomatic trace pleural fluid without prior intervention (e.g., thoracentesis) is allowed.
18. Evidence of pericardial fluid or effusion. Trace pericardial fluid is exclusionary.
19. Evidence of ascites. Trace peritoneal fluid is allowed.
20. Unresolved toxicity > Grade 2 related to prior therapy (i.e., prior chemotherapy, radiation, immunotherapy, etc.).
21. Contraindications to the use of corticosteroid treatment.
22. Employees of MacroGenics, Inc.
23. Prisoners or other individuals who are involuntarily detained.
24. Vaccination with any live virus vaccine within 30 days prior to initiation of study treatment. Inactivated annual influenza vaccination and non-live SARS-CoV-2 vaccinations are allowed at any time.

6 STUDY TREATMENTS

6.1 Description of Dosing Regimens

An overview of study treatments to be administered during this study is presented in **Table 2**.

Table 2 Overview of Study Treatments

Product	Dose	Schedule	Route of Administration
Vobramitamab duocarmazine	2.0 mg/kg [a, b]	Once every 4 weeks	IV
Vobramitamab duocarmazine	2.7 mg/kg [a, c]	Once every 4 weeks	IV

a Prednisone 40 mg PO twice daily will be administered on the first 3 days of each cycle **after** administration of vobramitamab duocarmazine.

b Part 2 dosing regimen. Participants may receive a maximum of 6 cycles of treatment.

c Per the Dear Investigator Letter, dated 22 July 2024, participants in Part 2 who were receiving 2.7 mg/kg must lower their dose to 2.0 mg/kg Q4W.

Abbreviations: IV: intravenous; PO: orally; Q4W: every 4 weeks.

6.1.1 Vobramitamab Duocarmazine Dosing Regimen

Vobramitamab duocarmazine is administered Q4W at the assigned dose for each arm. Vobramitamab duocarmazine is administered as an IV infusion over approximately 60 minutes (-5 or +15 minute window). Do not administer vobramitamab duocarmazine as an IV push or bolus.

Dosing is based on actual body weight. An exception to weight-based dosing is made for participants weighing ≥ 100 kg; doses will be based on 100 kg for these participants. Refer to the pharmacy manual for instructions on weight-based dosing.

Participants on vobramitamab duocarmazine will be monitored on site for 2 hours following completion of Cycle 1 Day 1 infusion. Monitoring may be reduced to 1 hour following subsequent infusions if no IRR occurs. Participants also may be requested to stay on site to facilitate PK sample collection per **Appendix 2**.

For participants who enrolled on Part 1 prior to Amendment 2 and were randomized to one of the two vobramitamab arms, their dosing regimen will not change upon implementation of Amendment 2.

6.1.2 Comparator Product Dosing Regimen(s) (Part 1)

For participants who enrolled on Part 1 prior to Amendment 2, were randomized to the control arm, and wish to continue to receive abiraterone (with prednisone) or enzalutamide, refer to the local prescribing information for details on dosage and administration.

6.2 Method of Assigning Participants to Treatment Groups

Part 1

Eligible participants will be randomized centrally using interactive response technology (IRT). Instructions for randomization will be provided via IRT. Every effort should be made to minimize the time between randomization and initiation of study treatment. It is recommended that subjects commence study treatment as soon as possible after randomization.

Enrollment will use a central randomization scheme with stratified permuted blocks. Note: for stratification, visceral disease is defined as liver, lung, or other non-nodal soft tissue metastases.

Participants will be randomized in a 1:1 ratio between the two treatment arms:

1. Experimental arm A: vobramitamab duocarmazine 2.0 mg/kg IV Q4W
2. Experimental arm B: vobramitamab duocarmazine 2.7 mg/kg IV Q4W

Randomization will use the following 3 stratification factors:

1. Presence of visceral disease (yes vs no)
2. Prior taxane (yes vs no)
3. Region (US/Canada vs other)

Participants assigned to the control arm prior to its removal in Amendment 2 who would like to receive vobramitamab duocarmazine treatment may discontinue the study and be re-randomized to one of the vobramitamab duocarmazine arms after a 4-week washout period if they meet eligibility criteria. Participants assigned to one of the vobramitamab duocarmazine arms prior to Amendment 2 will stay on their assigned arm under Amendment 2 onwards with no changes to their study treatment.

Part 2

Initially, eligible participants were assigned via IRT to receive vobramitamab duocarmazine at 2.7 mg/kg Q4W. Per the Dear Investigator Letter, dated 22 July 2024, participants who were receiving 2.7 mg/kg Q4W under Protocol Amendment 4 must lower their dose to 2.0 mg/kg Q4W. The total number of doses of vobramitamab duocarmazine is capped at 6.

6.3 Blinding

Not applicable. This is an open-label study. No blinding of site personnel or participants will be employed.

6.4 Emergency Unblinding

Not applicable. This is an open-label study.

6.5 Study Drugs and Supplies

The study sponsor will supply vobramitamab duocarmazine, comparator drugs (abiraterone or enzalutamide), and prednisone (for use as post-infusion prophylaxis). The sponsor is not responsible for the supply of any premedication or concomitant medication (e.g., ADT).

6.5.1 Vobramitamab Duocarmazine

Information on the formulation of vobramitamab duocarmazine is included in the pharmacy manual.

6.5.2 Comparator Products

For participants who enrolled prior to Amendment 2, were randomized to the control arm of Part 1, and wish to continue to receive their assigned ARAT, commercially available formulations of abiraterone, prednisone, and enzalutamide will be supplied.

For participants unable to visit the site (e.g., due to the COVID-19 public health emergency), direct-to-participant shipment of oral study treatment may be implemented, where allowed per local regulations and if requested by the investigator. Where direct-to-participant shipments are deemed necessary, the process must be coordinated between the site and sponsor staff following standard direct-to-participant procedures for arranging shipment and adhering to associated approvals and documentation requirements. For participants able to visit the site, but who request to reduce visit frequency or for who limited access to the site is expected, an additional supply of oral study treatment may be provided.

6.6 Preparation and Administration

Information on the storage, dose preparation, and administration of study treatments is included in the pharmacy manual.

6.7 Packaging and Labeling

Information on the packaging and labeling of study treatments is included in the pharmacy manual.

Clinical supplies will be affixed with a label in accordance with Good Manufacturing Practice (GMP) and regulatory requirements.

6.8 Treatment Compliance

Vobramitamab duocarmazine will be administered by healthcare professionals under the supervision of the investigator. For participants who enrolled prior to Amendment 2, were randomized to the control arm, and wish to continue to receive their assigned ARAT, ARAT will be dispensed at the study site.

Records of vobramitamab duocarmazine dose calculation, administration, and dosing regimen will be accurately maintained by site staff. The study monitors, designated by the sponsor, will review study pharmacy and participant medical records according to the clinical monitoring plan.

6.9 Accountability

Accurate accounting of all study treatments must be maintained. The investigator agrees to keep an inventory of study treatments using the institution's drug accountability logs or logs provided by the sponsor. The investigator will maintain records of temperature monitoring of study drug. Study drug disposition records must be kept in compliance with applicable guidelines and regulations.

A pharmacy manual will be provided to the investigator or designee. When the study is completed, copies of all study treatment accountability records must be provided to the sponsor. Original drug accountability records must be maintained with the rest of the documentation for inspection by the study monitors.

6.10 Study Drug Disposition at End of Study

All unused study drugs will be destroyed on site unless return to depot is authorized by the sponsor or its representative.

7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Premedication and Prophylaxis for Vobramitamab Duocarmazine

Premedication for Infusion Related Reaction

Premedication as specified below is strongly recommended to mitigate the potential occurrence of IRR with administration of vobramitamab duocarmazine. Equivalent medications may be substituted based on the local practice of medicine and availability.

Approximately 30 minutes before each vobramitamab duocarmazine infusion, administer:

- Acetaminophen 650–1000 mg orally (PO) or ibuprofen 400 mg PO
- Diphenhydramine 50 mg PO or IV, or equivalent H1 antagonist
- Famotidine 40 mg PO or 20 mg IV, or equivalent H2 antagonist
- Dexamethasone 4 mg IV, or equivalent corticosteroid

For subsequent administration of vobramitamab duocarmazine to participants who had IRRs that were not adequately or only moderately controlled, additional medications (e.g., ibuprofen 400 mg PO, or an increased dose of dexamethasone) may be considered as part of the premedication regimen. For participants who do not have an IRR of any grade after two consecutive infusions of vobramitamab duocarmazine, dexamethasone premedication may be reduced by 50% at the next infusion and discontinued at the infusion after that if no IRR is observed.

Prophylaxis for Fluid Retention and/or Palmar-Plantar Erythrodysesthesia

To mitigate potential occurrence of fluid retention and PPE, prednisone 40 mg PO twice daily (BID) will be administered on the first 3 days of each cycle after administration of vobramitamab duocarmazine.

To mitigate potential occurrence of PPE, consider clobetasol 0.05% cream, or corticosteroid cream per local practice, prophylactically applied to palms and soles for the first 12 weeks of vobramitamab duocarmazine treatment (see **Section 7.3.5**).

7.2 Dose Modification and Dose Delay

7.2.1 Vobramitamab Duocarmazine Dose Delay and Interruption

Participants who experience toxicity will have vobramitamab duocarmazine held pending assessment, management, and resolution of the toxicity. If the toxicity is assessed to be unrelated to vobramitamab duocarmazine or does not necessitate study treatment discontinuation, then the participant may reinstitute vobramitamab duocarmazine per guidelines outlined below and in **Section 7.3**.

A dose delay ≤ 28 days is allowed for AEs irrespective of attribution to study treatment or for reasons other than AEs. All protocol-specified procedures at the missed dosing visit should be performed and treatment reinstituted as if the delay had not occurred.

A dose delay > 28 days will result in discontinuation of vobramitamab duocarmazine unless the investigator and sponsor medical monitor (or qualified designee) agree that the participant is deriving benefit (e.g., evidence of ongoing disease control defined as radiographic stable disease (SD) or better and/or PSA response).

7.2.2 Vobramitamab Duocarmazine Dose Reduction

Vobramitamab duocarmazine dose may be reduced for toxicity per **Section 7.3**. Up to a maximum of 3 dose reductions are allowed for toxicity per participant. If a fourth dose reduction is required, permanently discontinue vobramitamab duocarmazine dosing. Dose reductions for vobramitamab duocarmazine are described in **Table 3**.

Table 3 Vobramitamab Duocarmazine Dose Reduction Algorithm

Initial Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
2.7 mg/kg	2.0 mg/kg	1.5 mg/kg	1.0 mg/kg
2.0 mg/kg	1.75 mg/kg	1.5 mg/kg	1.0 mg/kg

7.3 Management of Potential Adverse Events Related to Vobramitamab Duocarmazine

7.3.1 Guidelines for Management of Adverse Events Related to Vobramitamab Duocarmazine

Guidelines for management of specific vobramitamab duocarmazine-related AEs are detailed in **Section 7.3.2** through **Section 7.3.9**. Refer to **Table 4** for dose modification guidelines for all other vobramitamab duocarmazine-related AEs (i.e., for vobramitamab duocarmazine-related AEs not specified in the protocol). Follow local institutional guidelines for management of AEs considered not related to vobramitamab duocarmazine.

Note: For AE management, baseline is defined as the most recent measurement prior to the first dose of study treatment (e.g., Cycle 1 Day 1 pre-dose).

Table 4 Guidelines for Vobramitamab Duocarmazine-Related Adverse Events Not Specified in the Protocol

Grade	Dose Modification Guidelines
1	No dose modification required.
2	Consider holding vobramitamab duocarmazine until ≤ Grade 1 or baseline, then resume at current dose. If same toxicity recurs at Grade 2 consider dose reduction.
Intolerable 2 or any 3	Hold vobramitamab duocarmazine until ≤ Grade 1 or baseline. Reduce dose by one dose level.
4	Permanently discontinue vobramitamab duocarmazine.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.2 Infusion Related Reaction

Infusion reactions associated with vobramitamab duocarmazine administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section (**Table 5**).

Participants should be monitored for the development of IRR during infusions. Medications and resuscitation equipment for the treatment of severe hypersensitivity reactions must be available for immediate use for IRR. All supportive measures consistent with optimal care will be provided throughout the study according to institutional standards.

It may be difficult to distinguish between IRR and emerging infection as the cause of fever. Participants should be evaluated for presence of infection, with acquisition of cultures, viral testing, and implementation of empiric antibiotic therapy based on the investigator's assessment. Refer to the table below for guidance regarding the management of IRR.

Changes in the infusion of vobramitamab duocarmazine including interruption of the infusion, duration of interruption, and reduction in infusion rate must be recorded.

Table 5 Management of Infusion Related Reaction

Grade	Medical Care Guidelines	Infusion Modification Guidelines
1	Reduce infusion rate by 50% Monitor for worsening of IRR.	With evidence of improvement, infusion rate may be increased to original rate as tolerated after 30 minutes. Consider additional infusion prophylaxis prior to next infusion; see **Section 7.1**.
2	**Stop infusion** Administer supportive medications as appropriate: • Diphenhydramine 25-50 mg IV. • Acetaminophen (650–1000 mg) or ibuprofen (400 mg) PO. • Oxygen and bronchodilators as needed.	If improved to ≤ Grade 1, infusion may resume with a 50% reduction in infusion rate. Monitor for worsening of IRR. Discontinue infusion if symptoms recur. Consider additional infusion prophylaxis prior to next infusion; see **Section 7.1**.
3	**Stop infusion, disconnect tubing** **Aspirate drug from vascular access device.** Administer supportive medications as appropriate: • Diphenhydramine 25-50 mg IV. • Dexamethasone (or equivalent) 20 mg IV. • Acetaminophen (650 mg) or ibuprofen (400 mg) PO. • IV fluids, oxygen, bronchodilators. • Epinephrine.	Discontinue the current infusion. Participant may resume treatment with the next scheduled dose if symptoms completely resolve within 12 hours. A 50% reduction in infusion rate is required for the next scheduled dose of vobramitamab duocarmazine. Consider additional infusion prophylaxis prior to next infusion; see **Section 7.1**. **Permanently discontinue vobramitamab duocarmazine for Grade 3 IRR lasting > 12 hours or a second occurrence of Grade 3 IRR.**
4	**Stop infusion, disconnect tubing** **Aspirate drug from vascular access device.** Treat as for Grade 3 and as appropriate for a life-threatening condition.	**Permanently discontinue vobramitamab duocarmazine.**

7.3.3 Diarrhea

Participants should be monitored closely for evidence of diarrhea or other change in bowel habits. Participants with diarrhea should be treated per institutional standard practice. Guidelines for dose modification are provided in **Table 6**.

Table 6 Dose Modification for Diarrhea

Grade	Dose Modification Guidelines
Grade 1	Closely monitor until resolution. No dose modification required.
Grade 2	Hold vobramitamab duocarmazine until ≤ Grade 1, then resume at current dose.
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level.
Grade 4	Permanently discontinue vobramitamab duocarmazine.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.4 Pneumonitis

Noninfectious pneumonitis may result in fatigue, shortness of breath, cough, low oxygen saturation, or respiratory distress. If a participant presents with signs or symptoms of pulmonary toxicity, the participant should be evaluated for potential pneumonitis. An evaluation for infection should be performed. Advise participants to notify their treating physician immediately if they experience new or worsening shortness of breath, cough, or respiratory distress.

Management and dose modification guidelines are outlined in **Table 7**.

Table 7 Management of Noninfectious Pneumonitis

Grade	Definition (CTCAE v5.0)	Medical Care Guidelines	Dose Modification Guidelines
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Consider systemic corticosteroids (0.5–1.0 mg/kg/d prednisone or equivalent) until improvement, followed by gradual taper over > 4 weeks. Repeat chest imaging in 3–4 weeks or sooner if the patient becomes symptomatic. Monitor weekly for respiratory symptoms, lung exam, and pulse oximetry. If no radiographic improvement on follow-up, treat as Grade 2.	Hold vobramitamab duocarmazine until resolved, then resume current dose.
2	Symptomatic; medical intervention indicated; limiting instrumental ADL [a]	Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Give prednisone 1–2 mg/kg/d and taper over 4–6 weeks or sooner as clinically indicated. Participant must be evaluated by a pulmonary specialist. Consider bronchoscopy with bronchoalveolar lavage. Monitor at least once per week for respiratory symptoms, lung exam, and pulse oximetry. If no clinical improvement after 48–72 hours of prednisone, treat as Grade 3.	Permanently discontinue vobramitamab duocarmazine.

Table 7 Management of Noninfectious Pneumonitis

Grade	Definition (CTCAE v5.0)	Medical Care Guidelines	Dose Modification Guidelines
3	Severe symptoms; limiting self-care ADL [b]; oxygen indicated	Hospitalize and initiate supportive care. Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Give methylprednisolone IV 1–2 mg/kg/d. If no improvement after 48 hours, may add immunosuppressive agent (e.g., infliximab 5 mg/kg [c], or mycophenolate mofetil IV 1 g twice a day, or IVIG for 5 days, or cyclophosphamide. Taper corticosteroids over 4–6 weeks. Participant must be evaluated by a pulmonary specialist. Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. The pneumonitis event must be followed until resolution.	Permanently discontinue vobramitamab duocarmazine.
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Manage as Grade 3 event. Hospitalize and initiate maximal supportive care.	Permanently discontinue vobramitamab duocarmazine.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

a Instrumental ADLs include preparing food, shopping, using the telephone, housekeeping, doing laundry, using transportation, managing money, and managing medications.

b Self-care ADLs include feeding, continence, transferring/ambulating, using the toilet, dressing, bathing, and taking medications.

c Infliximab doses > 5 mg/kg contraindicated in moderate or severe heart failure (see Infliximab Prescribing Information).

Abbreviations: ADL: activities of daily living; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenously; IVIG: intravenous immunoglobulin.

7.3.5 Palmar-Plantar Erythrodysesthesia

Participants should limit sun exposure and apply broad-spectrum sunscreen to exposed skin when outdoors. Any measures such as frozen gloves or socks or scalp cooling cap to prevent cutaneous toxicity or alopecia are left to the investigator's judgment. Use of concomitant medications with a known risk for skin toxicity and/or photosensitivity are to be avoided if possible (see **Section 8.1.1**).

For any grade toxicity, evaluate participant use of concomitant medications and herbal supplements and discontinue any products known to exacerbate mucocutaneous toxicity.

Supportive care per institutional practice should be used to manage PPE. Guidelines for grading and dose modification are described in **Table 8**. Avoid pressure and tight clothing on palms and soles.

Consider clobetasol 0.05% cream, or corticosteroid cream per local practice, prophylactically applied to palms and soles for the first 12 weeks of vobramitamab duocarmazine treatment.

Table 8 Dose Modification for Palmar-Plantar Erythrodysesthesia

Grade	Definition (CTCAE v5.0)	Dose Modification Guidelines
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	No dose modification required. Initiate supportive care measures. Closely monitor; advise participant to conduct daily self-assessment.
2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL [a]	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level.
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL [b]	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

Note: Grade 4 and 5 severity are not available per CTCAE v 5.0.

a Instrumental ADLs include preparing food, shopping, using the telephone, housekeeping, doing laundry, using transportation, managing money, and managing medications.

b Self-care ADLs include feeding, continence, transferring/ambulating, using the toilet, dressing, bathing, and taking medications.

Abbreviations: ADL: activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events.

7.3.6 Ocular Adverse Events

Ocular toxicity, including, but not limited to, dry eye, photophobia or blurry vision, has been observed in participants treated with ADCs including vobramitamab duocarmazine, and could occur at any time during treatment with vobramitamab duocarmazine. Prophylactic eye drops (e.g., corticosteroid, antihistamine, artificial tears) are recommended for participants 3 times per day, or as needed. Participants are advised not to wear contact lenses or rub their eyes on the day of infusion. Baby shampoo and a soft cloth should be used to clean eyelashes and closed eyelids, and a warm compress at bedtime may be used to decrease any possible inflammation on the eyelid's surface.

Participants with dry eye, photophobia, or blurry vision that persists for more than 72 hours or worsens, or signs/symptoms suggestive of keratitis, conjunctivitis, or uveitis irrespective of duration, should obtain a prompt ophthalmology evaluation for further assessment and management, including local topical care and/or immune suppression as appropriate.

Management guidance for ocular toxicity is provided in **Table 9**.

Table 9 Management of Ocular Symptoms

Grade	Medical Care Guidelines	Dose Modification Guidelines
1	No specific therapy required. Daily cleansing with warm, clean cloth. Apply lubricating eye drops. Monitor for worsening symptoms.	No dose modification required.
2	Consider topical/ocular corticosteroids, antihistamine, artificial tears. Participants should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold vobramitamab duocarmazine until ≤ Grade 1. If event resolves to ≤ Grade 1 in ≤ 14 days, may resume vobramitamab duocarmazine at the same dose level. If the event takes > 14 days to resolve to ≤ Grade 1, reduce dose by one dose level.
3	Consider topical/ocular corticosteroids, antihistamine, artificial tears. Consider ophthalmology consultation. Participants should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level. Permanently discontinue vobramitamab duocarmazine if ≥ Grade 3 toxicity recurs on subsequent cycles despite best supportive care.
4	**Permanently discontinue vobramitamab duocarmazine** Consult ophthalmology within 24 hours. Treat as for Grade 3 and as appropriate for a life-threatening condition.	

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.7 Hematologic Adverse Events

Complete blood count (CBC) is monitored per **Appendix 1**. Consider monitoring CBC weekly or more frequently based on the participant's medical history and incidence of myelosuppressive events during vobramitamab duocarmazine administration.

No specific treatment or vobramitamab duocarmazine dose modifications are required for lymphopenia, regardless of CTCAE grade, unless associated with opportunistic infection. If the participant develops an opportunistic infection with concurrent lymphopenia, vobramitamab duocarmazine dosing should be delayed until resolution of lymphopenia and the opportunistic infection (see **Table 4** for general guidance).

7.3.7.1 Neutropenia

Use of granulocyte colony-stimulating factor (G-CSF) is permitted after Cycle 1 Day 1. Perform a CBC for a measured temperature of ≥ 100.4°F (38°C) or evidence of infection. Neutropenic complications, including neutropenic fever of any grade, should be managed promptly with antibiotic support per local guidelines and use of G-CSF according to current American Society of Clinical Oncology (ASCO) guidelines for use of white blood cell growth factors.

Table 10 Management of Neutropenia

Grade	Medical Care Guidelines	Dose Modification Guidelines
1	No specific therapy required. Consider G-CSF with next cycle per institutional standards.	No dose modifications are required.
2	No specific therapy required. Consider G-CSF with next cycle per institutional standards.	No dose modifications are required.
3	Monitor neutrophil counts weekly until ≤ Grade 1. Advise participant to take neutropenic precautions per institutional standards. G-CSF with next cycle is recommended.	Hold vobramitamab duocarmazine until ANC ≥ 1000/mm^3. Consider reducing dose by one dose level.
4	Monitor neutrophil counts weekly until ≤ Grade 1. Advise participant to take neutropenic precautions per institutional standards. G-CSF with next cycle is recommended.	Hold vobramitamab duocarmazine until ANC ≥ 1000/mm^3. Reduce dose by one dose level.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.7.2 Thrombocytopenia

Consider transfusion of platelets for thrombocytopenia. Monitor coagulation laboratory tests (**Table 17**). Use of anticoagulants (e.g., coumarins and indandiones, factor Xa inhibitors, heparins, thrombin inhibitors) and platelet inhibitors (e.g., aspirin or nonsteroidal anti-inflammatory drugs, e.g., ibuprofen) should be held until thrombocytopenia resolves.

Table 11 Management of Thrombocytopenia

Grade	Medical Care Guidelines	Dose Modification Guidelines
1	No specific therapy required.	No dose modifications are required.
2	No specific therapy required.	Hold vobramitamab duocarmazine until platelets ≥ 75,000/mm^3, then resume at current dose.
3	Monitor platelet counts at least once weekly until ≤ Grade 1.	Hold vobramitamab duocarmazine until platelets ≥ 75,000/mm^3. If dose is delayed by > 14 days to allow for platelet recovery, reduce dose by one dose level, otherwise resume at current dose.
4	Monitor platelet counts at least once weekly until ≤ Grade 1. Treat as appropriate for a life-threatening condition.	Hold vobramitamab duocarmazine until platelets ≥ 75,000/mm^3. Reduce dose by one dose level.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.7.3 Anemia

Anemia should be evaluated and treated for other underlying etiology e.g., iron, folate, or vitamin B_{12} deficiency, bleeding, thrombocytopenia, coagulopathy, and renal insufficiency. Consider transfusion of red blood cells or whole blood for anemia. Caution is recommended in participants with ≥ Grade 2 anemia, with appropriate measures taken as clinically indicated. The

investigator should refer to current ASCO guidelines for management of cancer-associated anemia with erythropoiesis-stimulating agents.

Table 12 Management of Anemia

Grade	Medical Care Guidelines	Dose Modification Guidelines
1	No specific therapy required.	No dose modification required.
2	Consider iron replacement therapy, erythropoiesis-stimulating agent.	No dose modification required.
3	Consider iron replacement therapy, erythropoiesis-stimulating agent. Consider transfusion if symptomatic.	Hold vobramitamab duocarmazine until ≤ Grade 2 or baseline, then resume at current dose. Consider reducing dose by one dose level if Grade 3 anemia recurs.
4	Transfuse with whole blood or packed red blood cells. Treat as appropriate for a life-threatening condition.	Hold vobramitamab duocarmazine until ≤ Grade 2 or baseline. Reduce dose by one dose level. Permanently discontinue vobramitamab duocarmazine for Grade 4 anemia that persists despite intervention.

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.8 Effusions

Supportive care per institutional practice should be used to manage pleural and pericardial effusions. Diuretics, thoracentesis, pericardiocentesis, and other surgical procedures to manage the effusions are allowed and should be used according to best practice. Chest x-ray should be obtained as indicated to monitor effusion fluid level. Close monitoring of heart and lung function is warranted in the presence of effusion.

For Grade 2 or higher pleural or pericardial effusions, consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids (e.g., 5 to 10 mg every 1 to 2 weeks from an initial dose above 40 mg prednisone per day) over 4 weeks or as clinically indicated.

Specific guidance for pleural and pericardial effusion is provided **Table 13** and **Table 14**, respectively.

7.3.8.1 Pleural Effusion

Table 13 Management of Pleural Effusion

Grade	Dose Modification Guidelines
1	No delay or dose modification required.
2	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level. If Grade 2 pleural effusion recurs, permanently discontinue vobramitamab duocarmazine.
3	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level. If Grade 3 pleural effusion recurs, permanently discontinue vobramitamab duocarmazine.
4	**Permanently discontinue vobramitamab duocarmazine**

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.8.2 Pericardial Effusion

Table 14 Management of Pericardial Effusion

Grade	Dose Modification Guidelines
2	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level. If Grade 2 pericardial effusion recurs, permanently discontinue vobramitamab duocarmazine.
3	Hold vobramitamab duocarmazine until ≤ Grade 1. Reduce dose by one dose level. If Grade 3 pericardial effusion recurs, permanently discontinue vobramitamab duocarmazine.
4	**Permanently discontinue vobramitamab duocarmazine**

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.3.9 Cardiac Adverse Events

Management guidelines for participants experiencing cardiac AEs are described below.

Table 15 Management of Cardiac Adverse Events

Grade	Medical Care Guidelines	Dose Modification Guidelines
1	No specific therapy required; close monitoring.	Hold vobramitamab duocarmazine until < Grade 1 or baseline. Consider one dose level reduction.

Table 15 Management of Cardiac Adverse Events

Grade	Medical Care Guidelines	Dose Modification Guidelines
2	Consider cardiology consultation. Evaluate cardiac biomarkers e.g., creatine kinase, troponin, and beta-natriuretic peptide. Echocardiogram, ECG, and CT imaging if clinically indicated. Consider corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper corticosteroids over 4 weeks or as clinically indicated.	Hold vobramitamab duocarmazine. Resume vobramitamab duocarmazine at next scheduled dose if toxicity improves to ≤ Grade 1, with or without treatment. Consider one level dose reduction. **Permanently discontinue vobramitamab duocarmazine for Grade 2 myocarditis** (regardless of time to improvement/resolution).
3-4	**Permanently discontinue vobramitamab duocarmazine** Consider hospitalization and cardiology consultation. Evaluate cardiac biomarkers e.g., creatine kinase, troponin, and beta natriuretic peptide. Echocardiogram, ECG, and CT imaging if clinically indicated. For Grade 3 or 4 myocarditis, begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Continue IV methylprednisolone 2 mg/kg/day for a total of 5 days then switch to oral prednisolone 1 mg/kg/day × 3 days, then reduce to 60 mg/day prednisolone. Reduce prednisolone dose by 10 mg every 7 days (as toxicity allows) until dose is 10 mg/day. Once steroid dose is 10 mg/day, reduce by 5 mg every 7 days then stop. Consider infliximab.	

Note: Dose delay > 28 days will result in treatment discontinuation unless otherwise specified (see **Section 7.2.1**).

7.4 Management of Potential Adverse Events Related to Comparator Products (Part 1)

For participants who enrolled prior to Amendment 2, were randomized to the control arm, and wish to continue to receive their assigned ARAT, management of toxicities related to abiraterone and enzalutamide should be per standard of care and based on approved local prescribing information or clinical practice guidelines.

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

All concomitant medications, including ADT, prophylactic pre-infusion medications, and blood products administered during the study until 30 days after the last dose of study treatment or until initiation of another anticancer therapy, if earlier, must be recorded in the source document and on the electronic case report form (eCRF).

8.1.1 Prohibited Therapy

The following rules concerning concurrent treatment(s) apply in this study:

- Use of any other antineoplastic therapy is prohibited, including but not limited to chemotherapy or other small molecules, biologics, radiotherapy (including radiopharmaceutical), hormonal therapy (other than protocol-specified treatment with a GnRH modulator for participants on Part 1), or other ARAT (e.g., apalutamide, darolutamide, enzalutamide, or abiraterone).
    - For participants who require palliative radiotherapy (i.e., cumulative dose less than 3000 rads, limited field distribution) for reasons other than PD, study drug may be interrupted for up to 28 days. Palliative radiotherapy may not be given concurrently with study drug. Treatment with palliative radiotherapy should be initiated at least 24 hours after receiving study drug, and re-initiation of study drug may begin 2 weeks after completion of palliative radiotherapy. If palliative radiotherapy fields overlap tumor lesions that are designated target lesions, the participant may continue on study but will no longer evaluable for objective response from the time palliative radiotherapy is initiated.
- Part 1 only: Use of saw palmetto and pomegranate juice/extract is prohibited. Use of 5-alpha reductase inhibitors is only allowed if the participant was on a stable dose for at least 2 months prior to study entry; they may not be newly started on study.
- Participants may not receive other investigational drugs during the period of study participation.
- Participants should not receive vaccination(s) with any live virus vaccine from 30 days prior to initiation of study treatment through 120 days after the last dose of study treatment. Inactivated annual influenza vaccination and non-live SARS-CoV-2 vaccinations are allowed.
    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, bacillus Calmette-Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed (inactivated) virus vaccines and are permitted. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are prohibited.

- Vobramitamab duocarmazine precautions:
    - The following medications have a known risk of skin toxicity and/or photosensitivity and are to be avoided if possible: retinoids, denosumab, tetracyclines, sulfonamides.

8.1.2 Permitted Therapy

Participants may receive the following concurrent therapy:

- Antiemetics, antidiarrheal, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended for supportive care.
- Transfusions or growth factors are permitted to treat symptoms or signs of anemia or thrombocytopenia.
- Prophylactic use of growth factors is allowed after Cycle 1 Day 1.
    - For any G-CSF product, the prescribing information or summary of product characteristics for details on description, administration, and precautions for use will be used.
- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors is allowed.

Participants with mCRPC who have not undergone bilateral orchiectomy must be maintained on a GnRH modulator throughout the study. The choice of GnRH modulator is at the discretion of the investigator. Dose and dose schedule (without interruption) will be consistent with the prescribing information and should only be adjusted if clinically indicated to maintain castrate concentrations of testosterone (serum testosterone ≤ 50 ng/dl or ≤ 1.7 nmol/L).

8.1.3 Contraception

Participants who may become pregnant are required to use highly effective contraceptive measures as specified below. Male participants are required to use a condom from the time of consent through 27 weeks after the last dose of study treatment regardless of the method of contraception of their female partner of childbearing potential. In addition, male participants must have their partners of childbearing potential use another method of contraception from the time of consent through 27 weeks after the last dose of study treatment.

Note: female of childbearing potential is defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause.

- 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
- Bilateral tubal occlusion
- Vasectomy is considered a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the female of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. 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.

8.2 Restrictions

8.2.1 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by participants on vobramitamab duocarmazine during the study. However, it is recommended that, to the extent possible, participants have an adequate fluid intake on days associated with PK sampling.

8.2.2 Participant Activity Restrictions

There are no restrictions on participant activities and no requirement for participant confinement during the study. However, participants on vobramitamab duocarmazine are advised to limit direct sun exposure and to use a broad-spectrum sunscreen when outdoors. Participants are advised not to wear contact lenses or rub their eyes on the day of infusion. Participants should be advised to avoid activities that promote skin chafing, prolonged or untoward skin pressure, occlusive skin dressings, or hot tub baths.

9 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of the study procedures, including allowable time windows, is presented in **Appendix 1**. All data should be recorded in source documents and entered into the eCRF.

Alternative methods for conducting study assessments may be considered when compliance, feasibility, and safety can be assured. These methods may include:

- Telemedicine visits, e.g., via telephone/video (using compliant video-conference tools as permitted by health authority regulations)
- Use of primary care centers and local laboratories for blood draws

If alternative methods are used, local laboratory reference ranges will be documented and submitted to the sponsor. Local laboratory test results, laboratory accreditation (if possible), and reports of tumor assessments should be retrieved and documented in the participant's study records.

9.1 Informed Consent

The investigator is responsible for ensuring that the participant provides informed consent prior to performing any study-related assessments, evaluations, or procedures that are not part of standard-of-care for the participant's disease. Informed consent for this study must be provided by signing an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form (ICF). A copy of the relevant signed ICF must be provided to the participant and the original maintained according to institutional procedures. The participant's medical records will include documentation of the informed consent process.

9.2 Screening Period

Participants may receive the first dose of study treatment up to 28 days from signing the ICF. The screening period is defined as the time from signing the ICF until treatment assignment in the IRT system. At the screening visit, participants will enter the study upon providing informed consent. No screening activities outside of usual standard-of-care should be performed prior to obtaining informed consent from the participant.

Participants who sign the ICF but fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Demographic information, reason for screen failure, and SAEs related to study procedures must be recorded on the eCRF for screen failures.

9.3 Registration and Enrollment

The participant must be registered with the sponsor after eligibility is confirmed.

The following information is required during registration:

- Participant identification number
- Date of signed informed consent
- Presence of visceral disease (yes or no) (Part 1 only)
- Prior taxane (yes vs no) (Part 1 only)
- Region (US/Canada vs other) (Part 1 only)
- Tumor type (Part 2 only)

Instructions for registration will be provided by the sponsor prior to site initiation. Instructions for randomization will be provided via IRT.

A participant is considered enrolled to the study once the participant has completed registration and has been assigned to a study treatment arm by randomization.

9.4 Medical History

A complete medical history should be obtained during the screening visit. All concurrent medical conditions in the last 60 days and any significant past medical conditions (e.g., hospitalizations, surgeries, chronic conditions, non-prostate cancer history, etc.) should be collected. Any untoward event that occurs prior to the first dose of study treatment should be recorded as medical history and not as an AE unless it is due to a protocol-related procedure.

9.4.1 Prostate Cancer History (Part 1)

Prostate cancer characteristics at initial diagnosis and at study entry will be collected. Prior prostate cancer treatment will be recorded on the eCRF.

Sites are requested to provide the following additional information:

- Type of disease progression at study entry per PCWG3 recommendations (**76**). Record whether progression was manifested by PSA alone, bone ± lymph nodes by location, lymph nodes by location only, or viscera (± other sites). Record whether progression by imaging at study entry involved the growth or enlargement of pre-existing lesions, the development of new lesions, or both.
- All available PSA values in the medical record up to 12 weeks prior to study entry or the 3 most recent values at least 2 weeks apart.
- Gleason score.
- Available BRCA1, BRCA2, and ATM results.
- Available microsatellite instability (MSI) status and tumor mutational burden (TMB) results.

9.4.2 Other Cancer History (Part 2)

Cancer characteristics at initial diagnosis and at study entry will be collected. Prior cancer treatment will be recorded on the eCRF.

Sites are requested to provide the following additional information:

- All cohorts: MSI status and TMB data (if available).
- Anal carcinoma: HPV status of the tumor (if available).
- HNSCC: HPV status of the tumor (if available).
- Melanoma: BRAF, KIT, and NRAS mutation status (if available).
- NSCLC: EGFR, KRAS, ALK, ROS1, BRAF, NTRK, MET, ERBB2/HER2/neu, and PD-L1 status (if available).

9.5 Prior and Concomitant Medications and Procedures

Record all medications, blood products, and procedures administered for 30 days prior to study treatment administration until 30 days after the last dose of study treatment or until initiation of another anticancer therapy. For participants in Part 1, record ongoing ADT on the concomitant medications eCRF.

9.6 Physical Examination

The investigator or qualified designee will perform physical examination of all participants. Full physical examination will be performed at screening and at the end of treatment visit (EOTV).

Full physical examination includes height (screening only), weight, and examination of HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, neurologic system, and total body skin examination (TBSE). In the absence of symptoms or disease-related requirements, examination of primary or secondary sexual organs may be deferred.

All other on-study physical examinations will be directed physical examinations based on participant signs, symptoms, and tumor location.

9.6.1 Vital Signs

Vital signs include temperature, pulse, blood pressure, respiratory rate, and oxygen saturation (pulse oximetry). It is recommended vital signs are obtained in a seated, semi-recumbent, or supine position after appropriate physical rest.

9.6.2 Height and Weight

Weight will be measured per the schedule in **Appendix 1**. Height is measured at screening only.

9.7 Performance Status

Performance status will be assessed using the ECOG scale (**Table 16**).

Table 16 Eastern Cooperative Oncology Group Performance Status

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

9.8 Laboratory Tests

9.8.1 Clinical Laboratory Tests

Blood and urine samples will be collected as described in **Table 17**. Both local and central laboratory testing will be used.

Local laboratories should be used for all clinical decision-making, including but not limited to decisions regarding study treatment dosing and dose adjustments, if needed. Necessary local laboratory testing should be performed as required by the clinical situation.

Central laboratory testing will be used to determine eligibility (with the exception of pregnancy testing, which will be performed locally) and to assess overall safety in the study, unless the sponsor medical monitor approves the use of a local laboratory test result, for example, in place of an unanalyzable or unavailable central laboratory test result.

Clinical laboratory tests should be performed and reviewed before administration of study treatment.

Table 17 Clinical Laboratory Tests

Hematology: Hemoglobin Hematocrit Platelets Leukocytes Absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils **Serum chemistry:** Albumin Alkaline phosphatase Alanine aminotransferase Amylase Aspartate aminotransferase Bicarbonate Bilirubin: total, direct, and indirect Blood urea nitrogen or urea Calcium Chloride Creatinine Gamma glutamyl transferase Glucose Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Protein, total Sodium Urate (uric acid)	**Cardiac:** Creatine kinase Creatine kinase myocardial band (CK-MB) **Coagulation (local lab only):** Activated partial thromboplastin time or partial thromboplastin time Fibrinogen Prothrombin international normalized ratio **Endocrine:** Thyroid-stimulating hormone Thyroxine, free; or triiodothyronine, free **Urinalysis (local lab only):** Protein Occult blood If abnormal protein or occult blood, perform reflex test for microscopic evaluation **Tumor marker/Other (Part 1 only):** Prostate-specific antigen Testosterone **Pregnancy test (local lab only; Part 2 only):** Serum or urine human chorionic gonadotropin (hCG) **Infectious disease (Czech Republic and other countries where required by local authorities only; local lab only):** HIV, HCV, and HBV tests at screening per local guidelines (see **Section 5.2**)

9.8.2 Central Laboratory Tests

Unless otherwise stated, PK, immunogenicity, and biomarker assays will be performed in a central laboratory designated by the sponsor. Additional details on collection, processing, storage, and shipping of central laboratory samples will be provided in the laboratory manual. PK, immunogenicity, and biomarker specimens will be collected according to the schedules in **Appendix 2**.

9.8.2.1 Blood Samples

It is recommended to collect blood samples contralateral to the site of IV infusion of vobramitamab duocarmazine. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of the blood sample.

PK sampling will be performed in participants receiving vobramitamab duocarmazine per **Table 24**. Select sites will not be required to collect PK samples. The sponsor will inform the study site on the need for PK sampling at that site.

9.8.2.2 Tumor Biopsy Specimens

Eligible participants must have an identified archival FFPE tumor specimen block or at least 5 unstained slides from archival tumor specimen or fresh biopsy (except participants with bone-only mCRPC not amenable to biopsy) for immunohistochemistry (IHC) determination of B7-H3. Results of B7-H3 IHC testing are not required for eligibility. Tumor specimens will be analyzed retrospectively and will not be used to determine eligibility.

Tumor lesions for biopsy should be lesions that are accessible with acceptable clinical risk in the judgment of the investigator and should not be the same lesions used as PCWG3 or RECIST target lesions. Multiple lesions may be used to obtain the biopsy sample. Lesions for biopsy should be of sufficient size to enable acquisition of at least 2 tumor biopsy cores using a 16-gauge biopsy needle. Exceptions to the gauge of the needle may be considered after consultation with the sponsor's medical monitor. Up to 3 additional biopsy cores may be obtained if this can be performed with acceptable clinical risk in the judgment of the investigator. Excisional biopsies are allowed if these can be performed with acceptable clinical risk in the judgment of the investigator. Immediate confirmation of the adequacy of the biopsy specimen and the presence of malignant cells in the tumor biopsy are strongly encouraged. Additional instructions for the processing and storage of tumor biopsy specimens are provided in the laboratory manual.

9.9 Tumor Assessments

Tumor assessments will be performed per the schedules in **Appendix 1**. If scans are performed outside of the scheduled visit window, and the participant has not progressed, every attempt should be made to perform subsequent scans at their originally scheduled time points (calculated from Cycle 1 Day 1).

Baseline (screening) tumor assessments include CT and/or MRI scan of the chest, abdomen and pelvis. Subsequent tumor assessments will image the chest, abdomen and pelvis. The same imaging modality and procedures (e.g., the same CT contrast protocol) as those of the baseline assessment should be used.

CT or MRI scan of the brain or other areas of disease involvement will be performed when clinically indicated (e.g., history of or suspicion of current brain metastases); these scans are to be repeated throughout the study if there is evidence of disease at screening.

For participants with mCRPC (Part 1) or any participant with signs and/or symptoms of bone involvement (Part 2), technetium-99m bone scan will be performed at screening and at each tumor assessment on study to evaluate bone lesions. For participants with equivocal new bone lesion(s) on bone scan consider obtaining additional imaging to evaluate new lesion(s) for tumor involvement, e.g., x-ray, CT, or MRI. In situations where bone scan findings are suggestive of a flare reaction or the apparent new lesion(s) may represent trauma, additional imaging with other modalities such as MRI or fine-cut CT, should be obtained to confirm these results.

Tumor response will be assessed according PCWG3 criteria (**76**) in Part 1 or RECIST v1.1 (**77**) in Part 2 (see **Section 11.1.1**).

9.10 Electrocardiography

Twelve-lead ECGs will be obtained per **Appendix 1** and as clinically indicated to evaluate potential cardiac AEs. The ECG acquired will be a single tracing. If the single ECG tracing demonstrates an abnormality, additional ECG tracings should be obtained to evaluate the ECG abnormality. ECGs will be performed at the local institution and interpreted by the investigator or medically qualified delegate.

ECG tracings must be performed after the participant has been resting in a supine position (or semi-recumbent if supine is not tolerated) for at least 5 minutes. ECGs should be obtained prior to other study procedures (e.g., blood draws) scheduled at the same time. Environmental distractions and other circumstances that may induce changes in heart rate should be minimized where possible.

At visits where ECGs and time-matched PK samples are collected, ECGs should be performed prior to obtaining the time-matched PK sample.

Actual times of the ECG tracings will be recorded on the eCRF. The original ECG tracing(s) will be stored in the participant's record as source data.

9.11 Echocardiography

Echocardiograms (or multigated acquisition [MUGA] scans) will be obtained and analyzed locally in all participants. The same modality should be used throughout the study for any given participant. Echocardiograms (or MUGA scans) performed will be evaluated for any change in LVEF from baseline (screening).

9.12 Ophthalmic Examination

Ophthalmic examination will be performed by an ophthalmologist per **Appendix 1**. The examination will include visual acuity testing (with correction), fundoscopic examination, and tonometry. Other directed studies (e.g., optical coherence tomography) will be performed as clinically indicated.

9.13 Symptomatic Skeletal Events (Part 1 Only)

Symptomatic skeletal events (SSEs) are a clinical study endpoint to describe skeletal morbidity defined as new symptomatic pathological fracture, requirement for radiation therapy to relieve bone pain, spinal cord compression, or tumor-related orthopedic surgical intervention. These events must be recorded in the source document and on the SSE eCRF regardless of relationship to PD.

9.14 End of Treatment Visit

The end of treatment visit (EOTV) should be performed within 30 days after the participant has met study treatment discontinuation criteria and before initiation of any subsequent anticancer therapies. It is recognized that participants may go to other facilities for continuing care or may elect not to return to the study site. Therefore, failure to return for an EOTV will not be considered a protocol deviation. Whenever possible, all required procedures and tests should be performed.

Tumor assessments are not required at the EOTV for participants who had a previous scan performed within 12 weeks of the EOTV.

9.15 Post-Treatment Follow-Up Period

The post-treatment follow-up period is approximately 6 months and includes the following assessments:

- Survival follow up: Survival status is assessed approximately Q12W (± 14 days) for up to 6 months from last dose of study treatment or until withdrawal of consent, LTFU, death, or end of study, whichever occurs first. The first survival follow-up assessment will be scheduled 12 weeks after the last dose of study treatment. Participants may be followed via clinic visit, telephone, paper mail, or other electronic contact. Updated survival status may be requested by the sponsor at any time during the study (i.e., regardless of the interval since the prior assessment).
- Tumor response status: Tumor imaging is performed approximately Q12W (± 14 days) from last tumor response assessment for up to 6 months from last dose of study treatment for all participants who discontinue from study treatment due to reasons other than PD (e.g., toxicity) until PD, death, initiation of another anticancer therapy, withdrawal of consent, LTFU, or end of study, whichever occurs first.
- Part 1 only: Serum testosterone and PSA are assessed approximately Q12W (± 14 days) from last tumor response assessment for up to 6 months from last dose of study treatment for all participants who discontinue from study treatment due to reasons other than PD (e.g., toxicity) until PD, death, initiation of another anticancer therapy, withdrawal of consent, LTFU, or end of study, whichever occurs first.

For Part 2, the duration of follow-up may be reduced from 6 months at the discretion of the sponsor. Any decision to reduce the follow-up duration will be communicated to the site.

The definition of another anticancer treatment after discontinuation of study treatment includes, but is not limited to, chemotherapy, hormonal therapy, gene therapy, immunotherapy, cryotherapy, biologics, systemic radiation, or surgery for prostate cancer.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetic Assessments

Serum concentrations of vobramitamab duocarmazine (conjugated and total antibody) will be measured using validated bioanalytical methods. Plasma concentrations of the payload, SYD986, will be measured using a liquid chromatography-tandem mass spectrometry assay.

Analysis of concentration data will be used to estimate PK parameters for vobramitamab duocarmazine (conjugated and total antibody) and SYD986 (and metabolites if appropriate) in participants with sufficient concentration data to calculate PK parameters. If applicable, these PK parameters may include maximum concentration (C_{max}), area under the concentration-time curve until time t (AUC_t), area under the concentration-time curve for a dosing interval (AUC_{tau}), trough concentration (C_{trough}), and time-to-maximal concentration (T_{max}).

Population PK analyses and exposure-response analyses may be conducted using data from this study alone or combined with data from other studies.

10.2 Immunogenicity Assessments

Anti-drug antibodies (ADAs) against vobramitamab duocarmazine will be detected using validated assay methods. Samples positive for ADA will be saved for future evaluation of neutralizing antibody activity. Exposure by ADA status analyses may be performed to assess the relationship between ADA positivity and vobramitamab duocarmazine (conjugated and total antibody) and SYD986.

10.3 Biomarker Assessments

Biomarker samples will be prospectively collected and retrospectively analyzed.

The following assessments may be performed:

- Analysis of B7-H3 expression by IHC on archival or fresh pre-treatment tumor specimens (if no archival specimen is available). Relationships between B7-H3 expression and efficacy and other endpoints may be assessed.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Assessments

11.1.1 Tumor Response Assessments

Tumor response assessments will be determined using CT and/or MRI. Bone scans will be obtained, in addition to CT and/or MRI, to evaluate bone metastasis. Target and non-target lesions will be designated per PCWG3 (Part 1) or RECIST v1.1 (Part 2) criteria at screening and evaluated approximately Q8W for the first 24 weeks and Q12W thereafter (or as clinically indicated) until PD, death, initiation of another anticancer therapy, withdrawal of consent, LTFU, or end of study, whichever occurs first. At each tumor response assessment time point, the overall tumor response status will be determined by investigators based on assessment of target and non-target lesions as well as appearance of any new lesions per PCWG3 criteria (**76**) in Part 1 or RECIST v1.1 (**77**) in Part 2.

After receipt of the last dose of study treatment, participants will enter a post-treatment follow-up period (**Section 9.15**).

For statistical analysis, objective tumor response will be determined by investigators. Study treatment dosing decisions will also be made on the basis of local investigator assessment of tumor response per PCWG3 (Part 1) or RECIST v1.1 (Part 2).

If the response assessment is equivocal, it is recommended to continue study treatment and reassess tumor burden at the next scheduled assessment or sooner if clinically indicated. Note, an isolated increase in PSA is not a condition for study treatment discontinuation in Part 1.

Requirements for determination and confirmation of radiographic progression per PCWG3 are summarized in **Table 18**. Refer to Eisenhauer et al. for RECIST v1.1 guidelines (**77**).

Table 18 Radiographic Progressive Disease per Prostate Cancer Working Group 3

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
Week 8	2 or more new lesions compared to baseline bone scan.	Progressive disease on CT or MRI
	Requires confirmation scan at least 6 weeks later with ≥ 2 additional lesions compared to week 8 scan.	No confirmation scan required.
Week 16 or later	2 or more new lesions compared to week 8 bone scan.	Progressive disease on CT or MRI
	Requires confirmation scan at least 6 weeks later for persistence or increase in number of lesions.	No confirmation scan required.

Note: Adapted from Scher et al. (76).
Note: The first bone scan completed after baseline will be considered the "Week 8 bone scan" regardless of whether the scan is obtained at Week 8 or at an unscheduled assessment.
Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging

11.1.2 Survival Assessments

Participants who discontinue from study treatment will be assessed for survival status as described in **Section 9.15**.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

The safety assessment is based on AEs occurring from the first administration of study treatment until 30 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever comes first. Events that occur during the follow-up period will be captured and followed if they are considered by the investigator to be treatment related. The safety assessment is based on signs, symptoms, physical examination findings, and laboratory test results.

12.1 Definitions

12.1.1 Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans. AEs may or may not be drug related. An AE is:

- Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product.
- Any medical occurrence that is new or has increased in severity or frequency from the baseline condition.
- Any abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is a noxious and unintended response to the medicinal product related to any dose. The phrase “response to a medicinal product” means that a causal relationship between a drug and an AE is at least a reasonable possibility.

12.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is an AE of scientific and medical concern specific to the sponsor’s study treatment, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. An AESI may be serious or non-serious.

12.1.4 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death.
- Life-threatening (immediate risk of death).
- Inpatient hospitalization for longer than 24 hours or prolongation of existing hospitalization (even if the event is Grade 1).

- Persistent or significant disability or incapacity.
- Congenital anomaly/birth defect.
- Important medical events (i.e., jeopardize the participant or require intervention to prevent one of the other outcomes listed above).

12.1.5 Assessment of Causality

Assessment of causality is a determination that describes the relationship or association of the drug with an AE.

This assessment of causality is made by the investigator based on 1) temporal relationship of the event to the administration of study treatment; 2) whether an alternative etiology has been identified, and 3) biological plausibility.

Causality assessments that are considered **not related** to study treatment:

- *None:* The event is related to an etiology other than the study treatment. An alternative etiology should be documented in the participant's medical record.
- *Unlikely:* The event is unlikely to be related to the study treatment and likely to be related to factors other than study treatment. An alternative explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an SAE causality assessment is "unlikely" or "none", the investigator should document the likely causative mechanism for the event.

Causality assessments that are considered **related** to study treatment:

- *Possible:* There is a temporal association of the event with the administration of the study treatment. There is a plausible mechanism for relationship to the study treatment. However, there is an alternative explanation, such as the participant's clinical status or underlying disease.
- *Probable:* There is a temporal association of the event with the administration of study treatment. There is a plausible mechanism for relationship to the study treatment. There is no other reasonable explanation.
- *Definite:* There is a temporal association of the event with the administration of study treatment. There is a plausible mechanism for relationship to the study treatment. Causes other than the study treatment are ruled out, or the event re-appeared on re-exposure to the study treatment.

12.1.6 Severity Criteria

Severity grade will be assessed using the National Cancer Institute (NCI) CTCAE v5.0.

For AEs not contained in CTCAE v5.0, the investigator may assign intensity according to the following general CTCAE v5.0 grading scale:

- Grade 1 = Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

12.2 Adverse Event Collection and Documentation

12.2.1 All Adverse Events

AEs and SAEs reported between the time the participant signs the ICF and the administration of the first dose of study treatment will be captured as concurrent medical history unless the events (AEs and SAEs) are attributed to protocol-specified procedures.

PD or events related to PD are considered efficacy endpoints, and **not reported** as AEs or SAEs. AEs and SAEs will be reported if it is unclear whether the event is due to PD.

Events attributed to protocol-specified procedures will be collected on the AE eCRFs and SAE report form, as appropriate.

AEs, regardless of seriousness, severity, or relationship to study treatment, are documented in the source and the eCRF, including:

- Duration, severity, and seriousness of each AE,
- Action taken with respect to the study treatment(s),
- Investigator’s attribution/causality assessment,
- Any medications used to treat the AE,
- Outcome of the event(s).

A diagnosis should be recorded when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper

respiratory infection"). All treatment measures for AE management will be recorded. All non-serious AEs should be entered into the eCRFs within 10 days of study site awareness.

Clinical Laboratory Changes: Clinical laboratory test results are evaluated by the investigator for clinical significance. The investigator is responsible for reviewing the results of all laboratory tests in a timely manner. The investigator may repeat the laboratory test or request additional tests to verify the results of laboratory tests.

Clinically significant laboratory abnormalities are reported as AEs. A laboratory abnormality is considered clinically significant if:

- Associated with discontinuation of study treatment, study treatment dose reduction or delay, or required intervention.
- Suggestive of disease or organ toxicity.

Laboratory abnormalities associated with a diagnosed AE are not reported as separate AEs. For example, report renal failure or hematuria, not the laboratory abnormality elevated creatinine or urine red blood cells increased.

The appropriate CTCAE v5.0 term should be used to report the laboratory abnormality; for example, as neutrophil count decreased (not neutropenia), platelet count decreased (not thrombocytopenia), and anemia (not hemoglobin decreased).

The sponsor reports all suspected unexpected serious adverse reactions (SUSARs) to the investigator according to applicable regulatory reporting requirements. The investigator must report SUSARs to the appropriate IEC/IRB as required by the IEC/IRB.

The participant may be provided with a Study CP-MGC018-03 wallet card.

12.2.2 Serious Adverse Events

All SAEs, regardless of causality, occurring from first administration of study treatment through 30 days after the last dose of study treatment or until initiation of another anticancer therapy, if earlier, must be reported to the sponsor. SAEs related to study treatment may be reported at any time, regardless temporal relationship to study treatment dosing. The investigator should report the SAE to the sponsor.

- **Within 24 hours** of becoming aware of an SAE, the investigator should send the sponsor a completed SAE report form by email,
  The SAE report form and completion guidelines, and contact information for reporting SAEs, are provided by the sponsor. Upon receipt of SAE follow-up information, a follow-up SAE report form should be submitted within 24 hours of becoming aware of the follow-up information. SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness.

- The investigator must follow all SAEs until resolution and record the date of resolution. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic. Unresolved SAEs must be followed until:
    - The event resolves.
    - The event stabilizes.
    - The event returns to baseline, if a baseline value/status is available.
    - The event can be attributed to etiology other than the study treatment or to factors unrelated to study conduct.
    - It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).
- Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the study must be reported as a SAE, except:
    - A standard hospitalization for administration of study treatment.
    - A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, PK or biomarker blood sampling).
    - Hospitalizations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in long-term care or hospice facility).
    - Surgery or procedure planned before entry into the study (must be documented in the eCRF).
- Any SAE of suspected transmission of an infectious agent via a medicinal product will be reported.

The sponsor reserves the right to request additional information for any participant with ongoing AEs/SAEs at the end of the study, if judged necessary.

12.2.3 Pregnancy

All pregnancies in female participants or female partners of male participants must be reported to the sponsor. The pregnancy exposure form is sent to the sponsor within 24 hours of study site awareness. The reporting period is from consent through 27 weeks after the last dose of study treatment, or initiation of another anticancer therapy. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and reported according to the method in **Section 12.2.2**.

The investigator must attempt to follow the pregnancy to term or termination and report the outcome and health status of the mother and child. The investigator should discuss with and encourage the pregnant partner to allow collection of follow-up information. The pregnant

partner information release form must be signed prior to collecting follow-up information. Follow-up information will be collected for all live newborns at birth and 6 months after birth. Information will be collected to assess study treatment effects on the newborn. If appropriate, follow up will be extended.

12.2.4 Special Reporting Situations

12.2.4.1 Sponsor Notification of Adverse Events of Special Interest

AESIs will be followed as part of standard safety monitoring activities by the sponsor. The sponsor must be notified of these AESIs regardless of seriousness (i.e., serious and nonserious AESIs). Some AESIs must be reported immediately to the sponsor within 24 hours of the study site's awareness of the event. See **Table 19** for a list of protocol-specific AESIs with reporting requirements including the timeframe within the events are entered in the eCRF.

Table 19 Adverse Events of Special Interest

Adverse Event of Special Interest	Reporting Requirement
Infusion related reaction ≥ Grade 2	**For Grade 2 events:** Within 10 days of the study site's awareness of the event.
	For ≥ Grade 3 events: Within 24 hours of the study site's awareness of the event.
Ocular toxicity (i.e., keratitis, conjunctivitis, blepharitis, keratoconjunctivitis sicca) ≥ Grade 2	**For Grade 2 events:** Within 10 days of the study site's awareness of the event.
	For ≥ Grade 3 events: Within 24 hours of the study site's awareness of the event.
Stevens-Johnson syndrome or toxic epidermal necrolysis	Within 24 hours of the study site's awareness of the event.
Pleural effusion ≥ Grade 3	Within 24 hours of the study site's awareness of the event.
Pericardial effusion ≥ Grade 3	Within 24 hours of the study site's awareness of the event.
Cardiac adverse event of any grade	**For ≤ Grade 2 events:** Within 10 days of the study site's awareness of the event.
	For ≥ Grade 3 events: Within 24 hours of the study site's awareness of the event.

12.2.4.2 Overdose

Overdose is any vobramitamab duocarmazine dose ≥ 20% more than the protocol-specified dose. In the event of an overdose, the participant should be closely monitored for AEs.

Any AE resulting from overdose must be reported to the sponsor **within 24** hours of awareness. All AEs associated with an overdose will be recorded in the eCRF.

12.2.4.3 Product Quality Issues

Any suspected transmission of an infectious agent via a medicinal product, or other product quality issue that results in an event of clinical consequence are considered AEs. The AE resulting from a product quality issue should be reported within 24 hours of awareness of the event. See **Section 13** for product quality complaint (PQC) handling.

12.2.4.4 Discontinuation of Study Treatment Due to an Adverse Event

Any AE not related to PD that results in study treatment discontinuation must be reported to the sponsor within 24 hours of discontinuation. Follow up of the AE will continue until resolution or stabilization of the AE unless the participant withdraws consent for further follow up.

13 PRODUCT QUALITY COMPLAINT HANDLING

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

Any PQC associated with an investigational product or non-investigational product supplied by the sponsor will be reported according to the instructions provided in the pharmacy manual.

All initial PQCs must be reported to the sponsor by study-site personnel **within 24 hours** of awareness of the event.

If the PQC occurs in the setting of an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to **Section 12.2.2**, SAEs). A sample of the suspected product should be maintained under the correct storage conditions for further investigation if requested by the sponsor.

13.2 Contacting Sponsor Regarding Product Quality

The name(s) (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs are listed on the contact information page(s) provided in the pharmacy manual.

14 STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles used for data analysis in this study. A separate statistical analysis plan (SAP) and statistical programming plan (SPP) will further describe the details regarding statistical methods and govern the statistical analysis.

14.1 Determination of Sample Size

The planned sample sizes are described below. Study enrollment is closed.

In total, up to approximately 382 participants were to enroll in the study, including 182 participants in Part 1 and approximately 200 participants planned in Part 2. However, the number of participants enrolled could not be determined precisely in advance and was to be determined by the safety profile and early evidence of clinical benefit.

Part 1

Approximately 100 participants as planned per Amendment 2 will be randomized in a 1:1 ratio to each of the two vobramitamab duocarmazine arms. Randomization will be stratified by 3 stratification factors: 1) visceral disease (yes vs no), 2) prior taxane (yes vs no), and 3) region (United States/Canada vs other). The historic benchmarks for each vobramitamab duocarmazine arm to compare with are 25% PSA response rate and 8 months median rPFS observed on the control arm of the PRESIDE trial of docetaxel after enzalutamide (**78**).

Since the goal of this part of the study is to select one of two vobramitamab duocarmazine doses for further study in participants with mCRPC, Simon's randomized Phase 2 selection design (**79**) was used to determine the sample size for each arm. The planned sample size of 50 per arm would provide 76% probability of correctly selecting the best dose assuming 66% and 59% rPFS rates at 6 months (equivalent to 10 vs 8 months median rPFS) for the two vobramitamab duocarmazine arms, respectively. Sample size determination based on traditional hypothesis testing would be prohibitively large for a Phase 2 study. A sample size of 350 per arm would be required to have 70% power to detect 59% vs 66% rPFS rate between two arms at 1-sided 0.1 alpha level. Comparing each arm to a fixed benchmark would also require an unfeasibly large sample size of 160 per arm in order to have 70% power to reject a fixed null rPFS rate of 59% at a 1-sided 0.1 alpha level under an alternative rPFS rate of 66% for each arm, respectively. As both doses being tested fall within the range of doses that demonstrated biological activity based on CP-MGC018-01 study data, there is minimal risk of choosing a dose that is not biologically active. All available safety and efficacy data from this study will be used to justify the dose ultimately selected for further study (e.g., in a later registrational study).

For PSA response rate, the planned sample size of 50 per arm would provide 84% power to reject 25% null rate at 1-sided 0.1 alpha level for each vobramitamab duocarmazine arm at an alternative rate of 40%.

Total enrollment in Part 1 was planned be up to approximately 120 participants to account for participants originally enrolled on the control arm per Amendment 1. Due to unexpected rapid enrollment in Part 1, this part of the study enrolled a total of 182 participants.

Part 2

Part 2 of the study was closed to enrollment prior to completing the Stage 1 enrollment target(s). Part 2 planned to enroll up to approximately 200 response-evaluable participants, consisting of approximately 40 participants for each of 5 tumor-specific cohorts (**Table 20**). For each cohort, Simon's 2-stage design (**80**) is used to test null hypothesis H_0: $p \leq p_0$ vs alternative hypothesis H_1: $p = p_1$ at 1-sided significance level ≤ 0.1 (alpha) with the power of approximately 80%, where p_0 is the benchmark response rate representing a lack of tumor response and p_1 is the target response rate representing evidence of sufficient tumor response worthy of further development. Specifically, for each cohort, Stage 1 will enroll n_1 response-evaluable participants. If the number of responses in a tumor-specific cohort enrolled in Stage 1 is less than or equal to the prespecified number of responses (r_1), then enrollment for the tumor-specific cohort will be stopped for futility, otherwise, cohort enrollment will continue to Stage 2 to enroll an additional n_2 response-evaluable participants. At the end of Stage 2, if the number of tumor responses out of all $n = n_1+n_2$ response-evaluable participants is at least r, then the null hypothesis H_0 will be rejected, and the cohort is considered to have sufficient efficacy for further development. Simon's 2-stage design parameters for each tumor-specific cohort are provided in **Table 20**.

Table 20 Simon's Two-Stage Design Parameters

14.2 Independent Data Monitoring Committee

An IDMC will oversee the ongoing monitoring and interpretation of safety data from all parts of this study (Part 1 and Part 2). An IDMC charter will be reviewed and approved by the IDMC prior to study initiation. The IDMC will evaluate aggregate safety data and efficacy data for the futility analysis in Part 1.

The first IDMC meeting will occur after 20 participants in each arm of Part 1 have been enrolled and completed at least 1 cycle of treatment or after approximately 6 months from first enrollment, whichever comes first. The IDMC may meet at any time if emergent safety data warrant a safety review. Reviews will continue in approximate 6-month intervals (± 1 month). If an IDMC meeting is scheduled to occur near the time of the planned futility analysis for Part 1, the timing of the meeting may be adjusted to align with the futility analysis.

The IDMC will be empowered to recommend changes to the study including discontinuation or modification of a study treatment arm, cohort, or overall termination of the study as appropriate.

The IDMC will be provided with clinical data tables and listings for these reviews. Additional details on the IDMC may be found in the IDMC charter.

14.3 Analysis Populations

Study analyses will be performed on the following populations:

- **Safety Population:** All participants who received any dose of study treatment. This population will be used to summarize safety data. Participants will be analyzed according to the actual study treatment received. This population will also be used to summarize baseline data for biomarker and immunogenicity analyses and for supplementary analyses of rPFS, PFS, and OS.
- **Intent-to-Treat (ITT) Population:** All participants*. Participants will be analyzed according to the study treatment assigned. This population will be used for summary of baseline data and analyses of rPFS, OS, and other efficacy endpoints where applicable.
- **Tumor Response Evaluable Population:** All participants* who received at least one dose of study treatment and had RECIST-evaluable disease per PCWG3 (Part 1) or RECIST v1.1 (Part 2) at baseline (i.e., participants with bone-only disease are excluded from this population). This population will be used for efficacy analyses related to tumor response and will be analyzed according to the study treatment assigned.
- **PSA Response Evaluable Population**: All participants in Part 1* who received at least one dose of study treatment, with a baseline PSA ≥ 2 ng/mL and at least one post-baseline PSA measurement. This population will be used to calculate and summarize PSA response rates according to the study treatment assigned.

- **PK Evaluable Population:** All participants who received at least one dose of study treatment, date and time of dose administration and relative PK sample collection are known, and have sufficient concentration data to derive at least one PK parameter. Participant data may be excluded from PK analysis at the discretion of the pharmacokineticist.
- **ADA Evaluable Population:** All participants who received at least one dose of vobramitamab duocarmazine and have at least one ADA sample.

* Note: participants in Part 1 who were assigned to the control arm prior to its removal in Amendment 2 and who were re-randomized to a vobramitamab duocarmazine arm will be analyzed as a separate cohort for safety and efficacy endpoints.

14.4 Demographics and Baseline Characteristics

Participant disposition, demographics, baseline characteristics, cancer history, prior cancer therapy, and medical history will be summarized using descriptive statistics.

14.5 Study Treatment Exposures and Concomitant Medications

Study treatment exposures and concomitant medications will be summarized by descriptive statistics. The summary of study treatment exposure will include descriptive statistics as well as frequency counts for the number of doses or cycles received, the total dose actually administered as well as the total dose intended, and the dose intensity which is calculated as percentage of total dose actually administered divided by total dose intended during whole treatment period. Concomitant medications are coded using the World Health Organization Drug Dictionary.

14.6 Pharmacokinetic, Exposure-Response, Immunogenicity, and Biomarker Analyses

14.6.1 Pharmacokinetic Analysis

Concentrations and PK parameters for vobramitamab duocarmazine will be summarized by dose cohort using descriptive statistics including number of participants, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation of the mean and geometric mean. Time-course of drug concentrations will be plotted as appropriate.

Population PK analyses may be conducted using nonlinear mixed effects methodology. Data from this study may be pooled with data from other studies for analysis. A covariate analysis may be performed to relate the effect of intrinsic and extrinsic participant factors to exposure.

14.6.2 Exposure-Response Analyses

Exposure-response analysis to assess the relationship between vobramitamab duocarmazine exposure indices derived from population PK analyses and select efficacy and AEs may be evaluated.

14.6.3 Immunogenicity Analysis

Incidence of ADA, including treatment-emergent and treatment-boosted ADA, will be assessed as absolute occurrence (n) and percent (%) of participants and will include ADA titer level. For participants who have a treatment-emergent ADA positive result, time to first treatment-emergent ADA positive result and the time course of ADA positivity will be summarized.

14.6.4 Biomarker Analysis

Summary statistics for parameters listed in **Section 10.3** will be summarized. Analyses may be presented graphically, with possible associations between baseline B7-H3 expression and efficacy (e.g., tumor response, rPFS) explored.

14.7 Efficacy Endpoints and Analyses

Efficacy analyses will consist of descriptive statistics and corresponding 95% 2-sided confidence intervals (CIs) when appropriate. Participants assigned to the control arm of Part 1 prior to its removal in Protocol Amendment 2 who were re-randomized to a vobramitamab duocarmazine arm will be analyzed for efficacy as a separate cohort.

14.7.1 Primary Efficacy Endpoints and Analysis

14.7.1.1 Radiographic Progression-Free Survival per PCWG3 (Part 1)

In Part 1, the primary efficacy endpoint is rPFS determined by the investigator. The rPFS is defined as the time from the date of randomization to the date of first documented PD per PCWG3 or death from any cause, whichever occurs first. Radiographic PD per PCWG3 is defined in **Section 11.1.1** and **Table 18** as follows:

- Progression in soft tissue lesions per RECIST v1.1 (**77**)
- Progression in bone lesions per PCWG3 criteria:
    - At least 2 new lesions (compared to baseline) are observed on first post-baseline scan (Week 8 scan), and the next scan (confirmatory at least 6 weeks later) on Week 16 shows at least 2 additional new lesions
    - At least 2 new lesions (compared to Week 8 scan) are observed on a scan performed after Week 8, and the next scan (confirmatory at least 6 weeks later) show persistence or increase in number of new lesions

For participants without an event of PD or death at the time of data cutoff for rPFS analysis, the rPFS will be censored at the date of the last tumor assessment. Specifically, the censoring rules described in **Table 21** will apply to the analysis of rPFS.

Table 21 Censoring Rules for Primary Analysis of Radiographic Progression-Free Survival

Situation	Date	Outcome
No baseline tumor assessment	Randomization date	Censored
Death prior to first scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessment in absence of death prior to first scheduled tumor assessment	Randomization date	Censored
Documented progressive disease	Date of progressive disease	Progressed
Initiation of subsequent anticancer therapy in absence of documented progressive disease	Date of last tumor assessment prior to initiation of subsequent anticancer therapy	Censored
Death or documented progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed tumor assessments	Censored

The Kaplan-Meier method will be used to generate rPFS curves and estimate the median rPFS along with 95% confidence intervals (CIs) for each study treatment arm. The method of Brookmeyer and Crowley (**81**) will be used to construct 95% CI for median rPFS. The 95% CIs for rPFS rates at 6, 8, and 12 months will be calculated by normal approximation after log(-log) transformation. A sensitivity analysis will be performed that includes documented PD or death as a rPFS event regardless of when it occurs during the study. Supplementary analyses may be performed based on the Safety Population.

The analysis of rPFS will occur when all participants in Part 1 have been followed for rPFS for at least 6 months. The 2.0 mg/kg Q4W dose of vobramitamab duocarmazine will be selected for further study if it demonstrates promising efficacy, unless there is compelling additional activity at the higher dose and it has an acceptable safety and tolerability profile. Efficacy, safety, and exposure-response variables will inform the selection decision.

14.7.1.2 Objective Response Rate per RECIST v1.1 (Part 2)

In Part 2, best overall response (BOR) will be categorized using RECIST v1.1 as CR, PR, SD, PD, or NE. To qualify as an objective response, CR and PR require confirmation at least 4 weeks after initial observation of CR or PR, and SD requires observation at least once after 6 weeks from the start of study treatment. BOR will be evaluated from the start of study treatment.

The number and percent of participants with BOR per RECIST v1.1 will be summarized. The ORR is estimated as the proportion of participants in the Tumor Response Evaluable Population who achieve a BOR of confirmed CR or PR per RECIST v1.1.

Disease control rate (DCR) is defined as the percentage of tumor response-evaluable participants who experienced response of CR, PR, or SD for at least 3 months.

ORR and DCR will be summarized and the 2-sided 95% exact binomial CI will be calculated.

14.7.2 Secondary Efficacy Endpoints and Analyses

14.7.2.1 Prostate-Specific Antigen Response (Part 1)

PSA response is defined as a ≥ 50% decline in PSA from baseline with PSA confirmation ≥ 3 weeks after the first documented reduction in PSA of ≥ 50%. The PSA response rate will be calculated as the proportion of participants with a PSA response in the PSA Response Evaluable Population. PSA response rates at 8 weeks, 12 weeks, and at any time will be summarized. The 2-sided 95% exact binomial CI for PSA response rate will be calculated.

Duration of PSA response is defined as the time from the date of first documented PSA response to the earliest date of PSA progression. Participants without PSA progression at the time of analysis will be censored to the date of their last PSA assessment. Kaplan-Meier method will be applied to estimate duration of PSA response.

The percent change in PSA from baseline over time will be summarized and presented by spider plot. The best PSA percent change from baseline will be presented by waterfall plot.

14.7.2.2 Time to Prostate-Specific Antigen Progression (Part 1)

Per PCWG3, PSA progression is defined as follows:

- In participants with a decrease in PSA from baseline: ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which is confirmed by a consecutive second value obtained ≥ 3 weeks later.
- In participants with no decrease in PSA from baseline: ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline value after 12 weeks.

Time to PSA progression is defined as the time from the date of randomization to the first documented PSA progression. Participants without PSA progression at the time of analysis will be censored to the date of their last PSA assessment. Kaplan-Meier method will be applied to estimate time to PSA progression.

14.7.2.3 Progression-Free Survival per RECIST v1.1 (Part 2)

In Part 2, PFS is defined as the time from the first dose date to the date of first documented PD per RECIST v1.1 or death from any cause, whichever occurs first. For participants without an event of PD or death at the time of data cut-off for PFS analysis, PFS will be censored at the date of the last tumor assessment. Specifically, the censoring rules described in **Table 21** will be applied as primary analysis of PFS. Supplementary analyses may be performed based on the Safety Population.

Analysis of PFS will be the same as that described for rPFS (**Section 14.7.1.1**).

14.7.2.4 Objective Response Rate per PCWG3 (Part 1)

In Part 1, BOR will be categorized using PCWG3 as CR, PR, SD, PD, or NE. To qualify as an objective response, CR and PR require confirmation at least 4 weeks after initial observation of CR or PR, and SD requires observation at least once after 6 weeks from the start of study treatment. BOR will be evaluated from the start of study treatment.

The number and percent of participants with BOR per PCWG3 criteria will be summarized. The ORR is estimated as the proportion of participants in the Tumor Response Evaluable Population who achieve a BOR of confirmed CR or PR without prior confirmed bone progression per PCWG3.

Disease control rate (DCR) is defined as the percentage of tumor response-evaluable participants who experienced response of CR, PR, or SD for at least 3 months.

ORR and DCR will be summarized and the 2-sided 95% exact binomial CI will be calculated.

14.7.2.5 Duration of Response (Part 1 and Part 2)

The DoR will be calculated as the time from the date of initial tumor response (CR or PR) to the date of first documented PD or death from any cause, whichever occurs first. DoR is calculated only for participants with a tumor response (CR or PR). For participants without an event of PD or death at the time of data cutoff for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last three situations described in **Table 21** will be applied. The Kaplan-Meier method will be used to generate DoR curves and estimate the median DoR along with 95% CIs. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

14.7.2.6 Tumor Size Change Over Time (Part 1 and Part 2)

For participants with measurable disease at baseline, the tumor size is defined as the sum of diameters of the target lesions. The tumor size change from baseline over time will be summarized and presented by spider plot. The best tumor size change from baseline will be presented by waterfall plot.

14.7.2.7 Time to First Symptomatic Skeletal Event (Part 1)

An SSE is defined as any of the following events: new symptomatic pathological fracture, requirement for radiation therapy to relieve bone pain, spinal cord compression, or tumor-related orthopedic surgical intervention. The time to first SSE is defined as the time from the date of randomization to the first occurrence of SSE. Participants without an event of SSE at the time of analysis will be censored at the last SSE assessment. The Kaplan-Meier method will be applied to estimate time to first SSE.

14.7.3 Exploratory Efficacy Endpoints and Analyses

14.7.3.1 Overall Survival (Part 1 and Part 2)

OS is defined as the time from the date of randomization (Part 1) or first dose (Part 2) to the date of death from any cause. For participants without an event of death at the time of data cutoff for OS analysis, OS will be censored at the time the participant is last known to be alive.

The Kaplan-Meier method will be used to generate OS curves and estimate the median OS along with 95% CIs. The method of Brookmeyer and Crowley (**81**) will be used to construct 95% CI for median OS. The 95% CIs for OS rates at 12, 18, and 24 months will be calculated by normal approximation after log(-log) transformation. Supplementary analyses may be performed based on the Safety Population.

14.8 Safety Endpoints and Analyses

Participants assigned to the control arm prior to its removal in Protocol Amendment 2 who were re-randomized to a vobramitamab duocarmazine arm will be analyzed for safety as a separate cohort.

14.8.1 Adverse Events

Treatment-emergent AEs will be summarized in tables and listings. Tables will display the number and percent of participants that experience the given AE. AEs prior to the first dose of study treatment (e.g., due to study-related procedures) will be presented in listings only.

AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will be summarized by system organ class (SOC) and preferred term (PT), relationship to study treatment, and highest severity. The following AEs will be summarized:

- All treatment-emergent AEs
- Treatment-emergent AEs with CTCAE severity ≥ Grade 3
- Treatment-related AEs
- Treatment-related AEs with CTCAE severity ≥ Grade 3
- SAEs
- Treatment-related SAEs
- AEs resulting in discontinuation of study drug
- AEs leading to interruption of study drug
- Fatal AEs
- AESIs

An overall summary of treatment-emergent AEs will display the number and percent of participants who experience at least one event of each of the above types.

14.8.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by laboratory panel and will be displayed by visit for each laboratory parameter. Shift tables may be produced.

14.8.3 Other Safety Endpoints

ECGs will be collected and analyzed for evidence of cardiac toxicity, including prolongation of QT interval. LVEF will be evaluated by echocardiogram or MUGA and changes from baseline summarized. Vital signs and weight will be summarized with descriptive statistics at each visit and time point collected. Shift tables may be produced.

14.9 Interim Analyses

In Part 1, one futility analysis will be performed on each vobramitamab duocarmazine arm based on PSA response rate at 8 weeks on the first 20 PSA evaluable participants in each vobramitamab duocarmazine arm. At the futility analysis, if the probability of true PSA response rate for a vobramitamab duocarmazine arm greater than or equal to 40% is <10%, that is, if ≤ 25% (5/20) PSA response rate is observed, enrollment to that arm may stop unless other data warrant continuing enrollment.

14.10 Other Assessments or Analyses

Additional analyses, if any, will be defined in the SAP.

15 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. The sponsor and/or its representatives will:

- Provide instructional material to the study sites, as appropriate.
- Conduct a study training session (investigator meeting or study initiation visit) to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general Good Clinical Practice (GCP) compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing, and Inspections

To ensure the safety of participants in the study, compliance with applicable regulations, and ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and medical records in the participant files as source documents for the study.

The sponsor or its designee will monitor the study on a regular basis throughout the study period according to the clinical monitoring plan. The investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of the participant data recorded on eCRFs against source documents at the study site. The investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The investigator and study site personnel must address all queries in a timely manner.

Participation as an investigator in this study implies acceptance of the potential for inspection by the study sponsor or representatives, US or non-US government regulatory authorities, IRB/IEC and applicable compliance and quality assurance offices. The investigator will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

If planned on-site monitoring visits are not possible (e.g., as a result of the COVID-19 public health emergency), the sponsor may perform remote monitoring visits to maintain oversight of the clinical site. Remote monitoring of clinical data using electronic medical records will follow all local and regional guidelines regarding access to and protection of participants' identifiable medical information.

15.2 Data Collection and Management

Site personnel record all data for each participant through eCRFs using an EDC system provided and approved by the sponsor. Study sites must complete eCRFs for each participant in a timely manner shortly after each participant's visit. The investigator must sign the investigator's statement in each participants eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system to ensure data accuracy, quality, consistency, and completeness. Manual queries resulting from review by monitors, medical coders, and data management staff are also generated from within the EDC system. Study sites are expected to resolve the queries and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, data management will lock the database and generate the SAS datasets necessary for analysis and reporting. Each study site will receive the eCRFs for each of their participants.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Institutional Review Board or Independent Ethics Committee Approval

The study protocol, any related documents, and participant-facing materials will be submitted to the IRB/IEC for review and approval. Written approval of the study protocol and ICFs will be in the possession of the investigator and the sponsor before the study treatment is shipped to the investigator's site. This approval must include the date of review, the protocol title and/or study number and version number, and ICF version number or date. A stamped version of the IRB-approved consent is acceptable. If the IRB/IEC or institution uses its own unique number for the protocol instead of the sponsor's number, that unique number should be noted on the approval statement. The investigator should provide the sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Protocol modifications or changes may not be initiated without approval from the sponsor and prior written IRB/IEC approval (when required), except when necessary to eliminate immediate hazards to the participants. Such modifications will be submitted to the IRB/IEC; and written verification that the modification was submitted should be obtained. The investigator must submit all changes and updates to required documents to the IRB/IEC.

16.2 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with current ICH Guidelines for Good Clinical Practice (ICH E6), and all applicable regulations including Protection of Human Subjects (21 CFR [Code of Federal Regulations] 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312.60–312.69).

16.3 Participant Information and Consent

The investigator will obtain, document, and retain IRB/IEC-approved written informed consent from the participant, as specified in **Section 9.1**. Where required, the investigator will use an appropriately translated and IRB/IEC-approved version. The sponsor reserves the right to delay initiation of the study at a site where ICFs do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the participant in both oral and written form, and participants must be given ample opportunity to inquire about details of the study. The ICF must be signed and dated by the participant and by the person who conducted the discussion of the informed consent.

16.4 Participant Confidentiality

Participants will be assigned a unique identifier by the sponsor. All laboratory specimens, evaluation forms, reports, and other records that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred. Clinical information will not be released without written permission of the participant except as necessary for monitoring by the relevant regulatory authorities, the sponsor, or the sponsor's representative. The investigator must comply with all local applicable privacy regulations regarding the protection of participant data.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

16.5 Source Documents

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the participant's medical file, original laboratory reports, histology, and pathology reports (as applicable). The investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered into the eCRFs.

16.6 Retention of Data

All essential documents, including eCRFs, source documents (regardless of media), and signed ICFs, should be retained by the investigator, per the guidance in ICH E6 or other regulatory retention requirements. There may be other circumstances for which the sponsor is required to maintain study records for longer periods; therefore, the sponsor should be contacted before study records are removed from the control of the study site for any reason. The investigator must obtain written permission from the sponsor prior to destruction of study documents.

16.7 Sample Retention and Secondary Research

Samples acquired for protocol-specified assays are retained according to local and regional regulatory requirements. If the participant consents to the use of their study samples for secondary research purposes, samples may be used for exploratory testing and retained up to 15 years from the end of study. Where allowed by local regulation, participant samples may be retained for long-term storage at a sponsor-designated facility in the US after the study has concluded.

16.8 Financial Disclosure

The investigator and sub-investigators are required to disclose in writing any applicable financial arrangement as defined in US regulation. The principal investigator's disclosure will be signed and dated prior to participating in the study.

The information, as defined in 21 CFR 54, will be collected about the investigators, their spouses and each dependent child. Investigators must update the sponsor with any changes in reported information up to 1 year following the end of the study.

In accordance with Securities and Exchange Commission regulation (17 CFR 229.404), investigators and sub-investigators must disclose if they are employees of the sponsor, or if an immediate family member of a sponsor employee, officer, or director.

16.9 Publication and Disclosure Policy

Data collected in this clinical study belong to the study sponsor. The publication terms regarding use of the study data will be noted in the clinical trial agreement and are outlined below. This includes authorship: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

- The sponsor will comply with all applicable requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

16.10 Discontinuation of the Study or Study Sites

Site participation may be discontinued by the sponsor, the investigator, a regulatory authority, or an IRB/IEC. The study may be discontinued by a regulatory authority or at the discretion of the sponsor.

Administrative or safety-related criteria for study termination include:

- Identification of an unacceptable safety risk to participants
- Poor enrollment or other evidence of study futility
- Business decision

If enrollment in the study is prematurely terminated by the sponsor for reasons other than a safety finding that poses unacceptable risk to study participants, participants already enrolled on the study may continue to receive study treatment until disease progression, a decision by the participant and/or physician that the treatment is no longer in their best interest, or other

treatment discontinuation criteria are met. The sponsor may elect to provide access to the study treatment via an alternative mechanism rather than leaving the study open (e.g., a Named Patient Program).

16.11 Summary of Results (European Union Member States)

Within 1 year from the end of the study in all EU Member States concerned, the sponsor will submit a summary of the clinical study results to the EU Clinical Trials Information System (CTIS). The content of the results summary is outlined in Clinical Trials Regulation (CTR) Annex IV. The results will be accompanied by a lay summary. The content of the lay summary is outlined in CTR Annex V.

16.12 Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor medical monitor prior to the end of the study.

The coordinating principal investigator's responsibilities include review of the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

17 REFERENCE LIST

Note: *Newly added literature references, if any, are in colored text. Previously cited submitted literature references are in black text.*

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Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study. Eur Urol, 2015. 68(1): p. 147–53.

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Appendix 1 Time and Events Schedule

Table 22 Schedule of Events (Every 4 Week Cycle)

EVALUATION/ PROCEDURE	Screening Day -28 to -1	Cycle 1 Day 1	Cycle 1 Day 8 (±1d)	Cycle 1 Day 15 (±1d)	Cycle 2 Day 1 (±3d)	Cycle 2 Day 8 (±1d)	Cycle 2 Day 15 (±1d)	Cycles 3–6 Day 1 (±3d)	Cycles 3–6 Day 15 (±1d)	EOTV
Administer vobramitamab duocarmazine		X			X			X		
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical/ cancer history	X									
Tumor specimen [a]	X									
Registration/randomization	X									
Telemedicine visit			X			X			X	
Full physical exam	X									X
Directed physical exam		X		X	X		X	X		
Vital signs [b]	X	X		X	X		X	X		X
Vital sign: oxygen saturation [b]	X	X		X	X		X	X		X
Height	X									
Weight [c]	X	X			X			X		X
ECOG performance status [c]	X	X			X			X		X
Electrocardiogram [c, d]	X	X		X	X		X	X		X
Echocardiogram (or MUGA)	X									X
Ophthalmic exam [f]	X							C4D1		X
Chemistry [c]	X	X		X	X		X	X		X [e]
Hematology [c]	X	X		X	X		X	X		X [e]
Endocrine	X									X
Coagulation	X									X

Table 22 Schedule of Events (Every 4 Week Cycle)

EVALUATION/ PROCEDURE	Screening Day -28 to -1	Cycle 1 Day 1	Cycle 1 Day 8 (±1d)	Cycle 1 Day 15 (±1d)	Cycle 2 Day 1 (±3d)	Cycle 2 Day 8 (±1d)	Cycle 2 Day 15 (±1d)	Cycles 3–6 Day 1 (±3d)	Cycles 3–6 Day 15 (±1d)	EOTV
Cardiac labs	X									X
Urinalysis	X									X
Pregnancy test (Part 2 only) [g]	X	X			X			X		X
HIV, HBV, HCV test (only where required) [h]	X									
PSA (Part 1 only) [c]	X	X			X			X		X
Testosterone (Part 1 only) [c]	X	X			X			X		X
SSE (Part 1 only) [i]		X			X			X		X
CT/MRI [j]	X	Q8W (± 7 days) from C1D1 for 24 weeks then Q12W (± 14 days)								X [j]
Bone scan [j, k]	X	Q8W (± 7 days) from C1D1 for 24 weeks then Q12W (± 14 days)								X [j]
Tumor assessment per PCWG3 (Part 1) or RECIST v1.1 (Part 2) [j]	X	Q8W (± 7 days) from C1D1 for 24 weeks then Q12W (± 14 days)								X [j]
Concomitant medications	Continuous									
Concomitant procedures	Continuous									
Adverse events	Continuous									
PK/ADA	See **Appendix 2**									

Note: Assessments/procedures are performed prior to dosing/dispensing of study treatment for each cycle unless otherwise specified. A treatment cycle is every 4 weeks (28 days ± 3 days). There must be at least 25 days between each vobramitamab duocarmazine administration in a given participant.

a Participants may undergo a fresh tumor biopsy to obtain a specimen for testing if a suitable archival tumor specimen is not available (see **Section 9.8.2.2**).

b Vital signs include temperature, pulse, blood pressure, respiratory rate, and oxygen saturation (pulse oximetry).

c If assessed within 72 hours before C1D1, the assessment does not need to be performed on C1D1. Blood samples may be collected up to 72 hours in advance of all cycles.

d On C1D1 and C2D1, ECG is assessed prior to infusion of vobramitamab duocarmazine and at end (± 15 minutes) of infusion. ECGs should be performed prior to obtaining the time-matched PK sample. At C3–C6 D1, ECG is assessed prior to infusion of vobramitamab duocarmazine. During non-dosing in-person visits, ECGs are assessed at one time point.

e If assessed within 2 weeks before EOTV, the assessment does not need to be performed at EOTV except if clinically indicated.

f Ophthalmic examinations including visual acuity testing (with correction), fundoscopic examination, and tonometry are performed at screening, C4D1 (± 7 days), and EOTV and at other time points as clinically indicated. Other directed studies (e.g., optical coherence tomography) will be performed as

clinically indicated. Participants with ocular symptoms or findings at the on-treatment exam should have repeat ophthalmic exams as clinically indicated (see also **Section 7.3.6**; participants should have weekly ocular assessments if AE ≥ Grade 2). If the most recent ophthalmic exam was within the last 60 days, a repeat ophthalmic exam at EOTV is not required unless clinically indicated.

g People of childbearing potential only. Samples may be obtained up to 72 hours in advance of all cycles. Results must be reviewed before study treatment infusion on C1D1 and all subsequent cycles. If screening test is performed within 72 hours of first infusion, repeat of the test on C1D1 is not required.

h HIV, HBV, and HCV testing only if required by local authorities (e.g., Czech Republic). Testing should follow local clinical practice guidelines/standards.

i SSE assessment for C1D1 should record events that occurred from time of signing informed consent to assessment on that day (C1D1).

j Target and non-target lesions will be designated at screening. Tumor assessments are performed Q8W (± 7 days) from C1D1 for 24 weeks then Q12W (± 14 days) (regardless of dose delay) until PD. Tumor assessments are performed at EOTV except if prior tumor assessment was ≤ 12 weeks of EOTV and results are available for tumor response assessment.

k Bone scans will be obtained for all participants with mCRPC (Part 1) or any participant with signs and/or symptoms of bone involvement (Part 2).

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; C: cycle; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOTV: end of treatment visit; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MRI: magnetic resonance imaging; MUGA: multigated acquisition scan; PCWG3: Prostate Cancer Clinical Trials Working Group 3; PD: progressive disease; PK: pharmacokinetics; PSA: prostate-specific antigen; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SSE: symptomatic skeletal event.

Table 23 Schedule of Events - Post-Treatment Follow-up Period

EVALUATION/ PROCEDURE	**Follow-up Visit** (before PD or subsequent anticancer therapy) [a] **Q12W (± 14 days)**	**Survival Follow Up Q12W (± 14 days)**
PSA (Part 1 only)	X	
Testosterone (Part 1 only)	X	
CT/MRI	X	
Bone scan [b]	X	
Tumor assessment per PCWG3 (Part 1) or RECIST v1.1 (Part 2)	X	
Survival follow up		X [c]

a Participants who discontinue study treatment for reasons other than PD (e.g., toxicity) will continue PSA (Part 1 only), testosterone (Part 1 only), and tumor assessments Q12W (calculated from Cycle 1 Day 1) from last tumor response assessment for up to 6 months from last dose of study treatment until PD, death, initiation of another anticancer therapy, withdrawal of consent, LTFU, or end of study, whichever occurs first.

b Bone scans will be obtained for all participants with mCRPC (Part 1) or any participant with signs and/or symptoms of bone involvement (Part 2).

c Survival status is assessed approximately Q12W for up to 6 months from last dose of study treatment or until withdrawal of consent, LTFU, death, or end of study, whichever occurs first. The first survival follow-up assessment will be scheduled 12 weeks after the last dose of study treatment.

Abbreviations: CT: computed tomography; EOTV: end of treatment visit; LTFU: lost to follow up; MRI: magnetic resonance imaging; PCWG3: Prostate Cancer Clinical Trials Working Group 3; PD: progressive disease; PSA: prostate-specific antigen; Q8W: every 8 weeks; Q12W: every 12 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.

Appendix 2 Pharmacokinetics and Immunogenicity Collection Schedules

Note: select sites will not be required to collect PK samples. The sponsor will inform the study site on the need for PK sampling at that site.

Table 24 Pharmacokinetic Sample Collection Schedule

Cycle	Day	Timepoint	Window	PK: Total Ab and Conjugated Ab (serum)	PK: SYD986 (plasma)	ADA: (serum)
1	1	Pre-infusion	N/A	X	X	X
1	1	EOI	+ 10 min	X	X	
1	1	2–4 h after EOI	N/A	X	X	
1	1	6–8 h after EOI	N/A	X	X	
1	15	Day 15	N/A	X	X	X
2	1	Pre-infusion	N/A	X	X	X
2	1	EOI	+ 10 min	X	X	
2	15	Day 15	N/A	X	X	
3, 4, 5, and 6	1	Pre-infusion	N/A	X	X	X
3, 4, 5, and 6	1	EOI	+ 10 min	X	X	
IRR [a]	N/A	N/A	N/A	X	X	X
EOTV	N/A	EOTV	N/A	X	X	X

Note: Actual start of infusion times, EOI times, and PK/ADA sample collection times will be recorded on the eCRFs. Do not collect PK samples from infusion port. Pre-infusion PK samples may be collected before start of infusion on visit day (dosing day) or day before infusion. When collecting multiple samples, collect the PK sample first.

a PK and ADA samples may be obtained at additional time points in participants who experience signs and symptoms of IRR. Samples should be obtained as soon as possible after onset of IRR, if feasible. See laboratory manual for details on sample collection.

Abbreviations: ADA: anti-drug antibody; Ab: antibody; EOI: end of infusion; EOTV: end of treatment visit; N/A: not applicable; IRR: infusion related reaction; PK: pharmacokinetic.

Appendix 3 Principal Investigator's Agreement

Study Title: A Phase 2, Open-Label Study of Vobramitamab Duocarmazine in Participants with Metastatic Castration-Resistant Prostate Cancer and Other Solid Tumors (TAMARACK)

Study Number: CP-MGC018-03

I have read the protocol described above.

I understand that the information in this protocol is confidential and must not be disclosed, other than to those directly involved in the execution of, or the ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide information to a participant to obtain consent.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

Signed: _____ Date: _____

Printed name: _____

Title: _____

Affiliation: _____

Address: _____

Phone number: _____

CP-MGC018-03 Protocol Amendment 5 (19-Aug-2024)
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