Title Page

Protocol Title:		A Phase 3, Open-label, Multicenter, Randomized Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Chemotherapy
Short Protocol Title:		Phase 3 Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Progressive Metastatic Castration-Resistant Prostate Cancer **(XALute)**
Protocol Number:		20230005
Investigational Product:		Xaluritamig (AMG 509)
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	Amendment 1 **Amendment 2**	20 August 2024 **08 April 2025**
Data Elements Standards Version:	9	

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonisation [ICH] E6).

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 3, Open-label, Multicenter, Randomized Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Chemotherapy, dated **08 April 2025**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc. I agree not to share the confidential information contained in this document without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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Title and Role of Investigator

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Institution Name

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 3, Open-label, Multicenter, Randomized Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Chemotherapy

Short Protocol Title: Phase 3 Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Progressive Metastatic Castration-Resistant Prostate Cancer **(XALute)**

Study Phase: Phase 3

Indication: Metastatic castration-resistant prostate cancer (mCRPC)

Study Rationale

Xaluritamig is a six transmembrane epithelial antigen of the prostate 1 (STEAP1)-targeted Xmab2+1 T-cell engager (TCE) in development for treatment of prostate cancer based on STEAP1 overexpression across the disease continuum, supported by pre-clinical data and clinical evidence of efficacy with manageable safety profile in subjects with mCRPC (first-in-human [FIH] Study 20180146). Based on available data, xaluritamig is being developed as an option to improve treatment outcomes and survival in post-taxane mCRPC.

Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To compare overall survival (OS) in subjects receiving xaluritamig vs investigator's choice (cabazitaxel or second androgen receptor-directed therapy [ARDT])	• Overall survival
Key Secondary	
• To compare radiographic progression-free survival (rPFS) in subjects receiving xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Radiographic progression-free survival per Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1, as assessed by blinded independent central review (BICR)
Secondary	
• To evaluate other measures of efficacy of xaluritamig vs	• Objective response per **modified** RECIST v1.1, as assessed by BICR

investigator's choice (cabazitaxel or second ARDT)	• Duration of response (DOR) per **modified** RECIST v1.1, as assessed by BICR • Disease control **per modified RECIST v1.1, as assessed by BICR** • Time to Response (TTR) per **modified** RECIST v1.1, as assessed by BICR
• To compare symptomatic skeletal events (SSE) in subjects treated with xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Time to first SSE
• To evaluate the safety and tolerability of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Treatment Emergent Adverse Events, Treatment Emergent Serious Adverse Events, and fatal adverse events
• To evaluate health-related quality of life (HRQoL) of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Change from baseline in: o Brief Pain Inventory - Short Form (BPI-SF) Worst pain score o BPI-SF Pain intensity scale o BPI-SF Pain interference scale o Functional Assessment of Cancer Therapy – Prostate (FACT-P) Total score and subscale scores o European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) Utility score o Change from baseline in the EQ-5D-5L Visual Analogue Scale (VAS) • Time to worsening in: o BPI-SF Worst pain score o BPI-SF Pain intensity scale o BPI-SF Pain interference scale o FACT-P Total score • Time to pain improvement in: o Subjects with moderate/severe pain at baseline • Time to improvement after worsening in: o BPI-SF Pain intensity scale o BPI-SF Pain interference scale

• To evaluate patient-reported safety and tolerability of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Patient-reported outcomes summary scores as assessed by: o Selected questions on symptomatic adverse events from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library o The GP5 question on overall bother of side effects from the FACT-P questionnaire
• Evaluate the biochemical response of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• PSA50 and PSA90 responses
• Characterize the pharmacokinetics (PK) of xaluritamig using intensive and sparse PK sampling	• PK parameters for xaluritamig such as maximum serum concentration (C_{max}), time to maximum concentration (T_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate the immunogenicity of xaluritamig	• Incidence of anti-xaluritamig antibody formation

Overall Design

This is a randomized, multi-center, open-label, phase 3 study to evaluate the efficacy and safety of xaluritamig versus investigator's choice of cabazitaxel or second ARDT in subjects with mCRPC previously treated with taxane chemotherapy.

Eligible subjects will be randomized with a 2:1 allocation ratio to receive either: xaluritamig monotherapy (experimental arm) or investigator's choice of cabazitaxel or second ARDT (control arm).

Randomization will be stratified by:

- lactate dehydrogenase (LDH) (≤ 260 IU/L vs > 260 IU/L)
- presence of liver metastases (yes vs no)
- prior treatment with Prostate-Specific Membrane Antigen (PSMA) radioligand therapy (RLT) (yes vs no)
- planned intention to treat with cabazitaxel vs second ARDT

Enrollment for the planned intention to treat with cabazitaxel vs second ARDT stratification factor will be equally allocated (ie, 50%/50%) to each level.

Subjects must begin study treatment within 10 days after randomization. Subjects will receive treatment until blinded independent central review (BICR)-confirmed radiographic disease progression per Prostate Cancer Working Group 3 (PCWG3)-modified Response Evaluation Criteria in Solid Tumors (RECIST v1.1), unacceptable toxicity, initiation of other anticancer therapy, withdrawal of consent, death or end of study as determined by the sponsor, whichever comes first.

A safety follow-up (SFU) visit will be performed approximately 30 (+3) days after the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s). Subjects will be in long-term follow-up **(**LTFU**)** for up to 3 years after the last subject is randomized, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. LTFU will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. **Ad hoc vital status (survival status) collection may be required to support key study analysis**.

Number of Subjects

Approximately 675 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years old) with progressive, metastatic (at least one confirmed metastatic lesion present at baseline within 28 days prior to enrollment) castration-resistant adenocarcinoma of the prostate who have previously received one prior taxane regimen in the mCRPC setting will be eligible for this study.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Experimental Arm:

- Xaluritamig will be administered with 3 step dosing in the first 28-day cycle comprising 0.1 mg cycle 1 day 1, 0.3 mg cycle 1 day 8, and 1.0 mg cycle 1 day 15 prior to reaching the target dose of 1.5 mg on cycle 1 day 22. Xaluritamig will then be administered at the 1.5 mg target dose every 2 weeks **(**Q2W**)** on days 1 and 15 of each subsequent 28-day cycle, starting with cycle 2 day 1.

Control Arm: Subjects in the control arm will be treated with investigator's choice of cabazitaxel or second ARDT according to the intention to treat indicated prior to randomization.

- Cabazitaxel 20 or 25 mg/m^2 as per local prescribing information and relevant guidelines

- Second ARDT (abiraterone acetate or enzalutamide) administered orally on a daily basis as per local prescribing information and relevant guidelines

Refer to Section 6.1 for complete treatment details.

Statistical Considerations

Approximately 675 subjects with progressive mCRPC will be randomized with a 2:1 randomization ratio (ie, 450 subjects in the experimental arm and 225 subjects in the control arm).

Overall Survival (OS)

A total of 464 OS events will provide approximately 90% power to demonstrate superiority at an alternative hazard ratio (HR) of 0.72 with log-rank test using 1-sided overall type I error of 0.025 in a group sequential design with 2 Interim Analyses (IA) for claiming early efficacy and 1 Primary Analysis (PA). It is estimated that the first OS IA will occur at 25 months, the second at 32 months, and the OS PA will be triggered at approximately 43 months after the first subject randomized.

For a full description of statistical analysis methods, please refer to Section 9.

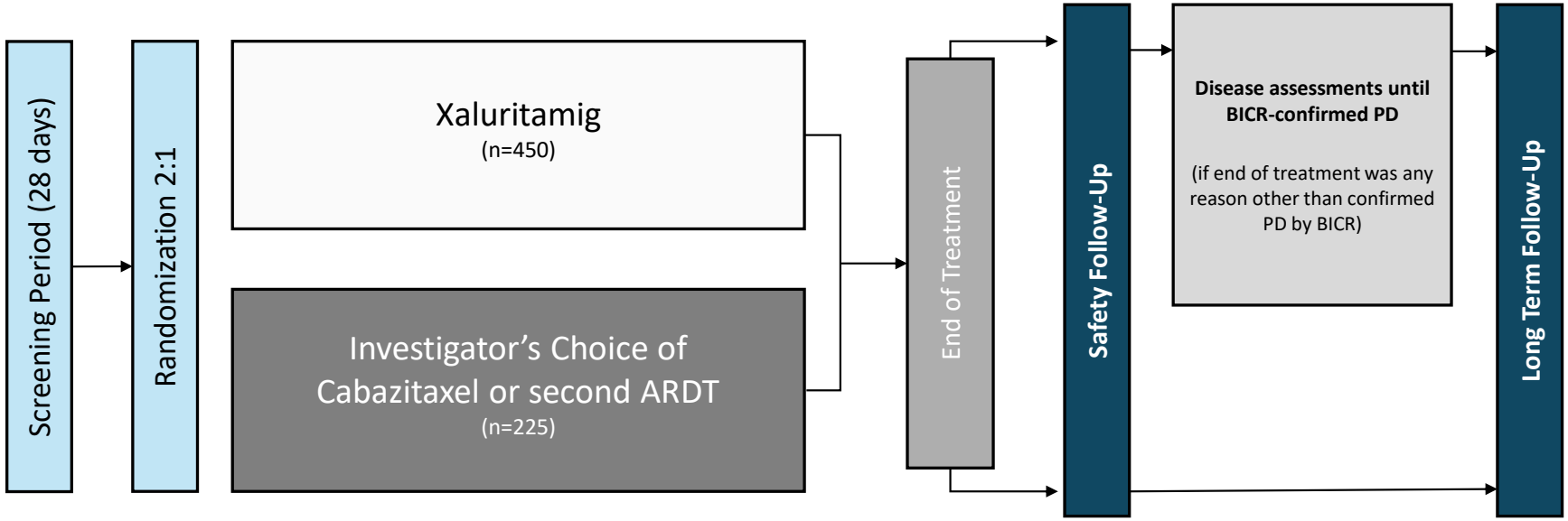
Statistical Hypotheses

The hypothesis of the primary efficacy endpoint (OS) and key secondary efficacy endpoint (radiographic progression-free survival [rPFS]) will be tested sequentially. The OS endpoint will be tested with 1-sided overall type I error (alpha) of 0.025. If OS is significant, the key secondary efficacy endpoint of rPFS will be tested with 1-sided overall type 1 error (alpha) of 0.025.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



ARDT = androgen receptor-directed therapy; BICR = blinded independent central review; PD = progressive disease.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
GENERAL/SAFETY ASSESSMENTS															
Informed Consent(s)	X														Main study and any associated informed consent form(s), as applicable.
Inclusion and exclusion criteria	X														
Demographics	X														
Physical examination[h]	X	(X)		(X)		(X)		(X)		(X)	(X)	(X)	(X)		(X) Focused review of systems/directed physical exam, as **clinically indicated**. Refer to Section **8.2.5**.
Neurological examination[h]		X													Neurological exam is required any time after randomization and before C1D1 dosing. During treatment, neurological examination required only if clinically indicated. Refer to Section **8.2.7**.
Physical measurements	X	X								X		X	X		Height collected at screening only. Refer to Section **8.2.6**.
Medical History	X														
Substance use history	**X**														**Substances: alcohol, tobacco, drugs**

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
GENERAL/SAFETY ASSESSMENTS (CONTINUED)															
12-lead ECG[h]	X												X		
Vital signs[h]	X	(X)		[X]		[X]		[X]		"X"	"X"	X	X		Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry and temperature. Refer to Section 8.4.1. (X) Vitals collected pre-infusion, EOI, 4 to 6 hours after EOI, and prior to discharge. [X] Vitals collected pre-infusion, EOI and 4 to 6 hours after EOI. "X" Vitals collected pre-infusion and EOI.
ECOG PS	X	X								(X)		X	X		(X) C3D1 and every other cycle thereafter.
Echocardiogram	(X)														(X) Required only in subjects with known history of cardiac disease (prior MI, angina pectoris, CABG, angioplasty, stent placement).
Adverse events		Continually throughout the study, through the end of SFU													
Serious adverse events	Continually throughout the study, through the end of SFU													(X)	(X) During the long-term follow-up phase and after end of study, serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. Please refer to Section **8.4.5.1.4** for additional details.

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Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
GENERAL/SAFETY ASSESSMENTS (CONTINUED)															
Prior therapies review	X														
Concomitant therapies review	Continually throughout the study, through the end of SFU														
Subsequent cancer therapy													X	X	
Vital status														X	
LOCAL LABORATORY TESTING[i]															
CBC with differential[h]	X	X				X				X		X	X		
Chemistry[h]	X	X				X				X		X	X		
PSA	X	X						**X**		(X)		X	X		**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments).**
LDH	X	X						**X**		(X)		X	X		
Hepatitis serology, HIV	(X)														(X) Required only for subjects with known history of HIV, hepatitis B or hepatitis C infection or those considered to be at risk.
Testosterone	X														

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Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
CENTRAL LABORATORY TESTS[i]															
PSA		X						**X**		(X)		X			**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments)**.
ctDNA		X						**X**		(X)		X	X		
PBMCs		X						**X**		(X)		X			
Anti-xaluritamig antibody		X								X		X	X		
Saliva (Optional PG)	X														Obtain confirmation that the PG informed consent(s) form has been signed before performing pharmacogenetic procedures.
Creatine Kinase		X								X		**X**	**X**		
Archival Tumor Sample (archival biopsy or radical prostatectomy sample)	X														An archival tumor sample**, preferably collected within 2 years of signing informed consent, is required to be submitted** prior to C1D1 **if available**. Additional biopsies may be collected on **study at the investigator's discretion, provided that the subject has been appropriately informed** and **provided written consent**.

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Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
SPARSE PK/PD ASSESSMENTS (FOR ALL SUBJECTS EXCEPT THOSE PARTICIPATING IN INTENSIVE PK/PD SUBSTUDY)															
PK (sparse)		(X)		(X)		(X)		(X)		(X)	(X)	X	X		**X: Collect 1 PK sample** (X): Collect PK samples at pre-infusion and EOI.
Cytokines (sparse)		(X)								[X]		X			**X: Collect 1 cytokine sample** (X): Collect cytokine samples at pre-infusion and 6 hours after EOI. [X]: Collect cytokine sample at C2D1 **and C3D1** pre-infusion only.
INTENSIVE PK/PD ASSESSMENTS (ONLY SUBJECTS IN INTENSIVE PK/PD SUBSTUDY)															
PK/PD substudy informed consent		X													To be completed before any PK/PD sample collection procedures are performed.

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Footnotes defined on last page of this table

Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
INTENSIVE PK/PD ASSESSMENTS (ONLY SUBJECTS IN INTENSIVE PK/PD SUBSTUDY) (CONTINUED)															
PK (intensive)		(X)[f]		[X]		[X]		"X"		[X]	[X]	X	X		**X: Collect 1 PK sample** (X) Collect PK samples at pre-infusion, EOI, 2 hours after EOI, 6 hours after EOI**,** and prior to discharge. [X] Collect PK samples at pre-infusion and EOI only. "X" Collect PK samples at pre-infusion, EOI, 2 hours after EOI, 4 hours after EOI and 6 hours after EOI.
Cytokines (intensive)		(X)[f]		[X]		[X]		"X"		[X]		X			**X: Collect 1 cytokine sample** (X) Collect cytokine samples at pre-infusion, 2 hours after EOI, 6 hours after EOI**,** and prior to discharge. [X] Collect cytokine sample **on C1D8**, **C1D15, C2D1, and C3D1 at** pre-infusion only. "X" Collect cytokine samples at pre-infusion, 2 hours after EOI, and 6 hours after EOI.

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Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
RADIOLOGIC ASSESSMENTS															
CT/MRI **and Bone Scan**	X	Imaging every 8 weeks from the date of randomization (± 7 days) for the first 48 weeks, followed by every 12 weeks (± 14 days) thereafter until BICR-confirmed disease progression per PCWG3-modified RECIST v1.1										(X)	(X)	**(X)**	Radiographic assessments are obtained as indicated, irrespective of dose delays. **Bone scans will be completed per PCWG3 recommendations. Please refer to Section 8.3.2 and Section 11.13 for further details.** **Blood samples or tumor biopsy must not be collected until at least 24 hours (or 1 day) following a bone scintigraphy scan.** **(X)** For subjects who discontinue study treatment for reasons other than confirmed radiographic PD, every effort should be made to perform scheduled radiographic imaging until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or end of study as determined by the sponsor, whichever occurs first.

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
RADIOLOGIC ASSESSMENTS (CONTINUED)															
Off-protocol PSMA-PET	Any unscheduled, off-protocol PSMA-PET scans performed at the investigator's discretion will be collected. However, this study does not support or require PSMA-PET scanning.														If off-protocol PSMA-PET data is available at screening (performed within 3 months of randomization) or is conducted off-protocol during the study (based on the investigator's discretion for ongoing subject care), these scans will be collected and uploaded to the imaging vendor according to the imaging manual. Please note that PSMA-PET is not a predefined method for tumor assessment as per PCWG3 guidelines and should not be performed as part of the study.
CLINICAL OUTCOME AND HEALTH ASSESSMENTS															
Patient-reported outcome questionnaires	Refer to Table 1-2. Schedule of Clinical Outcome and Health Assessments – Xaluritamig Arm														
STUDY TREATMENT															
Premedication		X		X		X		X		(X)	(X)				(X) Per investigator's discretion. Refer to Section 6.1.2.1.
Xaluritamig IV infusion		X		X		X		X		X	X				First dose/C1D1 must occur within 10 days of randomization. Refer to Section 6.1.2.1.1 and Table 6-1.

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities – Xaluritamig Arm

Procedure[a,b]	SCR	Study Treatment[b,i,k] (28-day cycles)										EOT[c]	SFU[d]	LTFU[e]	Notes
		Cycle 1								Cycles 2+					
Week		1		2		3		4		1	3				
Day	-28 to 0	1	2[g]	8	9[g]	15	16[g]	22	23[g]	1	15				
STUDY TREATMENT (CONTINUED)															
Hospital stay/ monitoring[j]		(X)	[X]	"X"	[X]	"X"	[X]	"X"	[X]						(X) **M**inimum 16 hours inpatient monitoring following C1D1 end of infusion. [X] Subjects must have a follow-up visit at **approx.** 24 hours after the EOI; visit can be conducted by telephone and performed by the investigator or a delegate. "X" 4 to 6 hours outpatient monitoring following C1D8, C1D15, and C1D22 infusions. Additional hospitalization beyond cycle 1 will be permitted.

BICR = blinded independent central review; C = cycle; CABG = coronary artery bypass graft; CBC = complete blood count; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = end of treatment; IV = intravenous; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; **PG = pharmacogenetic;** PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic; PSA = prostate-specific antigen; PSMA-**PET** = Prostate-Specific Membrane Antigen-**positron emission tomography**; **QW = weekly; Q2W = every 2 weeks**; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; SCR = screening; SFU = safety follow-up; SOC = standard of care

[a] Assessments are done pre-infusion unless specified. End of infusion (EOI) assessments or procedures are to be completed after the xaluritamig post-infusion flush. Laboratory assessments, **physical examinations, and PROs must be conducted within window and before the infusion. Assessments have a minus 24-hour window unless otherwise specified**. Assessments should not be performed from the infusion line.

[b] Cycle 1 **or dose re-escalation** visits have a ± 1-day window. **Cycle 2+ visits** have a ± 3-day window. **When resuming treatment after a dose delay (≤ 21 days in QW schedule or ≤ 42 days in Q2W schedule), align with the Schedule of Activities for the originally planned visit.**

[c] Upon permanent discontinuation from study treatment for any reason, an EOT visit will be performed as soon as possible (within 14 days) after last dose of study treatment and prior to start of subsequent anticancer therapy.

[d] Upon permanent discontinuation from the study treatment for any reason, the SFU visit will be performed approximately 30 (+3) days after the end of the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s). **The SFU visit will occur regardless of subsequent anticancer therapy within that period.**

[e] LTFU will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. Subjects will be in LTFU for up to 3 years after the last subject is randomized, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. **Additional survival sweeps may be requested**.

[f] **Discharge sample to be collected approximately 16 hours post EOI when feasible, if not, as soon as possible thereafter.**

[g] Visit can be conducted by telephone and performed by the investigator or a delegate and includes recording any adverse or serious adverse event(s) and concomitant medications.

[h] Additional assessment timepoint(s) as clinically indicated.

[i] If a subject has significant unexplained/possibly xaluritamig-related **localized inflammatory events**, consider additional diagnostic tests (eg, CT/MRI and/or electromyography) along with laboratory test results (eg, CBC with differential, serum aldolase, CRP, creatine kinase, myoglobin, auto-antibody panel, cytokines) if possible, prior to initiation of corticosteroid therapy. Consultation with a rheumatologist/neurologist with detailed examination at the time of the event is recommended.

[j] All subjects randomized to xaluritamig will be hospitalized for intensive monitoring for minimum 16 hours for cycle 1 day 1 after EOI and the subject will be evaluated prior to discharge. For subsequent cycle 1 dosing days (days 8, 15, and 22), subject should be monitored for 4 to 6 hours after EOI before discharge. For all cycle 1 infusions, subject must have a follow-up visit at 24 hours after the EOI; visit can be conducted by telephone and performed by the investigator or a delegate. A caregiver staying with the subject will be trained on CRS symptoms by the investigator or delegate. **After discharge, t**rained caregiver presence and support **is required** for a minimum of 24 hours **from the end of** cycle 1 xaluritamig infusion. Subject and caregiver must stay in proximity of the hospital or appropriate medical facility (within 1 hour) for 24 hours **from** the end of cycle 1 xaluritamig infusion. For cycle 2 and beyond, the subject should be monitored as per **SOC**.

[k] **For xaluritamig re-escalation following a dose delay of more than 21 days (QW dosing/cycle 1) or 42 days (Q2W dosing/cycle 2+), xaluritamig treatment should be restarted at 0.1 mg following the 3-step dosing schedule of cycle 1 to achieve the target dose. This includes all premedication (Section 6.1.2.1), hospitalization, and monitoring requirements according to guidance provided in Table 6-1. All cycle 1 assessments outlined in the Schedule of Activities should be repeated, with the exception of PRO assessments (which should continue with the respective frequency as outlined in Table 1-2). See Section 6.2 for additional details on dose delays.**

Table 1-2. Schedule of Clinical Outcome and Health Assessments – Xaluritamig Arm

Procedure[a]	SCR	Study Treatment (28-day cycles)																				EOT	SFU	LTFU[a]	Notes
		Cycle 1				Cycle 2				Cycle 3				Cycle 4		Cycle 5		Cycle 6		Cycle 7+					
Week		1	2	3	4	1	2	3	4	1	2	3	4	1	3	1	3	1	3	1	3				
Day	-28 to 0	1	8	15	22	1	8	15	22	1	8	15	22	1	15	1	15	1	15	1	15				
CLINICAL OUTCOME AND HEALTH ASSESSMENTS[b]																									
EQ-5D-5L		X		X		X		X		X		X		X	X	X	X	X	X	(X)		X	X	[X]	(X) C7D1 and every 6 weeks thereafter. [X] Telephone version is acceptable at LTFU if the visit is conducted by phone.
BPI-SF		X		X		X		X		X		X		X	X	X	X	X	X	(X)		X	X		
FACT-P		X		X		X		X		X		X		X	X	X	X	X	X	(X)		X	X		
FACT-P GP5 single question			X		X		X		X		X		X												At C1D1, C1D15, C2D1, C2D15, C3D1, C3D15, C4D1, EOT**,** and SFU**,** the FACT-P GP5 single question will be administered as part of the FACT-P questionnaire.
PRO-CTCAE		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**(X)**		X	X		Items: Nausea, Diarrhea, Shortness of breath, Numbness and tingling, Dizziness, General Pain, **Muscle pain, Joint pain**, **F**atigue, and Chills. **(X) C7D1 and every 6 weeks thereafter.**

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BPI-SF = Brief Pain Inventory-Short Form; C = cycle; EOT = end of treatment; EQ-5D-5L = European Quality of Life 5 Domain 5 Level Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; LTFU = long-term follow-up; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; SCR = screening; SFU = safety follow-up

[a] Collection of EQ-5D-5L in the LTFU should occur in clinic or via telephone every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. Subjects will be in LTFU for up to 3 years after the last subject is randomized**,** or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first.

[b] PRO questionnaires during the study treatment period, at the EOT visit and at the SFU visit will be collected by electronic device. Questionnaires will be completed either at the clinic **visit on a tablet device (EQ-5D-5L, BPI-SF, FACT-P, PRO-CTCAE)** or **at home on a handheld device (FACT-P GP5 single question, PRO-CTCAE)**, preferably at the same time of the day. If administered **during** clinic **visits**, the questionnaires are to be completed by the subject before receiving any study treatment, before any clinical assessments or consultation with the investigator, and before being informed **about** current disease status. **In case clinic visits are postponed due to dose delays, the in-clinic PRO assessments may be postponed until the next visit. Weekly assessments falling outside of scheduled clinic visits (during the first 13 weeks only) will be completed at home through a handheld electronic device and are not affected by dose delays**. If a questionnaire is not completed as indicated, the reason for missing the specific time point should be reported.

Table 1-3. Schedule of Activities - Investigator's Choice Arm - Cabazitaxel

Procedure[a,b]	SCR	Study Treatment[b]					EOT[c]	SFU[d]	LTFU[e]	Notes
Week		1	2	3	4	7+[h]				
Day	-28 to 0	1	8[g]	15[g]	22	43				
GENERAL/SAFETY ASSESSMENTS										
Informed Consent(s)	X									Main study and any associated informed consent form(s), as applicable.
Inclusion and exclusion criteria	X									
Demographics	X									
Physical examination[f]	X	(X)	(X)	(X)	(X)	**[(X)]**	(X)	(X)		(X) Focused review of systems/directed physical exam, as required. Includes neurological examination, if clinically indicated. [X] Week **7** and every 3 weeks thereafter. Refer to Section **8.2.5** and Section **8.2.7**.
Physical measurements	X	X			X	**(X)**	X	X		Height collected at screening only. (X) Week **7** and every 3 weeks thereafter. Refer to Section **8.2.6**.
Medical History	X									
12 lead ECG[f]	X							X		
Vital signs[f]	X	X			X	**(X)**	X	X		Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. Refer to Section 8.4.1. (X) Week **7** and every 3 weeks thereafter.
ECOG PS	X	**X**				**(X)**	X	X		(X) Week **7** and every 6 weeks thereafter.

Footnotes defined on last page of this table.

Table 1-3. Schedule of Activities - Investigator's Choice Arm - Cabazitaxel

Procedure[a,b]	SCR	Study Treatment[b]					EOT[c]	SFU[d]	LTFU[e]	Notes
Week		**1**	**2**	**3**	**4**	**7+[h]**				
Day	**-28 to 0**	**1**	**8[g]**	**15[g]**	**22**	**43**				
GENERAL/SAFETY ASSESSMENTS (CONTINUED)										
Echocardiogram	(X)									(X) Required only in subjects with known history of cardiac disease (prior MI, angina pectoris, coronary artery bypass graft, angioplasty, stent placement).
Adverse events		Continually throughout the study, through the end of SFU								
Serious adverse events	Continually throughout the study, through the end of SFU								(X)	(X) During the long-term follow-up phase and after end of study, serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. Please refer to Section **8.4.5.1.4** for additional details.
Prior therapies review	X									
Concomitant therapies review		Continually throughout the study, through the end of SFU								
Subsequent cancer therapy								X	X	
Vital status									X	
LOCAL LABORATORY TESTING										
CBC with differential[f]	X	X	X	X	X	(X)	X	X		**Defer to local SOC for additional collections.**
Chemistry[f]	X	X	X	X	X	(X)	X	X		(X) Week **7** and every 3 weeks thereafter.

Footnotes defined on last page of this table.

Table 1-3. Schedule of Activities - Investigator's Choice Arm - Cabazitaxel

Procedure[a,b]	SCR	Study Treatment[b]					EOT[c]	SFU[d]	LTFU[e]	Notes
Week		1	2	3	4	7+[h]				
Day	-28 to 0	1	8[g]	15[g]	22	43				
LOCAL LABORATORY TESTING (CONTINUED)										
PSA	X	X			**X**	(X)	X	X		**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments).**
LDH	X	X			**X**	(X)	X	X		
Hepatitis serology, HIV	(X)									(X) Required only for subjects with known history of HIV, hepatitis B, or hepatitis C infection or those considered to be at risk.
Testosterone	X									
CENTRAL LABORATORY TESTS										
PSA		X			**X**	(X)	X	X		**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments).**
ctDNA		X			X	**(X)**	X	X		
PBMCs		X			X	**(X)**	X			

Footnotes defined on last page of this table.

Table 1-3. Schedule of Activities - Investigator's Choice Arm - Cabazitaxel

Procedure[a,b]	SCR	Study Treatment[b]					EOT[c]	SFU[d]	LTFU[e]	Notes
Week		1	2	3	4	7+[h]				
Day	-28 to 0	1	8[g]	15[g]	22	43				
CENTRAL LABORATORY TESTS (CONTINUED)										
Saliva (Optional PG)	X									Obtain confirmation that the PG informed consent(s) form has been signed before performing pharmacogenetic procedures.
Cytokines		X				**(X)**	X			**(X) Week 13, Day 85 only.**
Archival Tumor Sample (archival biopsy or radical prostatectomy sample)	X									An archival tumor sample**, preferably collected within 2 years of signing informed consent, is required to be submitted** prior to D1 **if available**. Additionally, biopsies may be collected **on study at the investigator's discretion, provided that the subject has been appropriately informed and provided written consent**.
RADIOLOGIC ASSESSMENTS										
CT/MRI **and Bone Scan**	X	Imaging every 8 weeks from the date of randomization (± 7 days) for the first 48 weeks, followed by every 12 weeks (± 14 days) thereafter until BICR-confirmed disease progression per PCWG3-modified RECIST **v**1.1.					(X)	(X)	**(X)**	Radiographic assessments are obtained as indicated irrespective of dose delays. **Bone scans will be completed per PCWG3 recommendations. Please refer to Section 8.3.2 and Section 11.13 for further details.** **Blood samples or tumor biopsy must not be collected until at least 24 hours (or 1 day) following a bone scintigraphy scan.** **(X)** For subjects who discontinue study treatment for reasons other than confirmed radiographic PD, every effort should be made to perform scheduled radiographic imaging until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or end of study as determined by the sponsor, whichever occurs first.

Footnotes defined on last page of this table.

Table 1-3. Schedule of Activities - Investigator's Choice Arm - Cabazitaxel

Procedure[a,b]	SCR	Study Treatment[b]					EOT[c]	SFU[d]	LTFU[e]	Notes
Week		1	2	3	4	7+[h]				
Day	-28 to 0	1	8[g]	15[g]	22	43				
Off-protocol PSMA-PET	Any unscheduled, off-protocol PSMA-PET scans performed at the investigator's discretion will be collected. However, this study does not support or require PSMA-PET scanning.									If off-protocol PSMA-PET data is available at screening (performed within 3 months of randomization) or is conducted off-protocol during the study (based on the investigator's discretion for ongoing subject care), these scans will be collected and uploaded to the imaging vendor according to the imaging manual. Please note that PSMA-PET is not a predefined method for tumor assessment as per PCWG3 guidelines and should not be performed as part of the study.
CLINICAL OUTCOME AND HEALTH ASSESSMENTS										
Patient-reported outcome questionnaires	Refer to Table 1-5. - Schedule of Clinical Outcome and Health Assessments - Investigator's Choice									
STUDY TREATMENT										
Premedication		X			X	X				Premedication **based on local treatment guidelines administered per local prescribing information**. Refer to Section 6.1.2.1
Cabazitaxel		Q3W								First dose (D1) must occur within 10 days of randomization

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BICR = blinded independent central review; CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; IV = intravenous; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; **PG = pharmacogenetics;** PSA = prostate-specific antigen; PSMA-**PET** = Prostate-Specific Membrane Antigen-**positron emission tomography**; **Q3W = every 3 weeks; Q6W = every 6 weeks;** RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; **SOA = Schedule of Activities;** SCR = screening; SFU = safety follow-up; SOC = standard of care

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise noted. **Assessments have a minus 24-hour window unless otherwise specified.**

[b] **V**isits have a ± 3-day window unless otherwise specified. **When resuming treatment after a dose delay, align with the Schedule of Activities for the originally planned visit.**

[c] Upon permanent discontinuation from study treatment for any reason, an EOT visit will be performed as soon as possible (within 14 days) after last dose of study treatment and prior to start of subsequent anticancer therapy.

[d] Upon permanent discontinuation from the study treatment for any reason, the SFU will be performed approximately 30 (+3) days after the end of the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s). **The SFU visit will occur regardless of subsequent anticancer therapy within that period.**

[e] LTFU will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. Subjects will be in LTFU up to 3 years after last subject is randomized. **Additional survival sweeps may be requested.**

[f] Additional assessment timepoint(s) as clinically indicated.

[g] **Visit can be conducted by telephone and performed by the investigator or a delegate and includes recording any adverse or serious adverse event(s) and concomitant medications**. **In the case of telephone visit, relevant assessments must still be completed per SOA.**

[h] **From week 7 onwards the following minimum assessments are required Q3W (physical examination [if clinically indicated], physical measurements, vital signs, CBC, Chemistry) and Q6W (ECOG PS).**

Table 1-4. Schedule of Activities - Investigator's Choice Arm - Second ARDT

Procedure[a,b]	SCR	Study Treatment[b]			EOT[c]	SFU[d]	LTFU[e]	Notes
Week		**1**	**4**	**7+[h]**				
Day	**-28 to 0**	**1**	**22**	**43**				
GENERAL/SAFETY ASSESSMENTS								
Informed Consent(s)	X							Main study and any associated informed consent form(s), as applicable.
Inclusion and exclusion criteria	X							
Demographics	X							
Physical examination[f]	X	(X)	(X)	**[**(X)**]**	(X)	(X)		(X) Focused review of systems/directed physical exam, as required. Includes neurological examination, if clinically indicated. [X] Week **7** and every 3 weeks thereafter. Refer to Section **8.2.5** and Section **8.2.7**.
Physical measurements	X	X	X	**(**X**)**	X	X		Height collected at screening only. (X) Week **7** and every 3 weeks thereafter. Refer to Section **8.2.6**.
Medical History	X							
12 lead ECG[f]	X					X		
Vital signs[f]	X	X	X	**(**X**)**	X	X		Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry and temperature. Refer to Section 8.4.1. (X) Week **7** and every 3 weeks thereafter.
ECOG PS	X	**X**		**(**X**)**	X	X		(X) Week **7** and every 6 weeks thereafter.

Footnotes defined on last page of this table.

Table 1-4. Schedule of Activities - Investigator's Choice Arm - Second ARDT

Procedure[a,b]	SCR	Study Treatment[b]			EOT[c]	SFU[d]	LTFU[e]	Notes
Week		**1**	**4**	**7+[h]**				
Day	**-28 to 0**	**1**	**22**	**43**				
GENERAL/SAFETY ASSESSMENTS (CONTINUED)								
Echocardiogram	(X)							(X) Required only in subjects with known history of cardiac disease (prior MI, angina pectoris, coronary artery bypass graft, angioplasty, stent placement).
Adverse events		Continually throughout the study, through the end of SFU						
Serious adverse events	Continually throughout the study, through the end of SFU						(X)	(X) During the long-term follow-up phase and after end of study, serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. Please refer to Section **8.4.5.1.4** for additional details.
Prior therapies review	X							
Concomitant therapies review	Continually throughout the study, through the end of SFU							
Subsequent cancer therapy						X	X	
Vital status							X	
LOCAL LABORATORY TESTING								
CBC with differential[f,g]	X	X	X	**(**X**)**	X	X		(X) Week **7** and every 6 weeks thereafter.
Chemistry[f,g]	X	X	X	**(**X**)**	X	X		

Footnotes defined on last page of this table.

Table 1-4. Schedule of Activities - Investigator's Choice Arm - Second ARDT

Procedure[a,b]	SCR	Study Treatment[b]			EOT[c]	SFU[d]	LTFU[e]	Notes
Week		**1**	**4**	**7+[h]**				
Day	**-28 to 0**	**1**	**22**	**43**				
LOCAL LABORATORY TESTING (CONTINUED)								
PSA[g]	X	X	**X**	(X)	X	X		**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments).**
LDH[g]	X	X	**X**	(X)	X	X		
Hepatitis serology, HIV	(X)							(X) Required only for subjects with known history of HIV, hepatitis B, or hepatitis C infection or those considered to be at risk.
Testosterone	X							
CENTRAL LABORATORY TESTS								
PSA[g]		X	**X**	**(X)**	X	X		**X To be collected during dosing visits in addition to schedule indicated as (X).** **(X) Collected every 8 weeks (± 7 days) from the date of randomization for the first 48 weeks, every 12 weeks (± 14 days) thereafter (should be aligned to schedule of imaging assessments).**
ctDNA[g]		X	X	**(X)**	X	X		
PBMCs[g]		X	X	**(X)**	X			
Saliva (Optional PG)	X							Obtain confirmation that the PG informed consent(s) form has been signed before performing pharmacogenetic procedures.
Cytokines[g]		X		**(X)**	X			**(X) Week 13, Day 85 only.**

Footnotes defined on last page of this table.

Table 1-4. Schedule of Activities - Investigator's Choice Arm - Second ARDT

Procedure[a,b]	SCR	Study Treatment[b]			EOT[c]	SFU[d]	LTFU[e]	Notes
Week		**1**	**4**	**7+[h]**				
Day	**-28 to 0**	**1**	**22**	**43**				
CENTRAL LABORATORY TESTS (CONTINUED)								
Archival Tumor Sample (archival biopsy or radical prostatectomy sample)	X							An archival tumor sample, **preferably** collected within 2 years of signing informed consent, is required **to be submitted prior to D1 if available**. Additionally, biopsies may be collected **study at the investigator's discretion, provided that the patient has been appropriately informed and provided written consent**.
RADIOLOGIC ASSESSMENTS								
CT/MRI **and Bone Scan**	X	Imaging every 8 weeks from the date of randomization (± 7 days) for the first 48 weeks, followed by every 12 weeks (± 14 days) thereafter until BICR-confirmed disease progression per PCWG3-modified RECIST **v**1.1			(X)	(X)	**(X)**	Radiographic assessments are obtained as indicated irrespective of dose delays. **Bone scans will be completed per PCWG3 recommendations. See Section 8.3.2 and Section 11.14 for further details.** **Blood samples or tumor biopsy must not be collected until at least 24 hours (or 1 day) following a bone scintigraphy scan.** **(X)** For subjects who discontinue study treatment for reasons other than confirmed radiographic PD, every effort should be made to perform scheduled radiographic imaging until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or end of study as determined by the sponsor, whichever occurs first.
Off-protocol PSMA-PET	Any unscheduled, off-protocol PSMA-PET scans performed at the investigator's discretion will be collected. However, this study does not support or require PSMA-PET scanning.							If off-protocol PSMA-PET data is available at screening (performed within 3 months of randomization) or is conducted off-protocol during the study (based on the investigator's discretion for ongoing subject care), these scans will be collected and uploaded to the imaging vendor according to the imaging manual. Please note that PSMA-PET is not a predefined method for tumor assessment as per PCWG3 guidelines and should not be performed as part of the study.

Footnotes defined on last page of this table.

Table 1-4. Schedule of Activities - Investigator's Choice Arm - Second ARDT

Procedure[a,b]	**SCR**	**Study Treatment**[b]			**EOT**[c]	**SFU**[d]	**LTFU**[e]	**Notes**
Week		**1**	**4**	**7+**[h]				
Day	**-28 to 0**	**1**	**22**	**43**				
CLINICAL OUTCOME AND HEALTH ASSESSMENTS								
Patient-reported outcome questionnaires	Refer to Table 1-5. - Schedule of Clinical Outcome and Health Assessments - Investigator's Choice							
STUDY TREATMENT								
Second ARDT (eg, Abiraterone or Enzalutamide)		Continuous						First dose (D1) must occur within 10 days of randomization. Electronic Diary must be provided to the subject to self-record adherence to Abiraterone or Enzalutamide

ARDT = androgen receptor-directed therapy; BICR = blinded independent central review; CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; IV = intravenous; HIV = human immunodeficiency virus; **LFT = liver function test**; LDH = lactate dehydrogenase; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PBMCs = peripheral blood mononuclear cells; PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; **PG = pharmacogenetics;** PSA = prostate-specific antigen; PSMA-**PET** = Prostate-Specific Membrane Antigen-**positron emission tomography**; **Q3W = every 3 weeks; Q6W = every 6 weeks**; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; SCR = screening; SOC = standard of care; SFU = safety follow-up

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise noted. **Assessments have a minus 24-hour window unless otherwise specified.**

[b] **V**isits have a ± 3-day window unless otherwise specified. **When resuming treatment after a dose delay, align with the Schedule of Activities for the originally planned visit.**

[c] Upon permanent discontinuation from study treatment for any reason, an EOT visit will be performed as soon as possible (within 14 days) after last dose of study treatment and prior to start of subsequent anticancer therapy.

[d] Upon permanent discontinuation from the study treatment for any reason, the SFU will be performed approximately 30 (+3) days after the end of the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s).

[e] LTFU will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (±14 days) thereafter. Subjects will be in LTFU up to 3 years after last subject is randomized. **Additional survival sweeps may be requested.**

[f] Additional assessment timepoint(s) as clinically indicated.

[g] **Specified labs have a ± 7-day window on week 5 (day 29) and week 13 (day 84) to provide flexibility for patients receiving abiraterone requiring Q2W LFT monitoring as per local SOC.**

[h] **From week 7 onwards, the following minimum assessments are required Q3W (physical examination [if clinically indicated], physical measurements, vital signs) and Q6W (ECOG PS, CBC, and Chemistry).**

Table 1-5. Schedule of Clinical Outcome and Health Assessments – Investigator's Choice (Cabazitaxel or Second ARDT) Arm

Procedure	SCR	Study Treatment																	EOT	SFU	LTFU[a]	Notes
Week		1	2	3	4	5	6	7	8	9	10	11	12	13	16	19	22	25+				
Day	-28 to 0	1	8	15	22	29	36	43	50	57	64	71	78	85	106	127	148	169				
CLINICAL OUTCOME AND HEALTH ASSESSMENTS[b]																						
EQ-5D-5L		X			X			X			X			X	X	X	X	(X)	X	X	[X]	(X) Week 25 and every 6 weeks thereafter. [X] Telephone version is acceptable at LTFU if the visit is conducted by phone.
BPI-SF		X			X			X			X			X	X	X	X	(X)	X	X		
FACT-P		X			X			X			X			X	X	X	X	(X)	X	X		
FACT-P GP5 single question			X	X		X	X		X	X		X	X									At week 1, week 4, week 7, week 10, week 13, EOT, and SFU**,** the FACT-P GP5 single question will be administered as part of the FACT-P questionnaire.
PRO-CTCAE		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**(X)**	X	X		Items: Nausea, Diarrhea, Shortness of breath, Numbness and tingling, Dizziness, General Pain, **Muscle pain, Joint pain,** Fatigue, and Chills. **(X) Week 25 and every 6 weeks thereafter.**

BPI-SF = Brief Pain Inventory-Short Form; EOT = end of treatment; EQ-5D-5L = European Quality of Life 5 Domain 5 Level Scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; LTFU = long-term follow-up; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; SCR = screening; SFU = safety follow-up

[a] Collection of EQ-5D-5L in the LTFU should occur in clinic or via telephone every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. Subjects will be in LTFU for up to 3 years after the last subject is randomized, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first.

[b] PRO questionnaires during the study treatment period, at the EOT visit and at the SFU visit will be collected by electronic device. Questionnaires will be completed either at the clinic **visit on a tablet device (EQ-5D-5L, BPI-SF, FACT-P, PRO-CTCAE)** or **at home on a handheld device (FACT-P GP5 single question, PRO-CTCAE)**, preferably at the same time of the day. If administered **during** clinic **visits**, the questionnaires are to be completed by the subject before receiving any study treatment, before any clinical assessments or consultation with the investigator, and before being informed **about** current disease status. **In case clinic visits are postponed due to dose delays, the in-clinic PRO assessments may be postponed until the next visit. Weekly assessments falling outside of scheduled clinic visits (during the first 13 weeks only) will be completed at home through a handheld electronic device and are not affected by dose delays**. If a questionnaire is not completed as indicated, the reason for missing the specific time point should be reported.

2. Introduction

2.1 Study Rationale

Metastatic prostate cancer is an incurable disease responsible for over 34 700 (Siegel et al, 2023) deaths per year in the United States (US), and 375 304 (Wang et al, 2022) worldwide. The development of mCRPC signifies end-stage disease with a median OS of 21.5 months (Swami et al, 2023). Current therapeutic options for men with mCRPC, including taxane chemotherapy, ARDT, radiotherapeutics, poly adenosine diphosphate ribose polymerase (PARP) inhibitors, and immune checkpoint inhibitors provide limited therapeutic benefit. Consequently, mCRPC constitutes a significant unmet medical need.

Xaluritamig (also known as AMG 509) is an XmAb 2+1 TCE that targets STEAP1, a six-transmembrane epithelial antigen that is highly expressed on the surface of prostate cancer cells. High STEAP1 expression in prostate adenocarcinoma and low expression in normal tissue makes STEAP1 a compelling target (Xu et al, 2022). Non-clinical studies have demonstrated xaluritamig's pharmacological effect is mediated by redirected T cell lysis of STEAP1 expressing tumor cells.

In the FIH Study 20180146, xaluritamig demonstrated antitumor activity in subjects with mCRPC with a manageable safety profile. Consequently, the aim of Study 20230005 is to evaluate the efficacy, safety, and tolerability of xaluritamig compared to investigator's choice (cabazitaxel or second ARDT) in subjects with mCRPC.

2.2 Background

2.2.1 Disease

Prostate cancer is the most frequently diagnosed non cutaneous cancer in men with an estimated 299 010 new cases in the US in 2024, and an estimated 35 250 prostate cancer deaths in 2024 (11% of all male cancer deaths) (American Cancer Society, 2024). In the European Union, prostate cancer is the third predicted cause of cancer deaths, with 77 000 deaths estimated in 2022 (10.7% of cancer deaths) (ECIS Incidence and Mortality 2022).

2.2.2 Amgen Investigational Product Background: Xaluritamig

STEAP1 is a metallo-reductase **transmembrane protein** that is over-expressed and membrane-localized in > 80% of primary prostate cancer and > 88% of mCRPC samples (Bhatia et al, 2023). Xaluritamig is a novel humanized, bispecific XmAb 2+1 TCE, developed as a targeted immunotherapy for the treatment of STEAP1-expressing prostate cancer. Xaluritamig contains **2** identical humanized anti-STEAP1 fragment

antigen-binding domains that bind STEAP1-expressing cells, an anti-CD3 single-chain variable fragment domain that binds T cells to facilitate T cell-mediated lysis, and an effectorless Fc domain that extends serum half-life. The avidity from 2 STEAP1-binding domains drives high potency against STEAP1-expressing tumor cells. In preclinical studies, xaluritamig induced lysis of STEAP1-expressing prostate cancer cells and showed broad anticancer effects in prostate cancer xenograft models. In the FIH Study 20180146 the investigational product as monotherapy **demonstrated a** manageable **safety profile**. **A**dverse events were observed across all subjects, and cytokine release syndrome (CRS) was the most common adverse event. The adverse event profile was consistent with TCE mechanism of action were all resolved with standard of care **(SOC)**. A detailed description of the nonclinical pharmacology, PK, toxicology, **safety**, and preliminary clinical data of xaluritamig is provided in the xaluritamig investigator's brochure.

2.2.3 Non-Amgen Investigational Product Background

2.2.3.1 Cabazitaxel

Cabazitaxel is a microtubule inhibitor. Cabazitaxel binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions. Cabazitaxel is indicated in combination with prednisone or prednisolone for the treatment of patients with mCRPC previously treated with a docetaxel-containing treatment regimen.

Refer to the regional prescribing information for additional information.

2.2.3.2 Abiraterone Acetate

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with **gonadotropin releasing hormone** agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

Abiraterone is indicated in combination with prednisone (in some countries/regions also in combination with prednisolone) for the treatment of patients with:

- mCRPC

- Metastatic or high-risk **hormone**-sensitive prostate cancer (**mH**SPC)

Refer to the regional prescribing information for additional information.

2.2.3.3 Enzalutamide

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors; consequently, enzalutamide inhibits nuclear translocation of androgen receptors and their interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells in vitro, and decreased tumor volume in a mouse prostate cancer xenograft model.

Enzalutamide is indicated for the treatment of patients with mCRPC, and, in some countries/regions, for m**H**SPC.

Refer to the regional prescribing information for additional information.

2.3 Benefit/Risk Assessment

Based on available data, the anticipated benefit/risk profile supports clinical development as an option to improve OS in subjects with progressive mCRPC after taxane chemotherapy. The below benefit-risk assessment supports the conduct of this clinical study. Reference should be made to the investigator's brochure for further data on xaluritamig.

2.3.1 Therapeutic Context

In Part 1 of FIH Study 20180146, xaluritamig monotherapy was evaluated in 97 subjects with post-taxane mCRPC who received ≥ 1 intravenous dose ranging from 0.001 to 2.0 mg weekly **(QW)** or every 2 weeks **(Q2W)** (Kelly et al, 2024). The maximum tolerated dose (MTD) for xaluritamig with the full prophylactic regimen administered as a 3-step dosing regimen was day 1 dose of 0.1 mg, day 8 dose of 0.3 mg, day 15 dose of 1.0 mg, and day 22+ dose of 1.5 mg administered IV **QW**. The most common (≥ 20%) treatment-related adverse events were CRS (72%), fatigue (45%), myalgia (34%), pyrexia (32%), rash (28%), decreased appetite (25%), arthralgia (24%), and anemia (21%). CRS occurred primarily during cycle 1 and improved with premedication and step-dosing. PSA and RECIST **v1.1** responses across cohorts were encouraging (49% PSA50; 24% objective response rate [ORR]) with greater response to treatment at target doses ≥ 0.75 mg (59% PSA50; 41% ORR). Responses usually occurred early with PSA50 decline and RECIST **v1.1** responses observed at first assessment, between

4 and 8 weeks respectively. Detailed and most up-to-date safety and efficacy are provided in the investigator's brochure.

2.3.2 Key Benefits

Potential key benefits of xaluritamig include prolongation of OS, rPFS, and reduction or regression of mCRPC disease burden.

2.3.3 Key Risks

2.3.3.1 Key Safety Risks of Xaluritamig

Based on biological mechanism, nonclinical toxicity studies, and clinical experience with xaluritamig, CRS, rash, **localized inflammatory events**, immune effector cell-associated neurotoxicity syndrome (ICANS) including encephalopathy and neurotoxicity, **dysgeusia**, increased liver enzymes**,** and bilirubin are key safety risks with xaluritamig. Other potential safety concerns based on preclinical studies and experience with other STEAP1-targeting agents include inflammatory response involving organs with epithelial lining, other neurological toxicities, and tumor lysis syndrome (TLS). Key safety risks are summarized in Table 2-1. Risk mitigation measures including toxicity management guidelines for CRS, **localized inflammatory** events, ICANS, other neurological events, and TLS are described in Section 6.2.1.1.

Table 2-1. Key Safety Risks of Xaluritamig

Key Risk	Description
Cytokine Release Syndrome (CRS)	CRS is characterized by a release of cellular cytokines. Clinical hallmarks of CRS may include the following: • Constitutional – fever, rigors, fatigue, malaise • Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • Respiratory – dyspnea, tachypnea, hypoxia • Cardiovascular – tachycardia, hypotension • Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia • Hematological – bleeding, hypofibrinogenemia, elevated D-dimer • Skin – rash Infusion reactions may be clinically indistinguishable from manifestations of CRS.

Table 2-1. Key Safety Risks of Xaluritamig

Key Risk	Description
Localized Inflammatory Events	**Events observed during administration of xaluritamig include** myalgia, myofascitis, **myositis,** muscle weakness, arthralgia, **pain in extremity,** soft tissue swelling, orbital oedema, **periorbital oedema,** and genital oedema (including scrotal oedema)**, oropharyngeal pain, mucosal inflammation, stomatitis, and pharyngeal swelling. Vasculitis has been observed but there is insufficient evidence for association, therefore it is considered a potential risk**.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Administration of xaluritamig has been associated with ICANS which may be serious. Adverse events that may be associated with ICANS include encephalopathy and neurotoxicity. Patients should be closely monitored for signs and symptoms of ICANS during xaluritamig treatment.
Increased Liver Enzymes and Bilirubin	Aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyl transferase increased, hypertransaminasemia, hyperbilirubinemia, and liver function test increased have been observed during administration of xaluritamig.
Rash	**The most frequently reported events were rash, macular rash, and maculopapular** rash.
Potential Safety Concerns	
Inflammatory Response, Involving Organs with Epithelial Lining	Based on **6 transmembrane epithelial antigen of the prostate 1 (**STEAP1**)** expression in normal tissues (mainly epithelial cells) and inflammation observed in some cynomolgus monkeys administered xaluritamig, there is the potential for an inflammatory response resulting in organ system toxicities such as the following: • Gastrointestinal tract (eg, colitis, esophagitis, gastritis, duodenitis, ileitis) • Pulmonary (eg, pneumonitis, tracheitis) • Dermatologic (eg, rash, dry skin, erythema, pruri**t**us) • Renal (eg, cystitis, nephritis) • Hepatobiliary (eg, cholecystitis)
Other Neurologic Events	A wide range of commonly observed neurological symptoms have been associated with the use of another cluster of differentiation 3 (CD3) bispecific molecule, blinatumomab (anti-cluster of differentiation 19 [CD19] bispecific T-cell engager [BiTE®] molecules) in patients with acute lymphoblastic leukemia (ALL). However, the spectrum of neurologic events has not been observed in clinical studies for other CD3 bispecific molecules, and the neurotoxicity may in part be associated with targeting CD19.
Tumor Lysis Syndrome (TLS)	While rare in prostate cancer, TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. Signs and symptoms may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure.

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2.3.3.2 Key Safety Risks of Cabazitaxel

The most common all grade adverse reactions with cabazitaxel are anemia (99.0%), leukopenia (93.0%), neutropenia (87.9%), thrombocytopenia (41.1%), diarrhea (42.1%),

fatigue (25.0%), and asthenia (15.4%) (JEVTANA SmPC 2023). The most common grade ≥ 3 adverse reactions occurring in at least 5% of patients are neutropenia (73.1%), leukopenia (59.5%), anemia (12.0%), febrile neutropenia (8.0%), and diarrhea (4.7%) (JEVTANA USPI 2023, EU SmPC 2023). Key safety risks of cabazitaxel are summarized in Table 11-21.

Refer to the regional prescribing information for cabazitaxel for additional safety information.

2.3.3.3 Key Safety Risks of Abiraterone Acetate

The most common adverse reactions (≥ 10%) to abiraterone acetate include fatigue, arthralgia, hypertension, nausea, **o**edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase (ALP), hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, hypoglycemia, elevated aspartate aminotransferase (AST), hypophosphatemia, elevated alanine aminotransferase (ALT), and hypokalemia (ZYTIGA USPI, 2021). In an analysis of adverse reactions of composite phase 3 studies with abiraterone acetate, adverse reactions that were observed in ≥ 10% of patients were peripheral **o**edema, hypokalemia, hypertension, urinary tract infection, and ALT increased and/or AST increased. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis (ZYTIGA EU SmPC, 2022).

Abiraterone acetate is an inducer and substrate of several CYP isoenzymes and is therefore susceptible to drug interactions (see Section 6.1.5 for prohibited medications). Additionally, abiraterone acetate is an inhibitor of CYP2**D6** enzyme; therefore, subjects should be closely monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

The key safety risks for abiraterone acetate include **joint swelling or discomfort,** hypokalemia, hypertension, and fluid retention, due to mineralocorticoid excess, adrenocortical insufficiency, hepatotoxicity, and embryo-fetal toxicity (**Table 11-22**).

Refer to the regional prescribing information for abiraterone acetate for additional safety information.

2.3.3.4 Key Safety Risks of Enzalutamide

The most common adverse reactions (≥ 10%) that occur more frequently (≥ 2% over placebo) in the enzalutamide-treated patients are musculoskeletal pain, fatigue, hot

flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. Other important adverse reactions include ischemic heart disease and seizure (**XTANDI®** EU SmPc, 2022).

Enzalutamide is an inducer and inhibitor of several CYP isoenzymes and is therefore susceptible to CYP enzymes mediated drug interactions.

The key safety risks for enzalutamide include seizure, posterior reversible encephalopathy syndrome (PRES), hypersensitivity, ischemic heart disease, falls, fractures, and embryo-fetal toxicity (Table 11-23).

Refer to the regional prescribing information for enzalutamide for additional safety information.

3. Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To compare overall survival (OS) in subjects receiving xaluritamig vs investigator's choice (cabazitaxel or second androgen receptor-directed therapy [ARDT])	• Overall survival
Key Secondary	
• To compare radiographic progression-free survival (rPFS) in subjects receiving xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Radiographic progression-free survival per Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1, as assessed by blinded independent central review (BICR)
Secondary	
• To evaluate other measures of efficacy of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Objective response per **modified** RECIST v1.1, as assessed by BICR • Duration of response (DOR) per **modified** RECIST v1.1, as assessed by BICR • Disease control **per modified RECIST v1.1, as assessed by BICR** • Time to Response (TTR) per **modified** RECIST v1.1, as assessed by BICR
• To compare symptomatic skeletal events (SSE) in subjects treated with xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Time to first SSE

• To evaluate the safety and tolerability of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Treatment Emergent Adverse Events, Treatment Emergent Serious Adverse Events, and fatal adverse events
• To evaluate health-related quality of life (HRQoL) of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Change from baseline in: o Brief Pain Inventory - Short Form (BPI-SF) Worst pain score o BPI-SF Pain intensity scale o BPI-SF Pain interference scale o Functional Assessment of Cancer Therapy – Prostate (FACT-P) Total score and subscale scores o European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) Utility score o Change from baseline in the EQ-5D-5L Visual Analogue Scale (VAS) • Time to worsening in: o BPI-SF Worst pain score o BPI-SF Pain intensity scale o BPI-SF Pain interference scale o FACT-P Total score • Time to pain improvement in: o Subjects with moderate/severe pain at baseline • Time to improvement after worsening in: o BPI-SF Pain intensity scale o BPI-SF Pain interference scale
• To evaluate patient-reported safety and tolerability of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Patient-reported outcomes summary scores as assessed by: o Selected questions on symptomatic adverse events from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library o The GP5 question on overall bother of side effects from the FACT-P questionnaire

• Evaluate the biochemical response of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• PSA50 and PSA90 responses
• Characterize the pharmacokinetics (PK) of xaluritamig using intensive and sparse PK sampling	• PK parameters for xaluritamig such as maximum serum concentration (C_{max}), time to maximum concentration (T_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate the immunogenicity of xaluritamig	• Incidence of anti-xaluritamig antibody formation

Estimand for Primary Objective

The estimand for the primary endpoint consists of:

- Treatment: xaluritamig versus investigator's choice (cabazitaxel or second ARDT)
- Population: subjects with progressive mCRPC
- Endpoint: OS
- Intercurrent Event: Subsequent anticancer therapy. For the primary estimand, the treatment effect will be estimated regardless of subsequent anticancer therapy.
- Summary Measure: Hazard Ratio (HR)

Estimand for Key Secondary Objective

The estimand for the key secondary endpoint consists of:

- Treatment: xaluritamig versus investigator's choice (cabazitaxel or second ARDT)
- Population: subjects with progressive mCRPC
- Endpoint: rPFS
- Intercurrent Event: Subsequent anticancer therapy. For the primary estimand, the treatment effect will be estimated in the absence of subsequent anticancer therapy.
- Summary Measure: HR

Estimand(s) for Secondary Objective(s)

Not applicable

Exploratory	
• Evaluate the healthcare utilization of xaluritamig vs investigator's choice (cabazitaxel or second ARDT)	• Number of medical care encounters and other selected procedures (protocol mandated and not protocol mandated)

• To evaluate molecular mechanisms of resistance and response to xaluritamig	• Genomic alterations, RNA expression, protein expression detected at baseline or time of progression. • Correlation of biomarkers, including but not limited to serum proteins, STEAP1 protein expression, RNA expression, and cfDNA with selected efficacy and safety endpoints.

Endpoint Definitions

Endpoint	**Definition**
Objective response	Best overall response (BOR) of complete response (CR) or partial response (PR) **in soft tissue lesions** per modified RECIST v1.1 as assessed by blinded independent central review (BICR).
Disease control	Objective response or stable disease **in soft tissue lesions per modified RECIST v1.1, as assessed by BICR**.
Duration of Response (DOR)	The time from the first documented objective response **in soft tissue lesions until radiographic disease progression** per modified RECIST v1.1 as assessed by BICR**, or death due to any cause, whichever occurs first**.
Overall survival (OS)	The time from randomization until death due to any cause.
PSA50 and PSA90	**A ≥ 50% or ≥ 90% decrease from baseline confirmed by a second consecutive value obtained 3 or more weeks later. An increase in PSA in the first 12 weeks does not preclude a response thereafter**.
Radiographic disease progression	Soft tissue progressive disease or bone lesion progression as per **PCWG3-modified RECIST v1.1 by BICR**.
Radiographic progression-free survival (rPFS)	**The time from randomization until the first documentation of radiographic disease progression per PCWG3-modified RECIST v1.1 or death due to any cause, whichever occurs first**.
Time to Response (TTR)	The time from the date of randomization to the date of first documentation of

	objective response per modified RECIST v1.1, as assessed by BICR. **Only subjects who have achieved objective response will be evaluated for TTR**.
Time to first symptomatic skeletal events (SSE)	The date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, **or** tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain.

4. Study Design

4.1 Overall Design

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

This is a randomized, multi-center, open-label, phase 3 study to evaluate the efficacy and safety of xaluritamig versus investigator's choice of cabazitaxel or second ARDT in subjects with mCRPC previously treated with taxane chemotherapy.

The study consists of a 28-day screening period, a treatment period, a SFU period, and a LTFU period.

Approximately 675 subjects will be randomized in the study. The total study duration is expected to be approximately 56 months from the first subject randomized, with an enrollment duration of approximately 20 months and 36 months treatment and follow-up.

Eligible subjects will be randomized with a 2:1 allocation ratio to receive either: xaluritamig monotherapy (experimental arm) or investigator's choice of cabazitaxel or second ARDT (control arm).

Randomization will be stratified by:

- LDH (≤ 260 IU/L vs > 260 IU/L)
- presence of liver metastases (yes vs no)
- prior treatment with PSMA RLT (yes vs no)
- planned intention to treat with cabazitaxel vs second ARDT

Enrollment for the planned intention to treat with cabazitaxel vs second ARDT stratification factor will be equally allocated (ie, 50%/50%) to each level.

Subjects must begin study treatment within 10 days after randomization. Subjects will receive treatment until BICR-confirmed radiographic disease progression per PCWG3-modified RECIST **v**1.1, unacceptable toxicity, initiation of other anticancer

therapy, withdrawal of consent, death or end of study as determined by the sponsor, whichever comes first.

Radiologic imaging will be performed at screening, every 8 weeks (± 7 days) for the first 48 weeks from the date of randomization, and then every 12 weeks (± 14 days) until BICR-confirmed radiographic disease progression per PCWG3-modified RECIST v1.1. Radiographic disease response assessment will be reviewed by BICR in real-time. Radiographic progression of disease **should** be verified centrally **before** cessation of investigational product, local intervention, initiation of new anticancer therapy or treatment other than study drug beyond progression, as long as there are no safety concerns and the subject is clinically stable. Treatment beyond radiographic progression may be allowed as per PCWG3 guidelines. **For subjects with PD continuing treatment beyond progression, radiologic imaging should be continued as per Schedule of Activities (Section 1.3) as long as they continue on treatment.**

End of Treatment (EOT):

Upon permanent discontinuation from study treatment for any reason, an end of treatment (EOT) visit will be performed as soon as possible (within 14 days) after last dose of study treatment and prior to start of subsequent anticancer therapy.

Safety Follow-up (SFU):

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 30 (+ 3) days after the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s). The SFU visit will occur regardless of subsequent anticancer therapy within that period.

Long-term Follow-up (LTFU):

Subjects will be in LTFU for up to 3 years after the last subject is randomized, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. **Long-term follow-up** will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (± 14 days) thereafter. **Ad hoc vital status (survival status) collection may be required to support key study analysis**.

Subjects who discontinue treatment without having BICR-confirmed radiographic progression of disease (eg, due to unacceptable toxicity or initiation of new anticancer therapy) must continue with radiographic imaging during LTFU, until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or

end of study as determined by the sponsor, whichever occurs first. Radiographic images taken during LTFU up to the time of BICR-confirmed PD will be provided by the treating physician to facilitate determination of the rPFS primary endpoint. See Section 8.1.5 for additional details on LTFU.

In all subjects, information regarding the type and duration of subsequent therapies following disease progression, response to subsequent therapy, date of progression on subsequent therapy, and survival data will be collected. Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued LTFU, with or without withdrawing consent, and should include interrogation of public databases, if necessary and legally permissible.

Participants in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 9.2.

4.2 Patient Input into the Study Design

Patient Voice activities have been performed to engage with patients diagnosed with mCRPC to gain insight into their experience with the condition, as well as to obtain their input on the protocol. The input was collected from two different Patient Voice activities, as explained below.

In the US, a diverse and representative group of 6 to 8 mCRPC patients participated in a focus group consisting of 2 two-hour sessions. The sessions covered their experiences with prostate cancer, their perceptions about clinical trial participation, and a review of **Study** 20230005.

In France, selected key study design features were reviewed by the French oncology patient advocacy group, La Ligue Contre le Cancer. Reviewers were also asked to provide feedback on instructions to monitor for CRS post-infusion.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

4.3.1.1 Justification for Amgen Investigational Product: Xaluritamig

This study will evaluate a xaluritamig target dose level of 1.5 mg administered as a Q2W regimen. To mitigate the risk of CRS, xaluritamig will be initiated at a lower step dose of 0.1 mg on cycle 1 day 1, 0.3 mg on cycle 1 day 8, 1.0 mg on cycle 1 day 15, followed by target dose 1.5 mg on cycle 1 day 22. The target dose 1.5 mg will be administered Q2W from cycle 2 day 1 onwards. Both step doses and target dose are administered as **a** 60-minute infusion. This regimen was selected based on the totality of available safety, tolerability, PK and preliminary efficacy data from the Part 1 monotherapy dose

exploration and expansion of the FIH Study 20180146 in subjects with mCRPC. Based on a prespecified interim analysis (IA) in the dose expansion phase, the regimen using 1.5 mg Q2W target dose with 0.1, 0.3, and 1.0 mg QW step dose was selected to balance the efficacy/safety of xaluritamig. Please refer to the investigator's brochure for the latest efficacy and safety data from ongoing studies.

4.3.1.2 Justification for Non-Amgen Investigational Products

Standard of care cabazitaxel chemotherapy (all countries) and second ARDT (abiraterone acetate or enzalutamide [all countries]) will be administered per the regional prescribing information. Refer to Section 6.1.1 for additional information.

4.3.2 Justification for Noninvestigational Product/Auxiliary Medicinal Product Dose

Noninvestigational products/auxiliary medicinal products used as premedication or rescue medications as described in Section 6.1.2 will be administered with a dosing regimen as per the local prescribing information.

4.4 End of Study

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities (Section 1.3). The total anticipated study duration for an individual subject is 36 to 56 months.

The end of study date for the entire study is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, LTFU, antibody testing), as applicable. **Ad hoc vital status (survival status) collection may be required to support key study analysis**.

5. Study Population

Investigators will be expected to maintain a screening log to record details of all subjects screened that includes limited information about the screened subject (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

5.1 Inclusion Criteria

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

Key Inclusion Criteria:

101 Subject has provided informed consent(s) prior to initiation of any study specific activities/procedures.

102 Age ≥ 18 years (or ≥ legal age within the country if it is older than 18 years) at the time of signing the informed consent.

103 Subject must have histological, pathological and/or cytological confirmation of adenocarcinoma of the prostate. **Mixed histologies (eg, adenocarcinoma with neuroendocrine component) are not permitted**.

104 mCRPC with ≥ 1 metastatic lesion that is present on baseline computed tomography (CT), magnetic resonance imaging (MRI), or bone scan imaging obtained within 28 days prior to enrollment.

105 Evidence of progressive disease, defined as 1 or more PCWG3 criteria:

- Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL. This must be assessed locally for eligibility (see Schedule of Activities Section 1.3)**.**
- Soft-tissue progression defined as an increase ≥ 20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions **or unequivocal progression of existing non-target lesions**.
- Progression of bone disease **defined by the appearance of at least 2** new bone lesions(s) by bone scan (**as per the** 2+2 PCWG3 criteria).

106 Subjects must have prior orchiectomy and/or ongoing androgen-deprivation therapy and a castrate level of serum testosterone (< 50 ng/dL or < 1.7 nmol/L). This must be assessed locally for eligibility (see Schedule of Activities Section 1.3).

107 Prior **progression on** at least one ARDT **(enzalutamide, abiraterone, apalutamide, darolutamide)**.

108 Prior treatment with **only** one taxane therapy **in the mCRPC** setting.

Note: Prior treatment with docetaxel in the mHSPC setting is permitted; however, subjects must have also received one, and only one, taxane therapy in the mCRPC setting.

110 Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

111 Adequate organ function, defined as follows:

- Hematological function:
  - **W**hite blood cell count ≥ 2.5 x 10^9/L **AND** absolute neutrophil count ≥ 1.5 x 10^9/L.
  - **P**latelet count ≥ **100** x 10^9/L.
  - **H**emoglobin ≥ 9 g/dl (90 g/L) **without transfusion within 14 days of screening assessment used for eligibility**.

- Renal function:
  - **E**stimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 30 ml/min/1.73 m^2.
- Hepatic function:
  - AST and ALT ≤ 3 X upper limit of normal (ULN) (or ≤ 5 X ULN for subjects with liver involvement).
  - **T**otal bilirubin (TBL) ≤ 1.5 X ULN (or ≤ 2 X ULN for subjects with liver involvement). For patients with known Gilbert's Syndrome, **TBL** ≤ 3 X ULN is permitted.
- Pulmonary function:
  - Baseline oxygen saturation > 92% on room air at rest and no oxygen supplementation.
- Cardiac function:
  - **L**eft ventricular ejection fraction > 50% (screening echocardiography only required in subjects with known history of cardiac disease, prior MI, angina pectoris, coronary artery bypass graft [CABG], angioplasty, stent placement).

112 Life expectancy of ≥ 12 weeks per treating physician's assessment.

5.2 Exclusion Criteria

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

Prior & Concomitant Therapy

201 Prior STEAP1-targeted therapy.

202 Any anticancer therapy, immunotherapy, or investigational agent within 4 weeks prior to first dose of study treatment, not including androgen suppression therapy **(eg, luteinizing hormone-releasing hormone/gonadotropin-releasing hormone [LHRH/GnRH] analogue [agonist/antagonist]).**

203 Prior PSMA RLT within **3** months of first dose of study treatment unless subjects received < 2 cycles of therapy.

205 **Prior palliative radiotherapy within 2** weeks **of** first dose of study treatment. **Subjects must have recovered from all radiation-related toxicities.**

206 Concurrent cytotoxic chemotherapy, **ARDT**, immunotherapy, radioligand therapy, PARP inhibitor, biological therapy, investigational therapy.

Note: Prior treatment with a PARP inhibitor is permitted as long as not within 4 weeks before first dose of study treatment.

225 Prior radionuclide therapy (Radium-223) within 2 months of first dose of study treatment.

227 Treatment with live and live-attenuated vaccines within 4 weeks before the first dose of study treatment.

Disease Related

207 Patients with a history of central nervous system (CNS) metastasis.

Note: Subjects with treated, asymptomatic, and clinically stable dural metastases are eligible.

208 Unresolved toxicities from prior anti-tumor therapy **not having resolved to** Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 events grade above 1 or baseline, with the exception of alopecia or toxicities that are stable and well-controlled AND there is an agreement to allow inclusion by both the investigator and the sponsor.

Other Medical Conditions

209 History of malignancy that is expected to alter life expectancy or may interfere with disease assessments. Subjects with prior history of malignancy that have been adequately treated and who have been disease-free for > 3 years are eligible, as are subjects with adequately treated non-melanoma skin cancer or superficial bladder cancer.

210 History of allergic reactions or acute hypersensitivity reactions to the components of the study therapies and their analogs. **Subjects with known contraindications to high-dose corticosteroids are also excluded. Subjects** with a known hypersensitivity to docetaxel and pursuing intention to treat with second ARDT are eligible.

211 Active autoimmune disease that has required systemic treatment (except replacement therapy) within the past 2 years or any other diseases requiring immunosuppressive therapy while on study.

212 History or evidence of inflammatory bowel disease (ulcerative colitis or Crohn**'s** disease) or any other gastrointestinal disorder causing chronic nausea, vomiting, or diarrhea (defined as CTCAE $\geq$ grade 2).

213 Evidence of interstitial lung disease or active, non-infectious pneumonitis, or uncontrolled asthma.

214 Recent history of arterial **or venous thrombosis** (eg, stroke, transient ischemic attack, pulmonary embolism, or deep vein thrombosis) within 6 **and 3** months prior to first dose of study treatment**,** respectively**.**

Note: Subjects with a history of venous thrombosis must be on stable anticoagulation.

215 Recent history of myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association ≥ class II) within 12 months of first dose of study treatment, with the exception of ischemia or non-ST segment elevation myocardial infarction controlled with stent placement and confirmed by a cardiologist more than 6 months prior to first dose of study treatment.

216 Known:

- **H**uman immunodeficiency virus (HIV) infection (subjects with HIV infection on antiviral therapy and undetectable viral load are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on study).
- **H**epatitis C infection (subjects with hepatitis C that achieve a sustained virologic response after antiviral therapy are allowed).
- **H**epatitis B infection (subjects with hepatitis B surface antigen [HBsAg] or core antibody that achieve sustained virologic response with antiviral therapy are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on the study).

217 Concurrent serious medical conditions, including, but not limited to, uncontrolled **hypertension, uncontrolled** infection, **contraindications to or unacceptable risk associated with receiving the intended SOC control arm therapy (cabazitaxel, enzalutamide or abiraterone, depending on the planned intention to treat) or** other significant co-morbid conditions including somatic or psychiatric disease/condition that in the opinion of the investigator would impair study participation or cooperation.

218 History of solid organ transplant.

219 Major surgical procedures within 4 weeks prior to first dose of study treatment. **Port placement is not considered a major surgical procedure.**

226 Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as determined by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, corrected QT interval by Fredericia prolongation > 480 ms, electrolyte disturbances, etc), or patients with congenital long QT syndrome.

228 Patients receiving antiviral therapy who meet the aforementioned criteria are eligible only if their antiviral regimens do not pose significant drug-drug interactions with the study treatments.

Prior/Concurrent Clinical Study Experience

221 Currently receiving treatment in another investigational device or drug study, or less than **4 weeks** since ending treatment on another investigational device or drug study(ies). Other investigational procedures and participation in observational research studies while participating in this study are excluded.

Other Exclusions

222 Male subjects who are unwilling to abstain from donating sperm during treatment and male subjects with a pregnant partner or partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 6 months after the last dose of xaluritamig, an additional 4 months after last dose of cabazitaxel, an additional 3 months after last dose of enzalutamide, or an additional 3 weeks after last dose of abiraterone acetate. Refer to Section 11.5 for additional contraceptive information.

223 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

224 History or evidence of any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety, or interfere with the study evaluation, procedures, or completion.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written external review bodies (eg, the IRB/IEC/regulatory authorities) approval of the protocol, informed consent form(s), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally authorized representative and the investigator or authorized delegate must personally sign and date the external review body informed consent(s) before commencement of study-specific procedures.

Each subject who enters the screening period for the study (a 28-day period) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects are eligible to be enrolled in the study when the investigator confirms that the subject has met all eligibility criteria. Subjects are considered enrolled at the time of randomization. The investigator is to document enrollment decision and date, in the subject's medical record and in/on the Subject Enrollment Case Report Form (CRF) via IRT.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Patients are to be randomized to receive either xaluritamig or the investigator's choice of comparator therapy (cabazitaxel or second ARDT) after meeting eligibility criteria (Sections 5.1 and 5.2) and having completed screening assessments (see Section 1.3). The choice of comparator therapy is at the discretion of the investigator from the regimens described in this protocol and must be specified prior to randomization.

Subjects randomized to the control arm are expected to receive the comparator therapy indicated as part of the intent-to-treat stratification factor prior to randomization.

The first dose of study drug must be administered ≤ 10 days after randomization. The day of first dose is study day 1.

Study intervention is defined as any investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that according to local regulations in some countries, investigational product(s) described in Section 6.1.1 are referred to as investigational medicinal product(s) and noninvestigational product(s)/auxiliary medicinal product(s) described in Section 6.1.2 are referred to as noninvestigational medicinal product(s).

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Amgen Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Xaluritamig
Dosage Formulation	Xaluritamig drug product is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile water for injection. The IVSS is intended for pretreatment of IV bags prior to addition of reconstituted xaluritamig drug product. IVSS is supplied as a sterile solution in a 10-cc glass vial containing 7 or 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution containing citric acid **monohydrate**, lysine hydrochloride, and polysorbate 80, pH 7.0.
Unit Dose Strength(s)	Dose range: 0.1 to 1.5 mg Xaluritamig will be administered in a 28-day cycle.
Dosage Level(s)	• Cycle 1: xaluritamig will be administered QW and will include a 3-step dosing schedule to achieve the target dose of 1.5 mg: - Day 1: 0.1 mg - Day 8: 0.3 mg - Day 15: 1.0 mg - Day 22: 1.5 mg • Cycle 2 and beyond (upon achievement of target dose): xaluritamig will be administered Q2W of each cycle - Day 1: 1.5 mg - Day 15: 1.5 mg
Route of Administration	Short-term IV infusion (approximately 60 minutes)
Accountability	Product administration information is to be recorded on each subject's CRF(s).
Dosing Instructions	• Xaluritamig IV will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment. Xaluritamig may be administered through a peripheral venous line or a central venous access if available. Xaluritamig should not be administered as a bolus. • Xaluritamig should only be administered if the subject is hemodynamically stable. Consider holding anti-hypertensive drugs (except beta-blockers) on days of dosing during cycle 1.

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Footnotes defined on last page of this table.

Table 6-1. Amgen Investigational Products

	Amgen Investigational Product:[a]
Study Treatment Name	Xaluritamig
Dosage Preparation	• Xaluritamig is reconstituted with sterile water and added to a 0.9% sodium chloride IV bag pretreated with IVSS. Detailed information regarding dose preparation/administration will be provided to the site.
Hospitalization Guidance	**Cycle 1 day 1:** • All subjects will be hospitalized for intensive monitoring for a minimum of 16 hours **post** EOI. **Cycle 1 days 8, 15, 22:** • **No hospitalization required: Monitor for 4 to 6 hours after the EOI before discharge.** **Cycle 1 all:** • **After discharge, trained caregiver presence and support is required for a minimum of 24 hours from EOI. A caregiver staying with the subject will be trained on CRS and localized inflammatory symptoms by the investigator or delegate.** • **After discharge, subject and caregiver must stay in proximity of the hospital or appropriate medical facility (within 1 hour) for a minimum of 24 hours from the EOI.** • **Subjects must have a follow-up visit at approximately 24 hours from the EOI; visit can be conducted by telephone and performed by the investigator or a delegate.** **Cycle 2 onwards:** • **Monitoring for subsequent treatment visits is at the discretion of the investigator if asymptomatic and clinically stable. Consider monitoring if the subject experiences a grade 2 CRS, any grade ICANS, or any grade ICANS-related neurological adverse events at the immediate prior treatment (ie, following the dose given at the prior visit).**

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Footnotes defined on last page of this table.

Table 6-1. Amgen Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Xaluritamig
Hospitalization Guidance (continued)	**General discharge instructions (all cycles):** ***Safety Monitoring*** • **Subjects may be hospitalized at the investigator's discretion and according to local SOC.** • **In order to address logistic requirements at select centers, subjects may receive their C1D1 infusion in an outpatient infusion center, with subsequent admission to hospital as soon as clinically feasible, subject to prior written agreement by the Amgen medical monitor.** ***Subject and Caregiver Information:*** **The investigator should counsel the subject and their caregiver on signs and symptoms of CRS and the importance of remaining well hydrated (eg, 11 cups or 2.5 L of daily fluid consumption is recommended), as well as signs and symptoms of localized inflammatory events and how to react accordingly. The investigator should ensure the subject has a patient wallet card with information on these toxicities upon discharge.** ***Discharge Medications:*** • **Subjects should receive the following discharge medications and appropriate advice in case localized inflammatory event-related symptoms develop at home (eg, myalgia, myofascitis, muscle weakness, arthralgia, oropharyngeal pain, pharyngeal swelling, and soft tissue swelling):** - **Ibuprofen 400 mg every 8 hours with gastric protection (eg, omeprazole 20 mg every 12 hours) or local equivalent.** - **Dexamethasone 8 mg or prednisone 0.5 mg/kg (or local equivalent) once daily.** - **Additional analgesia such as paracetamol/acetaminophen 500 to 1000 mg every 4 to 6 hours (max 4000 mg in 24 hours) or local equivalent. (Ensure to avoid double dosing if subjects are receiving 24 hours of paracetamol as part of premedication).** - **Muscle relaxants (eg, methocarbamol 750 mg BID or local equivalent) may be considered for the treatment of muscle pain according to local availability.**

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BID = twice daily; CRF = case report form; CRS = cytokine release syndrome; EOI = end of infusion; ICANS = immune effector cell-associated neurotoxicity syndrome; IM = intramuscular; IV = intravenous; IVSS = intravenous solution stabilizer; NA = nonapplicable, PO = orally; QW = weekly; Q2W = every 2 weeks; SC = subcutaneous; **SOC = standard of care**.

[a] Xaluritamig will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

[b] If not specified, dexamethasone and acetaminophen/paracetamol can be administered orally or intravenously based on the investigator's discretion or in accordance with established institutional or regional protocols.

Table 6-2. Non-Amgen Investigational Products[c]

Study Treatment Name	Non-Amgen Investigational Product: Abiraterone[a]	Non-Amgen Investigational Product: Enzalutamide[a]	Non-Amgen Investigational Product: Cabazitaxel
Dosage and Administration[b]	Abiraterone will be dosed at the regionally or locally approved regimen of 1000 mg orally, once daily with prednisone 5 mg orally, twice daily (or in some regions, prednisolone 10 mg orally, once daily). Alternative formulations not consistent with 1000 mg once daily dose, such as Yonsa® (500 mg once daily administered with methylprednisolone 4 mg twice daily) are not permitted.	Enzalutamide will be dosed at the regionally or locally approved regimen of 160 mg orally once daily with or without food.	Cabazitaxel will be dosed according to local practice guidelines or regionally approved regimens of 20 or 25 mg/m^2 every 3 weeks as a 1-hour intravenous infusion in combination with oral prednisone 10 mg (or in some regions, prednisolone 10 mg) administered daily throughout the treatment.
Dosage forms and strengths	Abiraterone may be administered as either: • Two 500 mg tablets OR • Four 250 mg tablets	Enzalutamide may be administered as either: • Capsules: 160 mg (4 x 40 mg) OR • Tablets: 160 mg (4 x 40 mg or 2 x 80 mg)	
Dosing Instructions	Refer to the regional/local manufacturer prescribing information for dosing, dose adjustments, premedication, administration, and for additional information. • **Note for abiraterone: must be taken on an empty stomach and no food should be consumed for at least 2 hours before the dose of abiraterone is taken and for at least 1 hour after the dose of abiraterone has been taken. Abiraterone tablets should be swallowed whole with water (not chewed or crushed). Subjects receiving abiraterone should have LFTs (ALP, ALT, AST, BIL) assessed every 2 weeks for the first 3 months of treatment according to local prescribing guidelines.** • Note for cabazitaxel monitoring of complete blood counts **should be conducted according to local SOC, eg,** on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed.		

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BIL = bilirubin; EU = European Union; IMP = investigational medicinal product; LFT = liver function test; SOC = standard of care.

[a] Electronic Diary must be provided to the subject to self-record adherence.

[b] Corticosteroids: For the purpose of this study, corticosteroids (prednisone or prednisolone) co-administered according to the label for cabazitaxel or abiraterone acetate, are considered auxiliary medicinal products. Refer to the regional/local manufacturer prescribing information for additional information.

[c] **Per local regulations, some regions may classify these products as non-investigational. In the EU these are classified as authorized IMP.**

6.1.2 Noninvestigational Products/Auxiliary Medicinal Products

Noninvestigational products/auxiliary medicinal products that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these noninvestigational products/auxiliary medicinal products.

6.1.2.1 Premedication

6.1.2.1.1 Xaluritamig Premedication

Prior to the administration of xaluritamig, the following are recommended for all subjects unless contraindicated:

Cycle 1:

- Evening prior to xaluritamig infusion (eg**,** approximately 12-16 hours before xaluritamig infusion):
  - Dexamethasone* 8 mg (or local equivalent)
- 1 hour prior to xaluritamig infusion:
  - Dexamethasone* 8 mg (or local equivalent)
  - Acetaminophen/paracetamol* (or local equivalent) 1000 mg every 6 hours for 24 hours.
  - Prophylactic IV hydration using 1-liter isotonic crystalloid solution (0.9% saline or local equivalent) administered over **no fewer than 2** hours.
- **6-8 hours post xaluritamig infusion:**
  - **Dexamethasone 8 mg (or local equivalent) is required for cycle 1 day 1 and should be considered at the discretion of the investigator for subsequent cycle 1 doses**.

Cycle 2 and beyond:

- Premedication may be administered as in cycle 1 at the discretion of the investigator.

*If not specified, dexamethasone and acetaminophen/paracetamol can be administered orally or intravenously based on the investigator's discretion or in accordance with established institutional or regional **SOC**.

6.1.2.1.2 Cabazitaxel Premedication

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel and according to local guidelines which may include the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- Antihistamine (dexchlorpheniramine 5 mg or diphenhydramine 25 mg or local equivalent)
- Corticosteroid (dexamethasone 8 mg* or local equivalent)
- H2 antagonist (cimetidine or local equivalent)
- Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed.

Throughout cabazitaxel treatment, adequate hydration of the patient needs to be ensured, in order to prevent complications like renal failure.

*If not specified, dexamethasone can be administered orally or intravenously based on the investigator's discretion or in accordance with established institutional or regional **SOC**.

6.1.2.2 Rescue Medication

6.1.2.2.1 Interleukin-6 Inhibitors - Tocilizumab or Siltuximab

Sites are required to have tocilizumab**, tocilizumab biosimilar (other interleukin-6 receptor antagonist),** or siltuximab (if tocilizumab **or biosimilar** is not available) on site for potential treatment of CRS. For administration of dexamethasone or tocilizumab after occurrence of CRS, follow guidance in Table 11-4. Tocilizumab **or biosimilar** should be administered according to local prescribing information. If tocilizumab **or biosimilar** is not available, siltuximab (an anti-interleukin 6 monoclonal antibody) may be used in the management of CRS, following the criteria outlined in Table 11-4. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of xaluritamig. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

6.1.2.2.2 Corticosteroids

Corticosteroids (dexamethasone or local equivalent) will be used for management of specific adverse events, including CRS, **localized** inflammatory events, and other inflammatory events as described in Section 11.8.

6.1.3 Medical Devices

Investigational medical devices will not be used in this study.

Other noninvestigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen noninvestigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational product provisioned and/or repackaged/modified by Amgen:

- Xaluritamig

Any product complaint(s) associated with an investigational product supplied by Amgen are to be reported.

6.1.5 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments and/or procedures are excluded during the treatment period of the study (until SFU):

- Chronic systemic corticosteroid therapy (prednisone dose $>$ 10 mg per day or local equivalent) or any other immunosuppressive therapies (including anti TNFα therapies). (Note: Corticosteroid treatment for adverse events management during the study is allowed).
- Treatment with another investigational device or drug study. Other investigational procedures while participating in this study are excluded with the exception of investigational scans.
- Subjects must not schedule any major elective surgery during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes unplanned surgery during the course of the study, all study treatments must be withheld, and the investigator or designee should notify the Amgen Medical Monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and Amgen Medical Monitor agree to restart study therapy.
- **Any other concurrent anticancer therapy (ie, cytotoxic chemotherapy, ARDT, immunotherapy, RLT, PARP inhibitor, biological therapy, investigational therapy).**
- Live and live-attenuated vaccines are prohibited within **4 weeks** prior to the first dose of investigational product, during treatment with investigational product and for at least 3 months after the last dose of investigational product.
  - **Note: The use of vaccines (except live and live-attenuated) will be allowed during therapy per regional and institutional SOC.**
- **For subjects randomized to the control arm, local prescribing information should be reviewed and followed. Caution should be applied around the**

co-administration of drugs that prolong the QT interval or strongly induce/inhibit CYP enzymes. If co-administration of a strong CYP inducer/inhibitor is necessary, refer also to the dose modification guidance in Section 6.2.1.

6.2 Dose Modification, Supportive Care, and Adverse Events

6.2.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.1.1 Amgen Investigational Product: Xaluritamig

Xaluritamig will be discontinued or temporarily delayed in the event of a toxicity that, in the opinion of the investigator, warrants the discontinuation or dose delay. **Key identified or potential risks of xaluritamig requiring dose modification of xaluritamig include but are not limited to: CRS, ICANS, TLS, and localized inflammatory events (see Section 2.3.3.1 and Table 2-1 for risk details).**

Every effort should be made to **achieve** the **1.5 mg target dose in cycle 1 and maintain the** QW treatments **(during cycle 1 step dosing) or Q2W treatments (during cycle 2 and beyond) within 28-day cycles. Medical monitor approval is required to exit cycle 1 at a lower than 1.5 mg target dose.**

In case of dose delays outside the dosing window, if subjects are still attending clinic visits, safety assessments may be conducted at the investigator's discretion to assess feasibility of treatment continuation. In the event of dose delays within 21 days (QW schedule) or 42 days (Q2W schedule), assessments should align with the Schedule of Activities for the originally planned visit once dosing resumes. If dose is delayed for an extended period (ie, > 21 days on a QW schedule or > 42 days on a Q2W schedule), the decision to resume or discontinue treatment should be discussed with the medical monitor and dose re-escalation should be restarted at 0.1 mg following the 3-step dosing schedule of cycle 1 to achieve the target dose (see Table 6-3).

The reason for dose change of xaluritamig is to be recorded on each subject's CRF(s). For treatment interruptions, delays, and discontinuations, refer to xaluritamig's guidance in Section 11.8 as outlined below.

Management of Adverse Events Including Xaluritamig Dose Modification
Table 11-3. Infusion-related Reaction
Table 11-4. Cytokine Release Syndrome
Table 11-5. Immune Effector Cell-associated Neurologic Syndrome
Table 11-6. Neurological Events Not Meeting the Definition of ICANS
Table 11-7. Tumor Lysis Syndrome
Table 11-8. **Localized** Inflammat**ory Events**
Table 11-9. **Localized** Inflammatory Events **Dose Modification Guidelines – Before Target Dose (QW Step Dosing)**
Table 11-10. **Localized Inflammatory Events Dose Modification Guidelines – Following Target Dose (Q2W Schedule)**
Figure 11-4**. Xaluritamig Localized Inflammatory Event Algorithm**
Table 11-11. **Any** Other Xaluritamig **Related Events**

For all other treatment interruptions or delays, re-start xaluritamig in accordance with the following guidelines in Table 6-3.

Table 6-3. Instructions for Administering Delayed Doses of Xaluritamig

Last Dose Administered	Duration of Days From Last Dose Administered	Action
Step dosing during cycle 1	7 (± 1) days (no delay)	• Subsequent dose is within QW dosing window, no specific precautions.
	9 to 21 days	• Subsequent dose is out of QW dosing window. • QW dosing should resume as soon as clinically feasible, and no sooner than 7 (± 1) days since the last administered dose.
	> 21 days	• Subsequent dose is out of QW dosing window, with prolonged delay increasing risk of CRS. • The decision to resume or discontinue treatment should be discussed with the medical monitor. • If decision to resume, xaluritamig treatment should be restarted at 0.1 mg following the step dosing schedule of cycle 1 to achieve the target dose. This includes all assessments, premedication, hospitalization, and monitoring requirements (see Section 6.2.1.1.1 for details).
Cycle 2 and beyond	14 (± 3) days (no delay)	• Subsequent dose is within Q2W dosing window, no specific precautions.
	18 to 42 days	• Subsequent dose is out of Q2W dosing window. • Q2W Dosing should resume as soon as clinically feasible, and no sooner than 14 (± 3) days since the last administered dose.
	> 42 days	• Subsequent dose is out of Q2W dosing window, with prolonged delay increasing risk of CRS. • The decision to resume or discontinue treatment should be discussed with the medical monitor. • If decision to resume, xaluritamig treatment should be restarted at 0.1 mg following the step dosing schedule of cycle 1 to achieve the target dose. This includes all assessments, premedication, hospitalization, and monitoring requirements (see Section 6.2.1.1.1 for details).

CRS = cytokine release syndrome; QW = weekly; Q2W = every 2 weeks

6.2.1.1.1 Re-start of Dosing Following a Delay/Withholding

Subjects should be assessed for toxicity before each infusion of xaluritamig. Restarting the infusion after a dose modification and/or dose reduction due to toxicity will be performed according to the instructions described below and detailed in Section 11.8.

In case of dose delays within 21 days (for QW step dosing during cycle 1) or 42 days (for Q2W schedule during cycle 2+), assessments should align with the Schedule of Activities for the originally planned visit once dosing resumes. Additional safety monitoring and assessments, including CBC, coagulation, and chemistry, should be considered if clinically indicated.

Re-escalation Following Extended Delays

For an extended dose delay (defined as > 21 days on a QW schedule or > 42 days on a Q2W schedule) dose re-escalation is required to mitigate the risk of CRS beginning at 0.1 mg and following the 3-step dosing schedule of cycle 1 to achieve the target dose. Re-escalations following extended delays must adhere to cycle 1 requirements for premedication (see Section 6.1.2.1), hospitalization, and monitoring requirements according to guidance provided in Table 6-1. All cycle 1 assessments outlined in the Schedule of Activities (Section 1.3) should be repeated, with the exception of PRO assessments.

6.2.1.1.2 Dose Adjustments and Re-start at a Lower Dose Level/Re-escalation to Previous Dose Level

Treatment may be resumed at the same or lower dose following adverse events according to the dose modification guidelines detailed in Section 11.8.

Re-start at a Lower Dose Level

Dose reductions are not permitted below 0.3 mg xaluritamig unless re-escalation of the infusion is required following an extended delay. In case the lower dose level (0.3 mg) is intolerable, permanently discontinue treatment.

Re-escalation to Previous Dose Level

Re-escalation from a lower dose to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated with no adverse events leading to infusion interruption or delay/withholding and if the same adverse events do not re-occur at the same grade that led to initial dose reduction. During dose re-escalation, premedication requirements (as per

Section 6.1.2.1) and safety assessments should be performed per the Schedule of Activities for cycle 1 day 1 (see Section 1.3 and as described above in Section 6.2.1.1.1 for dose delays). The subject should be monitored per cycle 1 monitoring guidance provided in Table 6-1.

6.2.1.1.3 Infusion Interruptions due to Technical/Logistical Issues

Events leading to infusion interruption or delay for technical/logistical reasons may include a technical problem with the infusion pump or the investigational product being incorrectly prepared or administered.

The administration of xaluritamig should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible, and the infusion should continue at the earliest time possible.

In case of infusion interruption, **clinical handling details will be provided to the site to confirm the** stability **of the prepared xaluritamig** infusion **and determine if** a new infusion can be administered **(in case the infusion was not yet started) or if** the dose should be withheld.

If the remaining infusion can be administered, no specific precautions have to be taken. If a new infusion can be administered, follow the procedures in the Schedule of Activities (Section 1.3) for the cycle day on which the original (interrupted) infusion was administered. If the infusion will need to be delayed or withheld, follow the instructions for re-start after interruptions due to adverse events described below for the next infusion.

6.2.1.1.4 Infusion Interruptions/Delays/Withholding due to Adverse Events

Adverse events occurring during the infusion and requiring treatment interruption during the 1-hour administration time will be managed by immediate infusion interruption. The site should record any unscheduled interruption of an infusion on the CRF and provide the start and stop date/time of the infusion. The site should record any **events that lead to an interruption/**delay/withholding of an infusion and provide the start and stop date/time of the infusion in the CRF. Events requiring an infusion interruption **or a delay/withholding of the subsequent infusion** are detailed in Section 11.8. **In case of infusion interruption due to an adverse event, do not resume infusion; continue treatment at next planned infusion.**

6.2.1.2 Non-Amgen Investigational Products: Cabazitaxel, Abiraterone Acetate, and Enzalutamide

Safety monitoring, adverse event management, and dose modifications for treatment with enzalutamide, abiraterone acetate, or cabazitaxel should be conducted in accordance with local prescribing guidelines and is at the discretion of the investigator. Dose modification guidelines derived from Food and Drug Administration (FDA) and European Medicines Agency drug labels are included below for ease of reference. The reason for dose change of all medications in the control arms is to be recorded on each subject's CRF(s).

Dose Modifications Guidelines for Cabazitaxel

Dose modifications should be made if patients experience the following adverse reactions detailed in Table 6-4 (Grades refer to CTCAE version 5.0):

Table 6-4. Dose Modifications for Adverse Drug Reactions in Subjects Treated with Cabazitaxel

Adverse Reactions	Dose Modifications
Prolonged grade ≥ 3 neutropenia (longer than 1 week) despite appropriate treatment including G-CSF	Delay treatment until neutrophil count is > 1 500 cells/mm^3, then reduce cabazitaxel dose from 25 to 20 mg/m^2.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1 500 cells/mm^3, then reduce cabazitaxel dose from 25 to 20 mg/m^2.
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate treatment, including fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce cabazitaxel dose from 25 to 20 mg/m^2.
Grade > 2 peripheral neuropathy	Delay treatment until improvement, then reduce cabazitaxel dose from 25 to 20 mg/m^2.
Grade ≥ 3 peripheral neuropathy	**Discontinue cabazitaxel**

If subjects continue to experience any of these reactions at 20 mg/m^2, further dose reduction to 15 mg/m^2 or discontinuation of cabazitaxel may be considered. Data in patients below the 20 mg/m^2 dose are limited.

6.2.1.2.1.1 Dose Modification for Subjects with Hepatic Impairment

Cabazitaxel is extensively metabolized by the liver. Subjects with mild hepatic impairment (TBL > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN), should have cabazitaxel dose reduced to 20 mg/m^2. Administration of cabazitaxel to subjects with mild hepatic impairment should be undertaken with caution and close monitoring of safety.

In patients with moderate hepatic impairment (TBL > 1.5 to ≤ 3.0 x ULN), the MTD was 15 mg/m^2. If the treatment is envisaged in patients with moderate hepatic impairment the dose of cabazitaxel should not exceed 15 mg/m^2. However, limited efficacy data are available at this dose.

Cabazitaxel should not be given to patients with severe hepatic impairment (TBL > 3 x ULN).

See Section 11.7 for more detailed hepatotoxicity stopping rules.

6.2.1.2.1.2 Dose Modifications for Subjects with Renal Impairment

Cabazitaxel is minimally excreted through the kidney. No dose adjustment is necessary in patients with renal impairment, not requiring hemodialysis. Subjects presenting end stage renal disease (creatinine clearance [CLCR] < 15 mL/min/1.73 m^2), by their condition and the limited amount of data available should be treated with caution and monitored carefully during treatment.

6.2.1.2.1.3 Dose Modifications for Use with Strong CYP3A Inhibitors

Concomitant medicinal products that are strong inducers or strong inhibitors of CYP3A should be avoided. However, if subjects require co-administration of a strong CYP3A inhibitor, a 25% cabazitaxel dose reduction should be considered.

Additional dose modification of cabazitaxel to manage toxicities per institutional guidance is acceptable as long as these are per the regional prescribing information of cabazitaxel.

Refer to the regional prescribing information of cabazitaxel for additional information regarding the dose modification guidelines of cabazitaxel.

6.2.1.2.2 Dose Modifications Guidelines for Abiraterone Acetate

6.2.1.2.2.1 Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity

6.2.1.2.2.1.1 Hepatic Impairment

In subjects with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone acetate to 250 mg once daily.

In subjects with moderate hepatic impairment monitor ALT, AST, and bilirubin (BIL) prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST > 5 x ULN or TBL > 3 x ULN occur in patients with baseline moderate hepatic

impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.

Do not use abiraterone acetate in subjects with baseline severe hepatic impairment (Child-Pugh Class C).

See Section 11.7 for more detailed hepatotoxicity stopping rules.

6.2.1.2.2.1.2 Hepatotoxicity

For subjects who develop hepatotoxicity during treatment with abiraterone acetate (ALT and/or AST greater than 5 x ULN or TBL greater than 3 x ULN), interrupt treatment with abiraterone acetate. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and TBL less than or equal to 1.5 x ULN.

For subjects who resume treatment, monitor serum transaminases and BIL at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and TBL less than or equal to 1.5 x ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone acetate.

If subjects develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Permanently discontinue abiraterone acetate for patients who develop a concurrent elevation of ALT greater than 3 x ULN and TBL greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

6.2.1.2.2.2 Dose Modification Guidelines for Strong CYP3A4 Inducers

Avoid concomitant strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during abiraterone acetate treatment.

If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency to twice a day only during the co-administration period (eg, from 1000 mg once daily to 1000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued.

Additional dose modification of abiraterone acetate to manage toxicities per institutional guidance is acceptable as long as these are per the regional prescribing information of abiraterone acetate.

Refer to the regional prescribing information of abiraterone acetate for additional information regarding the dose modification guidelines of abiraterone acetate.

6.2.1.2.3 Dose Modifications Guidelines for Enzalutamide

6.2.1.2.3.1 Dosage Modifications for Adverse Reactions

If a patient experiences a ≥ grade 3 or an intolerable adverse reaction, withhold enzalutamide for one week or until symptoms improve to ≤ grade 2, then resume at the same or a reduced dose (120 or 80 mg) if warranted.

6.2.1.2.3.2 Dosage Modifications for Drug Interactions

6.2.1.2.3.2.1 Strong CYP2C8 Inhibitors

Avoid the coadministration of strong CYP2C8 inhibitors. If the coadministration of a strong CYP2C8 inhibitor cannot be avoided, reduce the enzalutamide dosage to 80 mg once daily. If the coadministration of the strong inhibitor is discontinued, increase the enzalutamide dosage to the dosage used prior to initiation of the strong CYP2C8 inhibitor.

6.2.1.2.3.2.2 Strong CYP3A4 Inducers

Avoid the coadministration of strong CYP3A4 inducers. If the coadministration of a strong CYP3A4 inducer cannot be avoided, increase the enzalutamide dosage from 160 to 240 mg orally once daily. If the coadministration of the strong CYP3A4 inducer is discontinued, decrease the enzalutamide dosage to the dosage used prior to initiation of the strong CYP3A4 inducer.

Additional dose modification of enzalutamide to manage toxicities per institutional guidance is acceptable as long as these are per the regional prescribing information of enzalutamide.

Refer to the regional prescribing information of enzalutamide for additional information regarding the dose modification guidelines of enzalutamide.

6.2.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.2.3 Supportive Care

Subjects can receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, **bone protection,** etc. **Supportive care should be initiated and optimized at least 4 weeks before start of study treatment and maintained until EOT, where feasible.**

6.2.3.1 Bone Disease Therapy

Initiation of bisphosphonates or other approved bone-targeting agents is permitted if clinically indicated, and should not result in study treatment discontinuation unless subject has BICR-confirmed radiographic evidence of disease progression. Treatment of prostate bone disease, hypercalcemia, and bone pain should be conducted according to institutional standards. Focal radiotherapy for palliative care such as bone pain is permitted should be recorded in the appropriate CRF.

6.2.3.2 Myelosuppression Therapy

Blood transfusion or growth factors such as erythropoiesis stimulating proteins as well as granulocyte-colony stimulating factor (G-CSF) will be allowed during therapy per regional and investigator local **SOC**. However, these therapies are not permitted within **14** days of applicable screening assessment.

6.2.3.3 Antimicrobial Prophylaxis

The use of antimicrobial prophylaxis for opportunistic infections should be considered in patients receiving prolonged and high doses of corticosteroids. For example, prophylaxis for pneumocystis carinii pneumonia/pneumocystis jiroveci pneumonia may be indicated for patients receiving a prednisone equivalent of ≥ 20 mg/d for ≥ 4 weeks. Antifungal or antiviral prophylaxis may also be appropriate for select patients. Antimicrobial prophylaxis should be guided by local SOC and individual patient risk factors, which may include, but are not limited to age, medical co-morbidities, concomitant immunosuppressive therapy, and the presence of lymphopenia. If patient develops an infection, please treat according to local SOC and institutional guidelines.

6.2.4 Vaccine

Every effort should be made to fully vaccinate subjects prior to 14 days from first dose of xaluritamig, and to complete any live and live-attenuated vaccines at least 4 weeks prior to the first dose of xaluritamig. The use of vaccines except live and live-attenuated vaccines will be allowed during therapy per regional and institutional **SOC** (Note: Live

viral non-replicating vaccine [eg, Jynneos] for Monkeypox infection is allowed during the study in accordance with local **SOC** and institutional guidelines). If possible, SARS-CoV-2 vaccinations should be avoided during screening (within a minimum of 14 days from first dose of xaluritamig) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the study, SARS-CoV-2 vaccination should be avoided within 3 days after the administration of xaluritamig due to the potential of CRS development. Throughout the study, whenever possible live and live-attenuated vaccination(s) should be avoided during treatment and for at least 3 months after the last dose of xaluritamig. In the event where a subject requires corticosteroids for CRS prophylaxis or treatment of adverse events, vaccination should be avoided while on corticosteroids.

6.2.5 Localized Inflammatory Events

Localized inflammatory events **are identified risks associated with administration of xaluritamig. These include** but **are** not limited **to** myalgia, myofascitis, muscle weakness, arthralgia, soft tissue swelling **events** including orbital oedema and genital oedema, **and oropharyngeal disorders. Vasculitis is a potential risk within this classification**. Some of the **localized inflammatory** events occurred in the setting of concurrent CRS. The severity of the **localized inflammatory** events appears to be dose dependent. Based on biological mechanism of action of xaluritamig, there is a possibility that the **localized inflammatory** events reported with the administration of xaluritamig may involve the fascia although the underlying pathophysiology is not well understood. Inflammation of the musculature may result in myalgia and/or myofascitis. **Localized inflammatory events** can present with muscle **pain and/or** weakness that **may** limit **activities of** daily **living**.

As part of further risk evaluation, at the time a subject has significant unexplained/possibly xaluritamig-related **localized inflammatory event**, consider additional diagnostic tests (CT/MRI, and/or electromyography at the time of **localized inflammatory** event, for example) along with laboratory test results (for example, CBC with differential, serum aldolase, C-reactive protein [CRP], creatine kinase, myoglobin, auto-antibody panel, cytokines) if possible, prior to initiation of corticosteroid therapy. Consultation with a rheumatologist/neurologist with detailed examination at the time of the event is recommended.

Anti-inflammatory medications, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, along with pain medications, should be utilized per **Table 11-8**

recommendations at the discretion of the investigator and per the institutional **SOC**, particularly consider corticosteroids **therapy** for severe **localized inflammatory** events. In case the **localized inflammatory** event is associated with CRS, or CRP is elevated, and corticosteroid therapy is not improving the subject's condition, **anti-interleukin 6 therapy** should be considered at the discretion of the investigator per **Table 11-8**. Some of the **localized inflammatory** events may require withholding doses or a reduction to manage the events per the instructions in **Table 11-8**. See **Figure 11-4** for a visual interpretation of the guidance for the management of **localized inflammatory** events.

6.2.6 Inflammatory Response

Based on low levels of STEAP1 expression in healthy tissues and the inflammatory response observed in the nonclinical toxicology studies conducted in cynomolgus monkeys (xaluritamig investigator's brochure), there is the potential for inflammatory adverse events following the administration of xaluritamig, which may result in organ system toxicities, such as but not limited to the gastrointestinal tract, lungs, skin, kidneys, liver, gallbladder, and adrenal glands.

Early recognition and management are important to reduce complications. Subjects should be monitored for inflammatory adverse events during xaluritamig treatment. Most signs/symptoms require adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, may be included as part of the evaluation.

Depending on the type and severity of the reaction, withholding or permanent discontinuation of xaluritamig may be required, in addition to treatment with corticosteroids and/or other therapies as per local **SOC** and institutional guidelines. Dose modification and toxicity management guidelines for **localized** inflammatory **events** are provided in **Table 11-9**.

6.2.7 Rash

After administration of xaluritamig**,** cutaneous rash events were reported in the ongoing clinical study. Some of the events were reported in the setting of CRS. The most frequently reported events were rash, macular rash, and maculopapular rash. These events were usually mild in nature and resolved after management based on local **SOC** and institutional guidelines. Consider dermatology consultation and biopsy to clarify diagnosis.

6.2.8 Tumor Lysis Syndrome

Tumor lysis syndrome is characterized by a group of metabolic disorders caused by the massive and abrupt release of cellular metabolites into the blood including lactase dehydrogenase, uric acid, phosphorus, potassium, and calcium after lysis of the malignant cells (Coiffier et al, 2008).

While rare in prostate cancer, TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. The metabolic complications predispose subjects with cancer to various clinical complications including renal failure, seizures, cardiac arrhythmias, and even sudden death. To allow for early diagnosis, all subjects must be monitored closely for laboratory and clinical evidence of a possible TLS as outlined in Section 11.9.

TLS most often occurs during the first cycle of therapy. Suspected TLS occurring beyond cycle 2 should be discussed with the medical monitor. Briefly, the diagnostic criteria system according to Coiffier et al (2008) comprise laboratory or clinical TLS criteria (LTLS or CTLS). LTLS is considered to be present if levels of two or more serum values of uric acid, potassium, phosphate, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after the initiation of treatment. CTLS requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures.

To prevent TLS, before administration of xaluritamig all subjects should receive, at the discretion of the investigator, appropriate hydration and supportive measures according to local **SOC** and institutional guidelines. Tumor lysis syndrome may occur in subjects with high tumor burden including liver metastases and extensive bone metastases. These subjects should be monitored carefully after their first dose with xaluritamig (cycle 1 day 1) and prophylactic measures for TLS may be considered. Monitor for evidence of TLS during treatment and manage promptly including interruption of xaluritamig infusion as outlined in **Table 11-7**. Subjects who experience TLS should be managed according to the local **SOC** and institutional guidelines, which may include additional hydration and treatment with allopurinol and rasburicase.

Supportive therapy, such as allopurinol, may be used as clinically indicated at the investigator's discretion.

6.2.9 Nausea, Vomiting, and Diarrhea

The causes of nausea, vomiting, and diarrhea in subjects with cancer can be multifactorial. Therefore, a careful assessment which includes a detailed history, physical examination, and investigations for causes is vital. Management of nausea, vomiting, and diarrhea should be tailored to the individual subject's clinical situation.

6.2.9.1 Nausea and Vomiting

Antiemesis prophylaxis may be given according to local **SOC** institutional standards if clinically indicated at the investigator's discretion. Treatment of nausea and vomiting with antiemetics such as metoclopramide should be considered according to the local **SOC** and institutional guidelines.

6.2.9.2 Diarrhea

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Consider gastrointestinal consultation and endoscopy to confirm or rule out colitis. Treatment with loperamide according to local guidelines is recommended after occurrence of the first episode of diarrhea. In cases with diarrhea lasting for $>$ 24 hours, additional treatment with corticosteroids (dexamethasone or prednisolone) should be considered depending on tolerability/duration of previous dexamethasone administration. Additional work-up and/or gastrointestinal consultation may be considered, as needed.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug preparation, handling, storage, and accountability for the investigational product(s) will be provided to the site.

6.4 Method of Treatment Assignment

Subjects will be randomized in a 2:1 allocation, to the xaluritamig treatment or the control arm, respectively, in an open-label manner. Subjects randomized to the control arm will receive investigator's choice of cabazitaxel or second ARDT (abiraterone or enzalutamide) based on the investigator's intention to treat indicated during screening. Enrollment for the planned intention to treat with cabazitaxel vs second ARDT stratification factor will be equally allocated (ie, 50%/50%) to each level.

The stratification factors are:

- LDH (≤ 260 IU/L vs > 260 IU/L)
- Presence of liver metastases (yes vs no)

- Prior treatment with PSMA RLT (yes vs no)
- Planned intention to treat with cabazitaxel vs second ARDT

The randomization will be performed by IRT, and the randomization number will be provided.

The randomization date is to be documented in the subject's medical record and on the Subject Enrollment CRF (via IRT).

6.5 Blinding

To maintain integrity in this open-label study, post baseline summaries or data analyses of primary and key secondary endpoints will not be produced or reviewed by the study team before the primary analysis snapshot analysis or an earlier interim analysis in the case that the futility or efficacy threshold has been met. Radiographic disease assessments will be conducted using BICR.

6.6 Treatment Compliance

When subjects are dosed at the site, they will receive the xaluritamig infusion directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the CRF.

When subjects are dosed at home (oral medication), they will complete an electronic (handheld device) subject diary and compliance with the treatment will be assessed at each visit and documented in the source documents and CRF.

6.7 Treatment of Overdose

6.7.1 Xaluritamig

The effects of overdose of xaluritamig are not known.

For this study, any dose of xaluritamig $>$ 10% of the intended dose will be considered an overdose.

In the event of an overdose, the investigator must:

1. Contact the Amgen medical monitor immediately.
2. Closely monitor the **subject** for any adverse event/serious adverse event (refer to Section 11.4) and laboratory abnormalities until all signs of toxicity are resolved or returned to baseline.

3. Obtain a blood sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.7.2 Cabazitaxel

There is no known antidote to cabazitaxel. The anticipated complications of overdose would consist of exacerbation of adverse reactions, such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcomes. In case of overdose, the subject should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed. Refer to regional prescribing information of cabazitaxel for additional information.

6.7.3 Abiraterone Acetate

Human experience of overdose with abiraterone acetate is limited. There is no specific antidote. In the event of an overdose, stop abiraterone acetate, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function. Refer to regional prescribing information of abiraterone acetate for additional information.

6.7.4 Enzalutamide

There is no antidote for enzalutamide. In the event of an overdose, stop treatment with enzalutamide and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at < 240 mg daily, whereas 3 seizures were reported, 1 each at 360, 480, and 600 mg daily. Subjects may be at increased risk of seizure following an overdose. Refer to regional prescribing information of enzalutamide for additional information.

6.8 Prior and Concomitant Treatment

6.8.1 Prior Treatment

Prior therapies that the subject receives from 3 months prior to signing the informed consent will be collected on each subject's CRF. All prior anticancer therapies for the treatment of prostate cancer and other eligible malignancies dating back to the initial diagnosis will be collected.

6.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.5.

Subjects must maintain castrate levels of testosterone throughout study and remain on anti-androgen therapy unless they have undergone orchiectomy.

Concomitant therapies that the subject receives are to be collected from informed consent through the end of the SFU period.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and/or protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), device, and/or protocol procedures, or the study as a whole at any time before study completion for the reasons listed in Section 7.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and product complaints (including device-related adverse events, as applicable) and must document this decision in the subject's medical records. Subjects who have discontinued investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to

ensure safety surveillance and/or collection of outcome data. **At minimal vital status (survival status) should be collected, through as an example, direct or family member contact or family members contact or through the attending physician or medical records, public registries, and public records, subject to local laws and regulations**.

Reasons for early removal from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and/or procedures may include any of the following:

- decision by sponsor
- lost to follow-up
- death
- adverse event
- subject request
- ineligibility determined
- protocol deviation
- noncompliance
- disease progression

Radiographic progression of disease should be verified centrally before cessation of investigational product, local intervention, initiation of new anticancer therapy or treatment other than study drug beyond progression, as long as there are no safety concerns, and the study subject is clinically stable.

Subjects who discontinue treatment without having BICR-confirmed radiographic progression of disease (eg, due to unacceptable toxicity or initiation of new anticancer therapy) must continue with radiographic imaging during LTFU, until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or end of study as determined by the sponsor, whichever occurs first.

7.1.1 Treatment Beyond Progression

Treatment beyond progression is allowed with medical monitor approval if the subject is deriving benefit in the opinion of the treating investigator, not meeting any other discontinuation criteria, has provided the additional informed consent, and continues safety assessments. For subjects continuing on treatment beyond progression without a BICR-confirmed rPFS event, radiologic imaging should be continued as per Schedule of Activities (Section 1.3) until they have BICR-confirmed PD. Every radiographic assessment must include a bone scan, a

CT or MRI of the chest, abdomen, pelvis, and all other known sites of disease, and MRI of the brain if a subject has signs or symptoms suggestive of CNS disease.

7.2 Subject Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the subject does not wish to, or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. **The subject is not considered to have ended the study until there is no means to continue collection of vital signs (survival status).** The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is **at risk to be** lost to follow-up, **where permitted per local regulation,** the investigator or designee must make every effort to regain contact with the subject.

- **The investigator or designee should attempt** 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods **(contact the patient's family or direct assigned contact**). These contact attempts are to be documented in the subject's medical record.
- **The investigator should contact the subject's attending physician.**
- If the subject continues to be unreachable **or vital status (survival status) cannot be obtained through any of the above actions**, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator should search publicly available records where permitted to ascertain **vital status (**survival status**)**. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent (main study and any associated informed consent form, as applicable) must be obtained before completing any screening procedure. After the subject has signed the informed consent form(s), the site will register the subject in the IRT and screen the subject to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3)**. The date of the first dose of investigational product(s) is defined as day 1.** Day 1 should occur on the day of randomization wherever possible, however day 1 can occur within 10 days of randomization, if needed, due to logistical reasons. **Investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s)** is to be administered as specified in the Schedule of Activities (Section 1.3) during each visit that it is required.

8.1.3 End of Treatment

Upon permanent discontinuation from study treatment for any reason, an EOT visit will be performed as soon as possible (within 14 days) after last dose of study treatment and prior to start of subsequent anticancer therapy.

8.1.4 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 30 (+ 3) days after the last dose of investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s). The SFU visit will occur regardless of subsequent anticancer therapy within that period.

8.1.5 Long-term Follow-up

LTFU will occur every 8 weeks (± 7 days) from the SFU visit for the first 12 months and every 12 weeks (±14 days) thereafter for up to 3 years after the last subject is randomized, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. Subjects will be followed by clinic visit, telephone, or chart review to assess for survival and/or the commencement of subsequent cancer therapy. Radiological imaging (if applicable) and clinical outcome assessment (EQ-5D-5L) may also be collected during the LTFU period. The procedures to be completed during LTFU are indicated in the Schedule of Activities (Section 1.3).

Subjects who discontinue treatment without having BICR-confirmed radiographic progression of disease (eg, due to unacceptable toxicity) must continue with

radiographic imaging during LTFU, until the occurrence of BICR-confirmed rPFS event, withdrawal of consent, death, or end of study as determined by the sponsor, whichever occurs first. Radiographic images taken during LTFU up to the time of BICR-confirmed PD will be provided by the treating physician to facilitate determination of the rPFS primary endpoint.

In all subjects, information regarding the type and duration of subsequent therapies following disease progression, response to subsequent therapy, date of progression on subsequent therapy, type of progression (radiographic or clinical), and survival data will be collected. Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued LTFU, with or without withdrawing consent, and should include interrogation of public databases if necessary and legally permissible.

8.1.6 End of Study

Refer to Section 4.4 for the end of study definition. The end of study visit is defined as the date of the final study visit shown in the Schedule of Activities (Section 1.3) (eg, final LTFU visit) when assessments and/or procedures are performed.

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the external review body approved informed consent(s) (main study and any associated informed consent form, as applicable) before any study-specific procedures are performed.

8.2.2 Demographics

Demographic data collection including age, race, and ethnicity will be collected to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarker variability and PK of the investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s).

8.2.3 Medical History

The investigator or designee will collect a complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, Prostate cancer history must date back to the original diagnosis. Known Prostate cancer

mutations (eg, Breast Cancer Gene [BRCA]1, BRCA2) and PSMA positron emission tomography (PET) status prior to start of treatment will also be collected. The current toxicity grade will be collected for each condition that has not resolved.

8.2.4 Substance Use History

Obtain a detailed history of prior and/or concurrent use of alcohol, tobacco, and any other recreational substance.

8.2.5 Physical Examination

A complete physical examination should be performed during the screening period and should include evaluation of the head, eyes, ears, nose, throat, and the cardiovascular, respiratory, gastrointestinal, **musculoskeletal**, neurologic, and dermatologic organ systems. Any abnormal findings found at baseline should be recorded on the Medical History CRF. At subsequent visits, a directed physical examination should be performed as clinically indicated prior to administration of study treatment. Any new or worsening abnormal findings should be recorded on the Adverse Event CRF.

Physical examination will be performed as per **SOC**. Physical examination findings should be recorded on the appropriate CRF (eg, Medical History, Event).

8.2.6 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

8.2.7 Neurological Examination

For subjects randomized to xaluritamig arm, neurological examination is only required after randomization and prior to cycle 1 day 1 infusion. During treatment, a neurological examination is only required if clinically indicated. For subjects randomized to cabazitaxel or second ARDT arm, a neurological examination is required only if clinically indicated. Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition, and emotion).

Abnormal findings found pre-dose will be reported on the medical history page of the CRF. Abnormal findings found after the subject is dosed will be reported on the Events page of the CRF.

8.2.8 Performance Status

The subject's performance status will be assessed using the ECOG PS (see Section 11.15) as specified in the Schedule of Activities (Section 1.3).

8.3 Efficacy Assessments

8.3.1 Clinical Laboratory Values

Time to PSA progression, PSA50 and PSA90 Response as defined in the endpoints (Section 3).

8.3.2 Radiographic Assessments

The extent of disease will be evaluated by contrast-enhanced CT **or** MRI and bone scintigraphy according to PCWG3-modified RECIST v1.1 (Section 11.13). **Bone lesions (excluding those with soft tissue component) should not be assessed by CT or MRI as they will be evaluated separately on bone scans alone.** All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. In order to reduce radiation exposure for subjects, low-dose CT should be utilized whenever possible.

8.3.2.1 Screening scans

The screening scans must be performed within 28 days prior to enrollment. If there are multiple screening scans, the one closest to the enrollment will be used as baseline. Assessments that were performed as **SOC** prior to signature of informed consent, but within the 28-day screening period, can be used as screening assessments and do not need to be repeated to confirm subject eligibility.

Radiological assessment must include CT **or** MRI of the chest, abdomen, and pelvis, as well as assessment of all other known sites of disease as detailed within the Site Imaging Manual.

Brain imaging (MRI or CT) of the brain should be performed if signs or symptoms suggestive of CNS metastases are present. All brain scans for subjects with brain metastasis are required to be contrast-enhanced MRI unless MRI is contraindicated, and then CT with contrast is acceptable.

Bone scans must be performed using technetium-99m labelled diphosphonate radiotracers.

8.3.2.2 Subsequent scans

All subsequent scans should be performed in the same manner (eg, with the same contrast, MRI field strength) as at screening preferably on the same scanner. **If the**

imaging modality must be altered (eg, unscheduled assessment) consultation with the Amgen medical monitor is recommended.

During treatment and follow-up, radiological imaging of the chest, abdomen, pelvis, as well as all other known sites of disease, will be performed independent of treatment cycle as specified in the Schedule of Activities (Section 1.3). Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiologic imaging and tumor assessment will be performed until disease progression as assessed by BICR, death, withdrawal of consent, or end of study, whichever occurs first. Radiographic disease response assessment will be reviewed by BICR in real-time. Radiographic progression of disease **should** be verified centrally **before** cessation of investigational product, local intervention, initiation of new anticancer therapy, or treatment other than study drug beyond progression, as long as there are no safety concerns and the subject is clinically stable. For subjects with progressive disease continuing on treatment beyond progression, radiologic imaging should be continued as per Schedule of Activities (Section 1.3) as long as they continue on treatment. Every radiographic assessment must include **a bone scan, CT or MRI of** the chest, abdomen, pelvis**, and** all other known sites of disease, and MRI of the brain if a subject has signs or symptoms suggestive of CNS disease.

Scans will be submitted to a central imaging core laboratory for archival, real-time response assessment including **PCWG3-modified** RECIST v1.1, and/or exploratory analysis (eg, volumetric and viable tumor measurements). Detailed information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

8.3.2.3 Bone Progression

Disease progression by bone scan will be defined as at least 2 new bone lesions relative to the first post-baseline scan confirmed on a subsequent scan (2+2 rule PCWG3 criteria). If the second scan confirms the 2 or more new lesions, then the date of progression is the date of the scan when the 2 or more new bone lesions were first documented. If 2 or more new lesions are already present at the first post-baseline scan, these must be confirmed on the subsequent scan and if so progression is dated at the first post baseline scan. Confirmation of bone disease progression by bone scan must be performed no sooner than 6 weeks per PCWG3 criteria.

See Section **11.13.1** for PCWG3-modified RECIST v1.1 criteria.

8.3.2.4 Soft Tissue Progression

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the modified RECIST v1.1 criteria (Section **11.13.2**).

8.3.2.5 Utilization of PET/CT in Evaluating Disease Progression

BICR will conduct **soft tissue** response assessments following the guidelines of PCWG3**-**modified RECIST v1.1. According to PCWG3, central blinded readers will not have access to any unscheduled (off-protocol) PET/CT scans (eg, 68Ga-PSMA, 18F-PSMA, 18F-FDG, 18F-NaF, etc) collected during the study, as these are considered new and unvalidated biomarkers. When evaluating subject local radiographic responses, investigators should account for the lack of clinical validation of these imaging agents and ensure that treatment cessation is based on BICR-confirmed radiographic disease progression.

8.3.3 Clinical Progression

Clinical progression will be assessed by the investigator. **Subjects who discontinue treatment due to clinical progression alone must continue radiographic assessments until BICR-confirmed radiographic progression according to the Schedule of Activities (Section 1.3). Any of t**he following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to be related to underlying disease progression and indicate the need for other systemic anticancer therapy
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG PS to ≥ grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

8.3.4 Clinical Outcomes Assessment

Clinical outcome assessment should be collected as indicated in the Schedule of Activities. If an assessment is not performed as indicated the reason for a missing assessment should be reported.

Patient-reported outcomes questionnaires include:

1. EuroQoL 5 Domain 5 Level (EQ-5D-5L)

2. Brief Pain Inventory – Short Form (BPI-SF)
3. Functional Assessment of Cancer Therapy - Prostate (FACT-P)
4. PRO-CTCAE item library (selected questions).

Refer to Section 11.14 for **detailed descriptions and** a copy of each of these PRO questionnaires. The PRO questionnaires administered in the clinic should be completed by the subject before **cycle 1 day 1 to avoid censoring due to lack of baseline information, and should be completed before** receiving any study medications, prior to any other clinical assessments or consultation with the investigator, and prior to being informed of their current disease status. In cases where PRO assessments are expected to be completed at home, patients should respond to questions using an electronic PRO device preferably at the same time of day. If the assessment instrument is unavailable in the subject's language, completion of the PRO questionnaire is not required, and this will not limit enrollment. If the assessment instrument for PRO questionnaire completion malfunctions, the site will provide the subject access to the vendor's web portal while on site in order to complete the PRO questionnaire assessments required at that visit.

Patient-reported outcome questionnaires should be personally completed by the subject in a language they can read and understand. Patient-reported outcomes will be collected as described in the Schedule of Activities (Section 1.3). Under the following circumstances, the electronic PRO (ePRO) assessments can be considered optional:

- ePRO tablet not available at site at the time of subject screening
- Technical issue prohibits use of ePRO tablet
- Local approval of translated ePRO materials not received at time of screening

8.3.4.1 EQ-5D-5L

The EQ-5D-5L questionnaire is a 2-page, standardized instrument for use as a measure of health outcome developed by the EuroQol group (Rabin and de Charro, 2001). It is comprised of a 5-dimension health status measure and a VAS. The 5-dimension health status measure evaluates mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on a 5-level scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). The VAS records the subject's self-rated health on a vertical scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state.' The EQ-5D-5L takes approximately 3 minutes to complete.

8.3.4.2 BPI-SF

The BPI-SF is a valid and reliable instrument, which is a commonly used tool to capture severity of pain and its impact on daily functioning (Cleeland, 2009). The BPI is a 9-item questionnaire which includes 2 body diagrams, four items to assess pain severity, four items to assess pain interference and one question about percentage of pain relief by analgesics. Assessed level of pain and its impact can be divided into categories based on score of mild (1 to 4), moderate (5 to 6), and severe (7 to 10). The recall period is the previous 24 hours. The BPI questionnaire takes approximately 5 minutes to complete.

8.3.4.3 FACT-P

The FACT-P is made up of 2 parts: the Functional Assessment of Cancer Therapy - General (FACT-G) comprising 27 questions, and the Prostate Cancer Subscale (PCS) comprising an additional 12 questions. The FACT-G questionnaire measures 4 domains of health-related quality of life in cancer patients in four different domains: physical, social, emotional, and functional well-being.

The GP5 is a single question ("I am bothered by side effects of treatment") rated on a 5-point Likert scale from "not at all" to "very much" included in the physical well-being subscale. The GP5 question has been evaluated and validated as a useful summary index of side effect impact or burden to the individual subject (Pearman et al, 2018).

The PCS is designed to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 5-point Likert scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better quality of life. FACT-P has a recall period of 7 days. Questionnaires of the FACT system are reliable, reproducible, and have been validated (Hamoen et al, 2015; Esper et al, 1997; Cella et al, 1993). The FACT-P questionnaire takes approximately 10-15 minutes to complete.

8.3.4.4 PRO-CTCAE

Treatment-related symptoms and impact on the subjects will be assessed using selected questions from the PRO-CTCAE library and a single question about how much patients are bothered by their side effects (GP5 of the FACT-P questionnaire).

PRO-CTCAE is a 78-item library used to measure patient-reported symptomatic adverse events. Users can select items that are most relevant to disease, treatment profile, and fit for purpose to document patients' experience. The PRO-CTCAE has been tested and

validated in terms of construct validity, test-retest reliability, and item responsiveness (Dueck et al, 2015).

Based on the safety profile of xaluritamig (Study 20180146 IA as of 4 October 2023), cabazitaxel and second ARDT in patients with mCRPC previously treated with chemotherapy, the questionnaire will address the following symptoms: Nausea (item 9), Diarrhea (item 16), Shortness of breath (item 19), Numbness and tingling (item 39), Dizziness (item 40), General pain (item 48), **Muscle Pain (item 50), Joint pain (item 51),** Fatigue (item 53) and Chills (item 74). Each symptom can be rated by up to 3 attributes, presence/frequency, severity, and/or interference of the adverse event (Basch et al, 2014). The recall period for PRO-CTCAE is the past 7 days. The PRO-CTCAE questionnaire comprising the selected items takes approximately 3 minutes to complete.

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature. Subject must be in a supine position (recumbent if supine not possible) in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. Record all measurements on the vital signs CRF.

For time points that include ECGs, vital signs, and blood draw assessments, the preferred order is vital signs, ECGs, then blood draws.

For subjects receiving xaluritamig on day 1 of cycle 1, vital signs should, **at minimum**, be assessed at the following time points:

- Pre-infusion (within 30 minutes prior to start of infusion)
- End of infusion (EOI) (+ 5 minutes)
- 4 to 6 hours (± 15 minutes) after EOI
- Prior to discharge

During all other infusions in inpatient setting, vital signs should be collected during the hospitalization/observation period only as per the time points listed above.

For xaluritamig infusion on days 8, 15, and 22 of cycle 1 or until target dose is achieved vital signs should, **at minimum**, be assessed at the following time points:

- Pre-infusion (within 30 minutes prior to the start of infusion)
- EOI (+ 5 minutes)
- 4 to 6 hours (± 15) minutes after EOI

For xaluritamig infusions in cycle 2 (and beyond) vital signs should, **at minimum**, be assessed at the following time points:

- Pre-infusion (within 30 minutes prior to the start of infusion)
- EOI (+ 5 minutes)

8.4.2 Electrocardiograms

Subject must be in supine position (recumbent if supine not possible) in a rested and calm state for at least 5 minutes before ECG assessment is conducted. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

8.4.3 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.4.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent

and should include interrogation of public databases, if necessary and legally permissible. If deceased, the date and reported cause of death should be obtained.

8.4.5 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.4.5.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.5.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 11.4 with the following exceptions:

CRS and ICANS will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) guideline (Lee et al, 2019) as described in Sections 11.12 and 11.11.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the **SFU Visit (**30 **[+3])** days after the last day of the dosing interval of investigational product or noninvestigational product(s)/auxiliary medicinal product(s), are reported using the Events CRF.

Disease progression is an efficacy endpoint. Disease progression of mCRPC is not considered an adverse event and should not be reported as an adverse event unless there is evidence suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the mCRPC as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the Tumor Response (PCWG3) CRF as part of efficacy data collection and not on the Events CRF. The events of disease progression including death due to disease progression will be monitored at appropriate intervals by the Data Monitoring Committee (DMC).

8.4.5.1.2 Adverse Events of Special Interest

Myalgia and myofascitis ≥ grade 3 are considered Adverse Events of Special Interest and these events should be collected and recorded in the electronic CRF immediately and no later than 24 hours of the investigator's awareness of the event.

8.4.5.1.3 Serious Adverse Events

Serious adverse events are defined in Section 11.4. The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through **the SFU Visit (**30 **[+3])** days after the last day of the dosing interval of investigational product or noninvestigational product(s)/auxiliary medicinal product(s) are reported using the Events CRF.

Hospitalization for CRS monitoring is a pre-planned safety measure and should not be recorded as a serious adverse event. The duration of pre-planned hospitalization is defined by the investigator according to local **SOC**. **Hospitalization that was required for patient monitoring outside of normal outpatient clinic operating hours (eg, extended monitoring of CRS) would not meet criteria for serious adverse events**. Only adverse events that prolong the pre-planned hospitalization beyond the local **SOC** should be reported as serious adverse events on the grounds of prolonged hospitalization alone.

Disease progression and death due to disease progression of mCRPC are not considered serious adverse events and will not be reported as serious adverse events unless there is evidence suggesting a causal relationship between the investigational product and/or noninvestigational product(s)/auxiliary medicinal product(s), and/or devices and progression or symptom/sign of progression of the mCRPC as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the tumor response (PCWG3) CRF as part of efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded in the end of study CRF and not on the Events CRF. The events of disease progression including death due to disease progression will be monitored at appropriate intervals by the DMC.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee immediately and no later than 24 hours of the investigator’s awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to **Amgen or designee** immediately and no later than 24 hours of it being available.

Since the criteria of the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator’s judgment to also report these

abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

8.4.5.1.4 Serious Adverse Events After the Protocol-required Reporting Period

During the LTFU period, if the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 8.4.5.1.3) is complete, then these serious adverse events will be reported to Amgen **or designee**. The investigator will report serious adverse events to Amgen immediately and no later 24 hours after the investigator's awareness of the event on the Events CRF.

Disease progression and death due to disease progression of mCRPC are not considered serious adverse events and will not be reported as serious adverse events unless there is evidence suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the mCRPC as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the tumor response (PCWG3) CRF as part of efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded in the end of study CRF and not on the Events CRF.

There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen **or designee** immediately and no later than 24 hours after the investigator's awareness of the event.

Serious adverse events reported after the end of the study will be captured within the safety database as clinical study cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.4.5.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.4.5.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen **or designee** immediately and no later than 24 hours after investigator's awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.4.5.4 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen **or designee**.

Prompt notification by the investigator to **Amgen** of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. **Amgen** will comply with country-specific regulatory requirements relating to safety reporting to the external review body and investigators.

Individual safety reports for suspected unexpected serious adverse reactions (SUSARs) will be reported by **Amgen** according to local regulatory requirements (eg, electronic submission to the Eudravigilance database in the European Union [EU] as per EU Clinical Trial Regulation 536/2014) as well as **Amgen** policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from **Amgen** will file it along with the investigator's brochure and will notify the external review body, if appropriate according to local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable.

8.4.5.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.4.5.6 Pregnancy

Details of all pregnancies of female partners of male subjects will be collected after the start of study treatment and until 6 months after the last dose of xaluritamig, an additional 4 months after last dose of cabazitaxel, an additional 3 months after last dose of enzalutamide, or an additional 3 weeks after last dose of abiraterone acetate.

If a pregnancy is reported, the investigator is to inform Amgen **or designee** immediately and no later than 24 hours of learning of the pregnancy and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy are provided in Section 11.5.

8.4.5.7 Other Safety Findings/Special Situations (OSF/SS)

All medication errors, misuse, or abuse of the investigational product when associated with a serious adverse event must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by collecting and recording the Other Safety Findings (OSF)/Special Situations (SS) event on the Clinical Trial electronic Serious Adverse Event (eSAE) Contingency Report Form and submitting the form to Amgen Global Patient Safety or designee.

Further details and definitions regarding OSF/SS - medication errors, misuse, and abuse, can be found in Section 11.4.

8.5 Pharmacokinetic Assessments

Only subjects randomized to the xaluritamig arm will have pharmacokinetic samples assessed.

Blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of xaluritamig as specified in the Schedule of Activities (Section 1.3) Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.6 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. This optional assessment is separate from genomic analysis of somatic mutations in the tumor sample included as part of the main study. The goals of the optional studies include the use of genetic markers to help in the investigation of prostate cancer and/or to identify subjects who may have positive or negative response to xaluritamig. A saliva sample is collected for this part of the study. For subjects who consent, DNA may be extracted. The final disposition of samples will be described in Section 11.6. Obtain confirmation that the pharmacogenetic informed consent form (ICF) has been signed before performing pharmacogenetic procedures.

8.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Section 1.3) for the measurement of anti-xaluritamig antibodies. Samples testing positive for anti-xaluritamig antibodies may be further characterized.

8.8 Biomarkers

8.8.1 Biomarker Assessment During the Study

When permitted by local regulations, whole blood, serum, plasma, and tissue samples are to be collected and assessed for pharmacodynamic biomarkers and biomarker development at the time points specified in the Schedule of Activities (Section 1.3).

8.8.1.1 Pharmacodynamic Assessments

Serum and plasma samples will be collected to understand the mechanism of action and biological effects of xaluritamig administration. Samples will be collected for pharmacodynamic assessment at the time points specified in the Schedule of Activities (Section 1.3). The pharmacodynamic assessments include but are not limited to assessment of cytokine levels related to T-cell activation.

8.8.1.2 Biomarker Development

Samples will also be collected to develop or address biomarker hypotheses related to xaluritamig activity, eg, to evaluate potential biomarkers that may correlate with treatment response.

Whole blood, serum, plasma, and tissue samples will be collected for biomarker development at the time points specified in the Schedule of Activities (Section 1.3).

The whole blood, serum, and plasma samples will be collected for evaluation of exploratory biomarkers including DNA, RNA, epigenetic alterations, and protein expression analyses, and their potential association with xaluritamig activity and/or clinical endpoints. These include but are not limited to:

- Soluble proteins – Serum and/or plasma will be analyzed to assess levels of PSA, cytokines, chemokines, and other disease-related proteins.
- Circulating tumor/cell-free DNA – Blood samples will be collected and assessed for circulating tumor/cell-free DNA mutational profiles or epigenetic alterations. Circulating tumor DNA plasma analysis may include mandatory paired analysis of subject blood samples to identify and select out germline variants to refine and determine tumor specific mutations. The circulating tumor/cell-free DNA assessments are used for profiling somatic mutations, mutational burden, or epigenetic alterations as well as other potential biomarkers of response for diagnostic development. Germline mutational results will not be reported by Amgen unless pharmacogenetic consent is provided by the subject.
- Peripheral immune characterization – Peripheral blood mononuclear cell samples may be analyzed for levels of gene and/or protein expression to assess disease or treatment-related changes in peripheral immune system.

Archival tumor tissue samples are required if available for exploratory biomarker evaluation and will be collected according to the time points specified in the Schedule of Activities (Section 1.3). Subjects must **provide** consent **prior** to **submission** of archival formalin-fixed, paraffin-embedded material by study personnel. A block(s) of archived formalin-fixed, paraffin-embedded tumor tissue collected prior to cycle 1 day 1 is to be sent to the central laboratory along with the corresponding pathology report. The tumor block should be carefully selected by a pathologist or a skilled experienced histology

associate to include sufficient quantity of tumor tissue to allow for immunohistochemistry, DNA, and transcriptional analyses. In lieu of a block, 20 unstained, consecutive sections of 4 to 6 μm thickness, mounted on charged slides can be submitted. Tissue will be used for DNA, RNA, and protein expression analyses including STEAP1 expression, immune-related markers, tumor-specific mutations (eg, somatic mutations), epigenetic alterations, and/or transcriptional analyses of the tumor microenvironment to evaluate potential biomarkers that may correlate with treatment response.

Exploratory genomic analyses of tumor biopsies may include mandatory paired analysis of subject blood samples to identify and select out germline variants to refine and determine tumor-specific mutations. Germline mutational results will not be reported to Amgen unless pharmacogenetic consent is provided by the subject.

8.8.1.3 Biomarker Future Research

In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s).

If consent is provided by subjects, any remaining samples collected at the time points specified in the Schedule of Activities, including samples collected for biomarker assessments may be used for future research as described in Section 11.6. No additional samples will be collected for future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to xaluritamig and to investigate and further understand solid tumors, including prostate cancer.

Obtain confirmation that the biomarker future research ICF has been signed before performing biomarker future research procedures.

8.9 Optional Intensive PK/PD Substudy

Approximately 25 subjects in the xaluritamig arm will be invited to participate in the intensive pharmacokinetic/pharmacodynamic (PK/PD) substudy at select sites. Sparse samples will be collected from all other subjects, eg, subjects who do not consent to participate in the optional intensive PK/PD substudy.

Documentation of informed consent for the optional intensive PK/PD study must be confirmed before beginning any intensive procedures. The procedures are outlined in the Schedule of Activities (Section 1.3).

8.10 Medical Resource Utilization and Health Economics

Medical Encounters

Medical resource utilization associated with medical encounters will be collected **in** the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-required procedures, tests, and encounters will be included**,** but will be reported separately from those that are not protocol-required. Medical encounters included will also be designated, when applicable, by site of care as being administered or occurring in either the inpatient or outpatient setting.

The data collected **may be used to conduct medical resource use analyses and will include:**

- **number and duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])**
- **number and type of diagnostic and therapeutic tests and surgical and nonsurgical procedures**
- **reason for hospitalization (eg, adverse event such as CRS/ICANS or other)**

Cytokine Release Syndrome

Medical resource utilization and health economics data related to CRS will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. The data may be used to conduct economic analyses and may include hospitalizations (by ward), concomitant medications, diagnostic and therapeutic tests and procedures related to CRS.

9. Statistical Considerations

9.1 Statistical Hypotheses

The hypothesis of the primary efficacy endpoint (OS) and key secondary efficacy endpoint (rPFS) will be tested. The OS endpoint will be tested with 1-sided overall type I error (alpha) of 0.025. If OS is significant, the key secondary efficacy endpoint of rPFS will be tested with 1-sided overall type 1 error (alpha) of 0.025.

9.2 Sample Size Determination

Approximately 450 subjects in the experimental arm and 225 subjects in the control arm, a total of 675 subjects will be enrolled.

Overall Survival

A total of 464 OS events will provide approximately 90% power to demonstrate superiority with respect to OS in the experimental arm compared to the control arm at a

1-sided 2.5% significance level, if the true treatment effect HR is assumed to be 0.72, corresponding to an assumed median OS of 18.2 months in the experimental arm versus 13.1 months for the control arm. **The assumptions for the control arm median OS are based on a systematic literature review of phase 3 trials containing cabazitaxel or ARDT treatment arms. The OS for cabazitaxel across relevant studies (CARD, PROSELICA, AFFINITY, CABASTY) averages 13.8 months, while the OS for ARDT switch (VISION, CARD, KEYLYNK-10) averages 12.3 months. Both treatments were weighted equally (50% each) in the control arm calculation, reflecting the 50:50 split that will be implemented to ensure subgroup comparability between the investigational arm and each of the two SOC options. The final control arm OS estimate of 13.1 months is a simple weighted average, ensuring that the chosen control arm reflects the efficacy of both therapeutic strategies. Exclusion of outlier studies (eg, older trials, small trials, and those with methodological concerns) was applied to improve reliability and external validity of these assumptions.**

The annual dropout rate for the OS endpoint is anticipated to be 5% per year, assuming an exponential distribution. A group sequential design will be implemented with 2 IAs for claiming early efficacy and 1 PA. The first IA is planned to be conducted when approximately 278 (60%) events have occurred, the second when approximately 371 (80%) events have occurred. The OS PA is planned to be conducted when approximately 464 OS events have been observed. The alpha spending at the OS IAs will be adjusted with the actual number of OS events observed. It is estimated that the first OS IA will occur at 25 months, the second at 32 months, and the OS PA will be triggered at approximately 43 months after the first subject randomized.

Radiographic Progression-free Survival

The primary analysis of rPFS will occur once the OS endpoint can claim statistical significance and will only be tested once, either at the time of the first or second OS IA if the trial stops early for efficacy or at OS PA. At the time of statistical significance of OS, rPFS will be tested with all observed rPFS events. It is anticipated that a minimum of 372 rPFS events will be observed by the first OS interim analysis, which will provide at least 90% power to demonstrate superiority with respect to rPFS in the experimental arm compared to the control arm at a 1-sided 2.5% significance level, if the true treatment effect hazard ratio is assumed to be 0.70, corresponding to an assumed median rPFS of 8.4 months in the experimental arm versus 5.9 months for the control arm. A dropout

rate of 2% per year and exponential distribution assumptions are used in the preceding calculations.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Intention-to-treat analysis set	All randomized subjects. All subjects will be analyzed according to the randomized treatment arm. The intention-to-treat analysis set will be used for the primary and secondary efficacy endpoints, unless specified otherwise.
Safety analysis set	All subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment they actually received.
PRO analysis set	All randomized subjects with a non-missing baseline and at least 1 non-missing post-baseline result in any scales/item of the instrument. These analysis sets will be used for the PRO endpoints.
Per Protocol Analysis Set	All randomized subjects who received at least one dose of their assigned study drug and did not have important protocol deviations (IPDs) that are considered to have an impact on efficacy outputs. All subjects will be analyzed according to the treatment they received.

9.3.1 Covariates

Covariates may be incorporated in selected models of efficacy endpoints. In addition to the stratification factors for randomization, additional covariates may be included.

9.3.2 Subgroups

In addition to subgroup analyses within the stratification factors for randomization, primary and selected secondary endpoints may be examined in the following subgroups:

- **a**ge (< 65 vs ≥ 65)
- **r**ace (White, Black, Asian, Other)
- **e**thnicity (Hispanic, Non-Hispanic)
- **region (North America, Europe, Asia)**
- ECOG PS (0 vs 1)
- **b**one only disease (yes vs no)
- **prior ARDT (abiraterone vs enzalutamide vs darolutamide vs apalutamide)**
- **prior docetaxel in hormone sensitive setting (yes vs no)**
- **p**rior PARP inhibitor (yes vs no)
- **p**rior **anti-programmed death-ligand 1** (yes vs no)

- **p**rior radionuclide therapy (Radium-223) (yes vs no)
- **prior PSMA RLT or radium-223 (yes vs no), may be performed as a combined subgroup analysis if numbers for each individual subgroup are small**
- **p**rior palliative radiotherapy (yes vs no)
- **p**rior definitive radiotherapy or radical prostatectomy (yes vs no)
- **prior definitive radiotherapy without prostatectomy (yes vs no)**
- **prior radical prostatectomy without radiotherapy (yes vs no)**
- **prior radical prostatectomy with radiotherapy (yes vs no)**
- ***BRCA* mutation (*BRCA*m vs non-*BRCA*m vs unknown)**
- PSMA PET status (PSMA positive vs negative) (to be collected if done during screening and conducted off-protocol. Note: PSMA PET is not performed as part of study)
- **concomitant denosumab (yes vs no)**
- **concomitant bisphosphonate (yes vs no)**
- **concomitant denosumab or bisphosphonate (yes vs no)**

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

A description of the IA and primary analysis is listed in Table 9-1. An average accrual rate of 40 subjects per month with a **4**-month ramp-up period is assumed. Depending on the actual enrollment rate, the number and timing of interim analyses could be different from what is projected here.

Table 9-1. Purpose and Timing of the Planned Analysis

Timepoint	Adaptive decision and analysis scope	Number of subjects or events	Timing
IA1 (60% OS)	Efficacy/Futility/Safety	Total of 278 OS events from both arms	25 months (the study is fully enrolled)
IA2 (80% OS)	Efficacy/Safety	Total of 371 OS events from both arms	32 months
OS PA	Efficacy/Safety	Total of 464 OS events from both arms	43 months

IA = interim analysis; OS = overall survival; PA = primary analysis

A DMC (external to Amgen) will be convened and will act in an advisory capacity to Amgen with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and providing recommendations on whether to continue, modify or stop the study based on these findings. The DMC will review safety data after **3**0 patients are enrolled and have had the opportunity to be treated for at least 1 month**,** then at periodic intervals thereafter at approximately 3-month intervals for 6 months and approximately 6-month intervals thereafter until the last subject has completed treatment**,** the study is terminated earlier, or the primary analysis, whichever occurs first. Additionally, the DMC will conduct evaluations of the grade 4 or higher treatment-related adverse events reported in subjects treated with xaluritamig (excluding grade 4 lymphopenia/lymphocyte count decreases and other laboratory adverse events of grade 4 not considered clinically relevant) to assess if the threshold for possible early study termination has been reached. The stopping rules will use a Bayesian approach proposed by Thall et al (1995) to stop the study if the posterior probability that the grade 4 or higher treatment-related adverse event subject incidence rate in the xaluritamig arm (excluding grade 4 lymphopenia/lymphocyte count decreases and other laboratory adverse events of grade 4 not considered clinically relevant) is $>$ 20% is $>$ 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60)**, and are presented in Appendix 11.17**. If the threshold is met the DMC will make a recommendation, and Amgen will choose to take 1 of the following actions:

- Terminate the study.
- Amend the protocol to potentially improve the benefit/risk for subjects.
- Continue the study without any changes.

The stopping rules above only apply to the xaluritamig arm.

The DMC will also monitor the proportion of subjects who received subsequent anticancer therapy prior to BICR-confirmed progressive disease. If the overall proportion is $>$ 10% or if there is $>$ 5% difference between the arms, the DMC will notify the study team. This notification will enable guidance for re-educating investigators on the protocol requirement to continue study treatment until radiographic progression is confirmed by real-time BICR.

Additionally, the DMC will be responsible for reviewing the interim efficacy analyses prior to the primary analysis. Refer to Section 11.3 for additional information about the DMC.

Interim Efficacy and Futility Rules

The testing of OS at the interim and primary analyses is adjusted using the Lan-DeMets alpha spending function with an O'Brien-Fleming approach. Table 9-2 shows the efficacy and **non-binding** futility boundaries.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the planned interim analyses will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

Table 9-2. Stopping Boundaries of OS

Analysis	Information Fraction	Cumulative Events	Alpha spending	p-value (primary inference)	HR boundary for efficacy	HR boundary for futility (non-binding)
IA1	60%	278	0.004	0.004	0.712	0.909
IA2	80%	371	0.012	0.011	0.777	NA
PA	100%	464	0.025	0.021	0.819	NA

HR = hazard ratio; OS = overall survival; NA = not applicable

9.4.1.2 Primary Analysis

The timing for the PA of OS will be event driven and will happen when approximately 464 OS events are reached cumulatively in the 2 treatment arms. If OS early success is achieved in the IA1 or IA2 (interim efficacy boundary specified in Table 9-2 is crossed), that IA will serve the purpose of PA of OS.

The primary analysis of rPFS will occur once the OS endpoint can claim statistical significance and will only be tested once, either at the time of the first or second IA if the trial stops early for efficacy or at OS PA.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the primary analysis will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

9.4.1.3 Final Analysis

The final analysis will occur when enrollment is complete and each subject completes the study, including LTFU.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the final analysis will be locked to prevent future changes. It is expected that all outstanding data issues are resolved ahead of the final lock.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamics, and biomarker data. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

The primary inferential comparisons of the OS primary endpoint between experimental and control arms will be made using a stratified log-rank test controlling for the randomization stratification factors. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. Stratum that is too small may be collapsed in the stratified log-rank analysis. The distribution of OS, including the median and quartiles and their corresponding 95% CIs will be characterized using the Kaplan-Meier method. Overall survival rates for selected landmarks (eg, 1 year and 2 years) will be reported with the 95% CI.

Radiographic progression-free survival will be analyzed using the same approach as OS. The rPFS rate at 1 year will be reported with the 95% CI.

Further details of secondary endpoint testing will be described in the SAP.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods	Additional Analyses
Primary		
The primary endpoint is overall survival	OS will be conducted on the intention-to analysis set. Censor at last known to be alive date. Kaplan-Meier (K-M) curves will be estimated and graphically displayed for each randomized treatment arm. The primary test comparing the 2 survival functions will be performed using a 1-sided log rank test stratified by randomization stratification factors. K-M estimates at timepoints [eg, 1 year, and 2 years] and 95% CIs will be calculated by each randomized treatment arm. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors	Sensitivity Analysis: • Repeat per Protocol Analysis Set
Key Secondary		
The Key secondary endpoint is rPFS	For the key secondary endpoint, rPFS will be censored at the last evaluable post-baseline tumor assessment prior to subsequent anticancer therapy; otherwise, at randomization. K-M curves will be estimated and graphically displayed for each randomized treatment arm. The primary test comparing the 2 survival functions will be performed using a 1-sided log rank test stratified by randomization stratification factors. K-M estimates at timepoints [eg, 6 months,	Supplemental Estimand: • Censor at the last evaluable post-baseline tumor assessment regardless of subsequent anticancer therapy; otherwise, at randomization. • Include subsequent anticancer therapy as an event along with first documentation of radiologic disease progression or death due to any cause. rPFS will be censored at the last evaluable post-baseline tumor assessment; otherwise, at randomization.

	1 year, and 2 years] and 95% CIs will be calculated by each randomized treatment arm. The HR and its corresponding 95% CI will be estimated from a stratified Cox model, stratified by the randomization stratification factors.	• Censor at the last evaluable post-baseline tumor assessment or the earlier of the following, where applicable: (a) the last evaluable post-baseline tumor assessment prior to subsequent anticancer therapy, or (b) the last post-baseline assessment followed > X days (pre-specified in the statistical analysis plan [SAP]) later by disease progression or death; otherwise, at randomization. Sensitivity Analyses: • Repeat per Protocol Analysis Set • Censor at the last evaluable post-baseline tumor assessment unless disease progression or death occurs > X days (pre-specified in the SAP) after the last post-baseline assessment, in which case it will be censored at the last post-baseline assessment prior to disease progression or death; otherwise, at randomization • A rPFS event due to disease progression or censoring at a visit outside a scheduled visit window will be moved to the next scheduled visit (unless after death). • A rPFS event due to disease progression or censoring at a visit outside a scheduled visit window will be moved to the closest scheduled visit (unless after death). • rPFS event and censoring times will be mapped to an interval defined by the visit schedule. Interval 1 will be from randomization to the end of the visit window for the first post-baseline tumor

		assessment, Interval 2 will be after Interval 1 to the end of the visit window for the second post-baseline tumor assessment, etc.
Secondary		
Objective response	The descriptive analysis of objective response rate (ORR) will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the stratification factors. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect. ORR will be calculated and the 95% CI will be estimated using the Clopper-Pearson Method.	• Unstratified analyses • To evaluate the robustness, sensitivity analyses of subgroup
Duration of Response (DOR)	The descriptive analysis of DOR will be provided using the same methods as OS.	
Disease control rate	The descriptive analysis of disease control rate will be provided using the same methods as objective response.	
Time to response (TTR)	The descriptive analysis of TTR will be provided using the same methods as OS.	
Time to first symptomatic skeletal event (SSE)	The descriptive analysis of time to first SSE will be provided using the same methods as OS.	
Change from baseline in: • Brief Pain Inventory - Short Form (BPI-SF) worst pain score • BPI-SF Pain Intensity Scale • BPI-SF Pain Interference Scale • Functional Assessment of Cancer Therapy – Prostate (FACT-P) Total Score and subscale scores	Will be described in the patient-reported outcomes (PRO) supplemental SAP finalized before database lock.	

• European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) Utility Score • Change from baseline in EQ-5D-5L Visual Analogue Scale (VAS)		
• Time to worsening in: o BPI-SF worst pain score o BPI-SF Pain Intensity scale o BPI-SF Pain Interference scale o FACT-P Total Score • Time to pain improvement in: o Subjects with moderate/severe pain at baseline • Time to improvement after worsening in: o BPI-SF Pain Intensity scale o BPI-SF Pain Interference scale	Will be described in the PRO supplemental SAP finalized before database lock.	
Patient-reported outcomes summary scores as assessed by: • Selected questions on symptomatic adverse events from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library • The GP5 question on overall bother of side effects from the FACT-P questionnaire	Will be described in the PRO supplemental SAP finalized before database lock.	
PSA50 and PSA90 responses	The descriptive analysis of PSA50 and PSA90 response will be provided using the same methods as ORR.	
Exploratory		

• Number of medical care encounters and other selected procedures (protocol mandated and not protocol mandated) • Genomic alterations, RNA expression, protein expression detected at baseline or time of progression • Correlation of biomarkers, including but not limited to serum proteins, STEAP1 protein expression, RNA expression, and cfDNA with select efficacy and safety endpoints	Will be described in the SAP finalized before database lock.	

9.4.2.3 Safety Analyses

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set. The statistical analysis methods for the safety endpoints are described in Sections 9.4.2.3.1 through 9.4.2.3.5.

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or noninvestigational product(s)/auxiliary medicinal product(s), and treatment-emergent adverse events will also be provided.

9.4.2.3.2 Laboratory Test Results

The analyses of selected safety laboratory endpoints will include summary statistics over time. Shifts in grades of selected safety laboratory values between the baseline and the worst on-study value may be tabulated.

9.4.2.3.3 Vital Signs

The analyses of vital signs may include summary statistics over time. The incidence and percentage of abnormal changes in vital signs may be tabulated.

9.4.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics at baseline.

9.4.2.3.5 Electrocardiogram

The ECG measurements from this clinical study were performed as per SOC for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of single ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.4.2.3.6 Antibody Formation

The incidence and percentage of subjects who develop anti-xaluritamig antibodies at any time will be tabulated.

9.4.2.3.7 Exposure to Investigational Product

The number of cycles, duration, the cumulative dose, and the average dose of investigational product administered will be summarized.

9.4.2.3.8 Exposure to Noninvestigational Product(s)/Auxiliary Medicinal Product(s)

Descriptive statistics will be produced to describe the exposure to noninvestigational product(s)/auxiliary medicinal product(s).

9.4.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment arm as coded by the World Health Organization Drug dictionary.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AQA	analgesic quantification algorithm
ARDT	androgen receptor-directed therapy
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
BICR	blinded independent central review
BIL	bilirubin
BiTE®	bispecific T-cell engager (BiTE®)
BOR	best overall response
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory – Short Form
BRCA	Breast Cancer Gene
CABG	coronary artery bypass graft
CBC	complete blood count
CFR	US Code of Federal Regulations
CLCR	creatinine clearance
CNS	central nervous system
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	**complete response**
CRF	Case Report Form
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLS	Clinical tumor lysis syndrome
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DOR	duration of response
DSUR	Development Safety Update Report
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status

EDC	electronic data capture
EOI	end of infusion
EOT	end of treatment
ePRO	electronic Patient-Reported Outcome
EQ-5D-5L	European Quality of Life 5 Domain 5 Level Scale
eSAE	electronic serious adverse event
EuroQol	European Quality of Life
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
FDG	**fluorodeoxyglucose**
FIH	first-in-human
FSH	follicle-stimulating hormone
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IBG	Independent Biostatistics Group
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LTLS	laboratory tumor lysis syndrome
mCRPC	metastatic castration-resistant prostate cancer
m**H**SPC	metastatic **hormone**-sensitive prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

NCT	National Clinical Trials
NE	not evaluable
ORR	objective response rate
OS	overall survival
OSF	Other Safety Findings
PA	Primary Analysis
PARP	poly adenosine diphosphate ribose polymerase
PCS	Prostate Cancer Subscale
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PG	**pharmacogenetics**
PK	pharmacokinetics
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSMA	Prostate-Specific Membrane Antigen
Q2W	every 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	radioligand therapy
rPFS	radiographic progression-free survival
SAP	statistical analysis plan
SD	**stable disease**
SFU	safety follow-up
SOC	standard of care
SS	Special Situations
SSE	symptomatic skeletal events
STEAP1	six transmembrane epithelial antigen of the prostate 1
$t_{1/2}$	half-life
TBL	total bilirubin
TCE	T-cell engager
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration

TTR	Time to Response
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Hematology	Other Laboratory Analytes
Routine Sodium Potassium CRP Creatinine eGFR Albumin Total bilirubin ALP LDH AST (SGOT) ALT (SGPT) **If clinically indicated or as specified in SOA** Direct bilirubin[a] Adjusted calcium **Amylase**[b] **Lipase**[b] Chloride **Bicarbonate** Total protein Magnesium Phosphorus **BUN or Urea** Glucose Calcium Uric acid	**If clinically indicated:** **PT/INR** **PTT/APTT** **Fibrinogen** **Fibrin split products** **D-dimer**	**Routine** Hemoglobin Hematocrit **MCV** **RDW** Platelets WBC Differential • Eosinophils • Basophils • Lymphocytes • Monocytes • ANC	**Local Laboratory, Routine** Testosterone PSA Hep B surface antigen Hep B core antibody Hep C antibody HIV **Local Laboratory, if clinically indicated**[c] **Creatine kinase** Serum aldolase Auto-antibody panel **Cytokine panel** **Central Laboratory** PBMCs Cytokines PSA[d] ctDNA Saliva **(**optional **PG research)** Tumor tissue (archival) Xaluritamig PK Anti**drug** antibodies Creatinine Kinase

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; **APTT = activated partial thromboplastin time;** AST = aspartate aminotransferase; **BUN = blood urea nitrogen;** CRP = C-reactive protein; ctDNA = circulating tumor DNA; eGFR = estimated glomerular filtration rate; **EOT = end of treatment; Hep = hepatitis;** HIV = human immunodeficiency virus; **INR = international normalized ratio;** LDH = lactate dehydrogenase**; MCV = mean corpuscular volume;** PBMC = peripheral blood mononuclear cell; **PCWG3 = Prostate Cancer Working Group 3; PG = pharmacogenetics;** PK = pharmacokinetics**;** PSA = prostate-specific antigen; **PT = prothrombin time; PTT = partial thromboplastin time; RDW = Red cell distribution width; SFU = safety follow-up;** SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; **SOA = Schedule of Activities;** WBC = white blood cell count.

[a] **If total bilirubin abnormal or otherwise clinically indicated.**
[b] **If liver function tests abnormal or otherwise clinically indicated.**
[c] **In case of localized inflammatory event.**

[d] According to PCWG3 guideline, PSA will be collected until confirmed PSA progression with a minimum collection period of 12 weeks, unless other evidence of progression or a new therapy has been started. If for any reason PSA is not collected, it should be collected at the next cycle visit. PSA declines/progression need to be confirmed by consecutive assessments no earlier than 3 weeks from previous assessment. EOT and SFU PSA assessments should be adjusted accordingly.

If the subject is being followed for possible DILI, the following analytes may be tested at the local laboratory depending on the clinical situation (see Section 11.7).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee

An independent (external to Amgen) DMC will be convened and will act in an advisory capacity to Amgen with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and providing recommendations on whether to continue, modify or stop the study based on these findings. The DMC will review safety data after 30 patients are enrolled and have had the opportunity to be treated for at least 1 month, then at periodic intervals thereafter at approximately 3-month intervals for 6 months and approximately 6-month intervals thereafter until the last subject has completed treatment, the study is terminated earlier, or the primary analysis, whichever occurs first. Additionally, the DMC will conduct evaluations of the grade 4 or higher treatment-related adverse events reported in subjects treated with xaluritamig (excluding grade 4 lymphopenia/lymphocyte count decreases and other laboratory adverse events of grade 4 not considered clinically relevant) to assess if the threshold for possible early study termination has been reached. The stopping rules will use a Bayesian approach proposed by Thall et al (1995) to stop the study if the posterior probability that the grade 4 or higher treatment-related adverse event subject incidence rate in the xaluritamig arm (excluding grade 4 lymphopenia/lymphocyte count decreases and other laboratory adverse events of grade 4 not considered clinically relevant) is $> 20\%$ is $> 80\%$. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60). If the threshold is met the DMC will make a recommendation, and Amgen will choose to take 1 of the following actions:

- Terminate the study.
- Amend the protocol to potentially improve the benefit/risk for subjects.
- Continue the study without any changes.

The stopping rules above only apply to the xaluritamig arm.

The DMC will also monitor the proportion of subjects who received subsequent anticancer therapy prior to BICR-confirmed progressive disease. If the overall proportion is $> 10\%$ or if there is $> 5\%$ difference between the arms, the DMC will notify the study team. This notification will enable guidance for re-educating investigators on the protocol requirement to continue study treatment until radiographic progression is confirmed by real-time BICR.

Additionally, the DMC will be responsible for conducting the interim efficacy analyses prior to the primary analysis. An Independent Biostatistics Group (IBG) will provide the

analyses to the DMC. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study-site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file at the conclusion of the study. Further details are provided in the DMC charter.

Data Access Plan Team

The Data Access Plan (DAP) team will convene for decision-making when DMC's recommendation is to stop study early, either for safety or for efficacy. Details will be included in a separate DAP charter document.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, investigator's brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an external review body (eg, IRB/IEC/regulatory authorities) by the investigator and reviewed and approved by the external review body. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the external review body for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter, if applicable, from the external review body and amended protocol Investigator's Signature page to Amgen before implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the external review body, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the external review body annually or more frequently in accordance with the requirements, policies, and procedures established by the external review body.
- Obtaining, if applicable, annual external review body approval/renewal throughout the duration of the study. Copies of the investigator's reports and the external review body continuance of approval must be sent to Amgen.
- Notifying the external review body of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures.
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the external review body, and all other applicable local regulations.

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral subjects through existing professional networks or other community sources such as patient advocacy groups. All patient-facing materials must be reviewed/approved by the sponsor and the local IRB/IEC.

Informed Consent Process

An initial sample informed consent form(s) is provided for the investigator to prepare the informed consent document to be used at their site. Updates to the sample informed consent form(s) are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form(s) is to be prepared in the language(s) of the potential patient population.

The investigator or their delegated representative will explain to the subject, or their legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's

participation in the clinical study will then be required to sign a statement of informed consent(s) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the external review body or study site.

The medical record must include a statement that written informed consent(s) was obtained before the subject was enrolled in the study and the date the written consent was obtained. The person who conducted the informed consent discussion (investigator or their delegated representative) must also sign the informed consent form(s).

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have their primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, (or it is a local requirement) the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of their notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form(s) is to be signed and personally dated by the subject or a legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

If important new information becomes available that may be relevant to the subject's consent during their participation in the study, subjects will be reconsented.

The original signed informed consent form(s) is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9).

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

The ICF will contain a separate consent that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

The subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the external review body direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to their study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- GCP
- the clinical trial protocol
- an applicable regulation

That is likely to impact to a significant degree either of the following:

- the safety, physical, or mental integrity and the rights of the subject
- the reliability and robustness of the data and the scientific value of the trial

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication

Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICJME, 2019) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Results Reporting

Results will be reported to clinical study registries in accordance with applicable regulatory requirements. The final summary results will be reported after the global end of study (as defined in Section 4.4) to ensure data from all sites globally are included in the reported results.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all the following:

- A recognized expert in the therapeutic area
- An investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

The investigator must permit study-related monitoring, audits, external review body review, review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor or designee will perform ongoing source data verification to confirm that data entered on the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and,

upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, investigational product[s], and/or noninvestigational product[s]/auxiliary medicinal product[s] storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom they have delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the external review body and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Noninvestigational product(s)/auxiliary medicinal product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those subjects who participate in the study and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. To prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the study. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the external review body in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism.

However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse events will be defined in the SAP.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae on the Events CRF. Accidental/unintentional overdose will be captured as a medication error. • Disease progression is an efficacy endpoint. Progression or symptom/sign of progression of the mCRPC should ONLY be reported as an adverse event or serious adverse event if there is evidence suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the mCRPC. The event should be recorded on the Events CRF. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Progression of the mCRPC should be considered disease progression and not considered an adverse event or serious adverse event. Progression of the subject's underlying malignancy will be recorded in the tumor response (PCWG3) CRF as part of efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded on the End of Study CRF and not on the Events form.

  The following are not considered adverse events or serious adverse events:

  - Progression of mCRPC (Progressive disease): If progressive disease is consistent with progression of the underlying malignancy as defined by tumor response PCWG3 criteria.
  - Clinical symptoms or signs that meet the expected pattern of disease progression of the mCRPC in the presence of documented evidence of progression underlying malignancy as defined by tumor response PCWG3 criteria.
  - Deaths that are attributed by the investigator to progression of mCRPC.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event. Hospitalization for CRS monitoring is a pre-planned safety measure and should not be recorded as a serious adverse event. The duration

of pre-planned hospitalization is defined by the investigator according to local **SOC**. **Hospitalization that was required for patient monitoring outside of normal outpatient clinic operating hours (eg, extended monitoring of CRS) would not meet criteria for serious adverse events.** Only adverse events that prolong the pre-planned hospitalization beyond the local **SOC** should be reported as serious adverse events on the grounds of prolonged hospitalization alone.

Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Other Safety Findings/Special Situations

All medication errors, misuse, or abuse of the investigational product when associated with a serious adverse event, the OSF/SS must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by submitting the paper-based Clinical Trial eSAE Contingency Report Form.

Definitions	**Medication Error:** A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the

	subject (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice).
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Events CRF.
- The investigator must assign the following mandatory adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
  - Dates of onset and resolution (if resolved)
  - Did the event start before first dose of investigational product
  - Assessment of seriousness
  - Severity (or toxicity defined below)
  - Assessment of relatedness to investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and/or study-required activity and/or procedures
  - Action taken
  - Outcome of event
- If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Events CRF.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the

medical records. In this case, all subject identifiers, except for the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 5 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

with the exception of ICANS, which must be graded using the criteria referenced in the publication by Lee et al (2019) (see Section 11.11), and CRS, which must be graded using the criteria referenced in the publication by Lee et al (2019) (Section 11.12).

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each adverse event.
- The investigator is obligated to assess the relationship between investigational product, noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in their assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that they have reviewed the adverse event/serious adverse event and has provided an assessment of causality. For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub-investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events CRF.

- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change their opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a subject is permanently withdrawn from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the EDC system.
- If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based **Clinical Trial** Serious Adverse Event Contingency Report Form (also referred to as the **Clinical Trial** eSAE Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event.
- The primary mechanism for the site to report the OSF/SS associated with a serious adverse event to Amgen is by submitting the Clinical Trial eSAE Contingency Report Form immediately and no later than 24 hours of the investigator's awareness of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based **Clinical Trial** Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen **or designee** immediately and no later than 24 hours of the investigator's awareness of the event. The investigator should use the paper-based **Clinical Trial** Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Clinical Trial Electronic Serious Adverse Event Contingency Report Form (Paper-based Form)

AMGEN Study # 20230005 AMG 509	**Clinical Trial Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation

Reason for reporting this event using the Serious Adverse Event Contingency Report Form:

The Clinical Trial Database (eg, Rave):

☐ Is not available due to internet outage at my study site
☐ Is not yet available for this study
☐ Has been closed for this study
☐ Other Safety Finding/Special Situation associated with a Serious Adverse Event

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the serious adverse event term: _____ and start date: Day _____ Month _____ Year _____

<<Amgen Safety Fax Number to be populated by the Study Manager/Protocol Author/designee prior to providing to sites: SELECT OR TYPE IN A FAX#>>

If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites, Vendor/Supplier, Study Sites and Amgen.

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. PARTICIPANT INFORMATION

Participant ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

3. SERIOUS ADVERSE EVENT or Other Safety Finding/Special Situation associated with a Serious Adverse Event

Provide the date the Investigator became aware of this information: Day _____ Month _____ Year _____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report OR Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or the investigational medical device? xaluritamig No✓	xaluritamig Yes✓	abiraterone No✓	abiraterone Yes✓	enzalutamide No✓	enzalutamide Yes✓	cabazitaxel No✓	cabazitaxel Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization or prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was participant hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

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AMGEN Study # 20230005 AMG 509	**Clinical Trial Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Participant ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/ Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
xaluritamig	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
abiraterone	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
enzalutamide	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
cabazitaxel	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

AMGEN Study # 20230005 AMG 509	**Clinical Trial Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

Site Number	Participant ID Number

10. CASE DESCRIPTION *(Provide narrative details of events/other safety findings/special situations listed in section 3)*
Provide additional pages if necessary. For each event/other safety finding/special situation in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy Information

Study-specific contraception requirements for males are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Male subjects should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they father a child during treatment and for 6 months after the last dose of xaluritamig, 4 months after last dose of cabazitaxel, 3 months after last dose of enzalutamide, or 3 weeks after the last dose of abiraterone acetate.

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with investigational product[s] and/or noninvestigational product[s]/auxiliary medicinal product[s]; the reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject).
- Use a condom during treatment and for an additional 6 months after the last dose of xaluritamig, 4 months after last dose of cabazitaxel, 3 months after last dose of enzalutamide, or 3 weeks after the last dose of abiraterone acetate.

The female partner should consider using an acceptable method of effective contraception such as hormonal, intrauterine contraceptive device, intrauterine system, or female barrier method (diaphragm, cap, sponge [a female condom should not be used because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of nonchildbearing potential or has had a bilateral tubal ligation or if the male has had a vasectomy and testing confirms there is no sperm in the semen, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male Subjects

Birth control methods that are considered unacceptable in clinical studies include:

- periodic abstinence (calendar, symptothermal, post ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

Definition of Females of Childbearing Potential

A female is considered fertile after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented

hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: (1) review of subject's medical records; (2) subject's medical examination; or (3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause.
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 follicle-stimulating hormone (FSH) measurement is required.

Collection of Pregnancy Information

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 6 months after the last dose of xaluritamig, 4 months after last dose of cabazitaxel, 3 months after last dose of enzalutamide, or 3 weeks after the last dose of abiraterone acetate. The information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 6 months after the last dose of xaluritamig, 4 months after last dose of cabazitaxel, 3 months after last dose of enzalutamide, or 3 weeks after the last dose of abiraterone acetate must practice sexual abstinence or use a condom through 6 months after the last dose of xaluritamig, 4 months after last dose of cabazitaxel, 3 months after last dose of enzalutamide, or 3 weeks after the last dose of abiraterone acetate.
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Figure 11-2. Pregnancy Notification Form (Paper-based Form)

Amgen Proprietary - Confidential

Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: Amgen Protocol Number 20230005

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Xaluritamig (AMG 509)				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm_____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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11.6 Appendix 6. Sample Storage and Destruction

When permitted by local regulations, any blood sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

When permitted by local regulations and if informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the dose response and/or prediction of response to xaluritamig, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. After the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values such as AST, ALT, TBL**,** and/or international normalized ratio (INR) and/or signs/symptoms of hepatotoxicity (as described below) may meet the criteria for interruption or permanent discontinuation of Amgen investigational product(s) or other noninvestigational product(s)/auxiliary medicinal product(s). This instruction is based on the US Food and Drug Administration (FDA) *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (US FDA, July 2009)*.

Reporting and management of hepatotoxicity in subjects in clinical trials is described below and management is summarized in the flow chart in Figure 11-3.

11.7.1 Criteria for Stopping Amgen Investigational Product(s) and Noninvestigational Product(s)/Auxiliary Medicinal Product(s) Due to Potential Hepatotoxicity

Stopping rules apply to each of the following criteria in subjects for whom another cause for the changes in liver biomarkers (TBL, INR and transaminases) has not been identified**:**

- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for more than 2 weeks
- ALT or AST > 3x ULN and (TBL > 2x ULN or INR > 1.5)
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Of note in **subjects** with elevated values at baseline (before exposure to the investigational medicinal product), fold increases above the baseline values will guide the interruption and close observation.

11.7.2 Reporting Criteria

Cases with events of elevation of AST**,** ALT**,** TBL**,** INR, mentioned above require the following:

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of potential hepatotoxicity are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

11.7.3 Follow-up Actions

All subjects in whom investigational product(s) or protocol-required therapies is/are interrupted (either permanently or conditionally) due to potential hepatotoxicity should undergo a period of "close observation" until elevated laboratory values return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours
- In cases laboratory values are still elevated perform repeat measurement of liver laboratory tests every 2 to 3 days until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the laboratory abnormalities stabilize**,** or the study drug(s) has/have been discontinued AND the subject is asymptomatic.

The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of study drug(s).

The hepatotoxicity events and additional information such as medical history, concomitant medications**,** and laboratory results must be captured in the corresponding CRFs.

Initiate investigation of alternative causes for hepatotoxicity (Section 11.7.3.1).

If laboratory values improve, consider rechallenging with the study drug(s) only if the benefit/risk ratio is supportive (and as described in Section 11.7.4). Otherwise, discontinue study drug(s) permanently.

11.7.3.1 Investigating Alternative Causes of Hepatotoxicity

The following assessments are to be considered depending on the clinical situation:

- Blood count with differential to assess for eosinophilia**.**
- Serum total immunoglobulin (Ig)G, antinuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis**.**
- Serum acetaminophen (paracetamol) levels**.**
- A more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents

- symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting**,** and fever
- prior and/or concurrent use of alcohol, recreational drugs, and special diets
- concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies**.**
- Creatine phosphokinase, haptoglobin, LDH**,** and peripheral blood smear**.**
- Appropriate liver imaging if clinically indicated**.**
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected**.**
- Hepatology consult (appropriate liver biopsy may be considered in consultation with a hepatologist)**.**

11.7.3.1.1 Important Alternative Causes

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease**.**
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)**.**
- Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia**.**
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms**.**
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)**.**
- Alpha-1 antitrypsin deficiency**.**
- Alcoholic hepatitis**.**
- Autoimmune hepatitis**.**
- Wilson's disease and hemochromatosis**.**
- Nonalcoholic fatty liver disease including steatohepatitis**.**
- Nonhepatic causes (eg, rhabdomyolysis, hemolysis)**.**

Special consideration is warranted when using products known to cause transient elevation of liver enzymes, such as TCE molecules. For example, in the instances of CRS following exposure to bispecific TCE (BiTE®) molecules, transient elevations of isolated liver parameters were frequently noted.

Careful monitoring of laboratory parameters and the clinical status of subjects is required, and continuation of the medication maybe considered and will be at the discretion of the investigators.

11.7.4 Rechallenge and Dose Modification in Subjects with Suspected Hepatotoxicity in Oncology Trials

- The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen. If rechallenge is considered appropriate, the subject must be fully informed about the risk and should give written consent. Any rechallenge must be accompanied by close monitoring, with at least weekly liver biochemistry until response to the rechallenge is fully characterized.
- If signs or symptoms recur with rechallenge, then Amgen investigational product(s) or other noninvestigational product(s)/auxiliary medicinal product(s), as appropriate **is** to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation are never to be rechallenged.
- For oncology drugs that demonstrate potential benefit but also potential hepatotoxicity, consideration of rechallenge or dose modification (with a reduced dose) should be based on benefit/risk and clinical and biochemical characteristics of the original liver injury.
- Rechallenge is not recommended when there is no evidence of benefit for the individual subject, or where alternative treatment options are available.
- Rechallenge is generally not recommended for cases of suspected or confirmed severe hepatocellular injury (clinical evidence of liver dysfunction with jaundice or INR elevation), in the presence of underlying cirrhosis, or where there are features of immunologic hepatotoxicity.
- Before undertaking a rechallenge, there should be sufficient resolution of liver biochemistry abnormalities; although these depend on the patient population, reasonable options include ALT reducing to $<$ 3x ULN for those with normal baseline ALT or returning to $<$ 4x ULN and $<$ 6x ULN for those with elevated baseline ALT of 1.5 to 3x ULN and 3 to 5x ULN respectively.

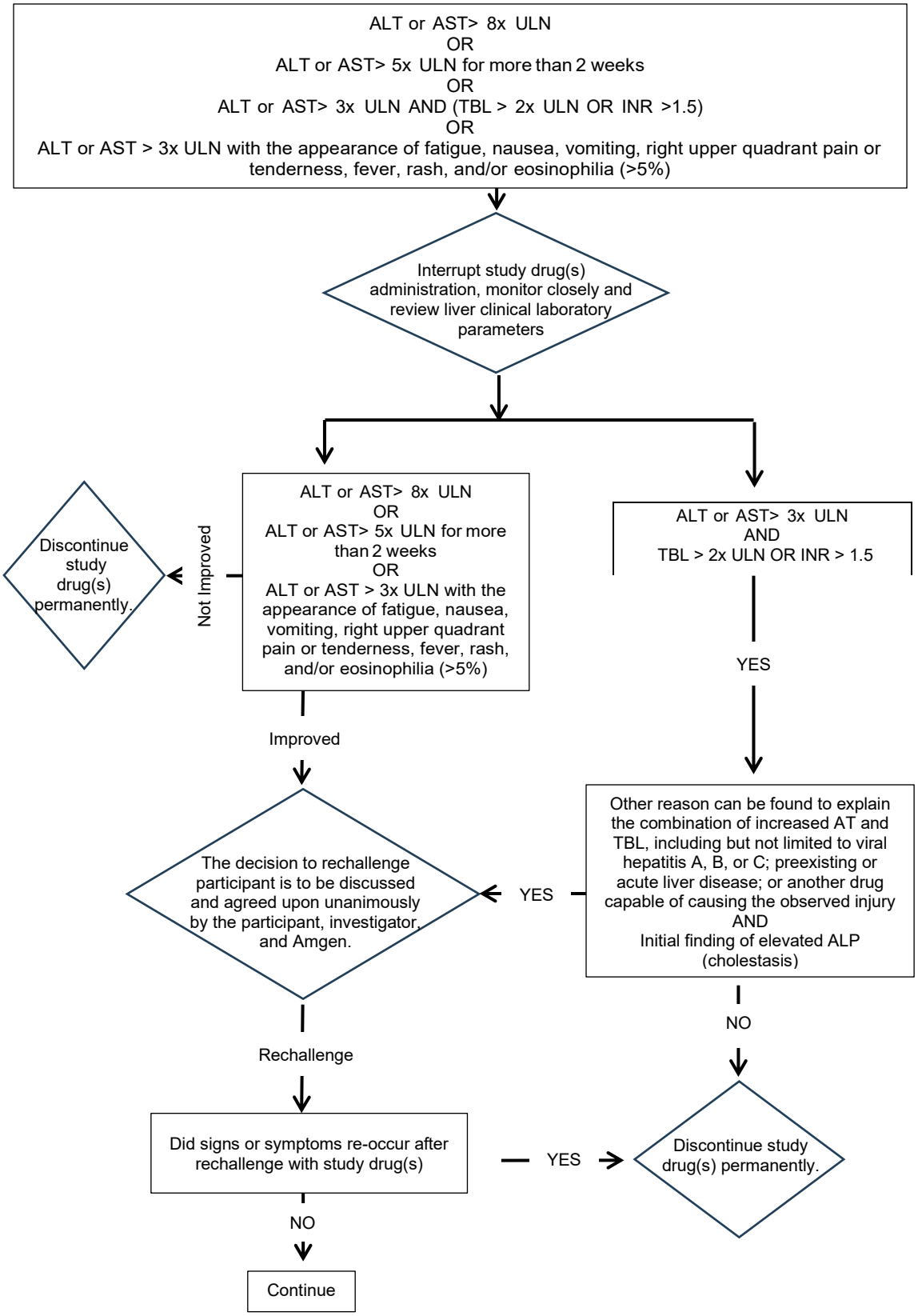
11.7.5 Permanent Discontinuation of Study Drug(s)

In the absence of acceptable enzyme level decrease or lack of a plausible alternative explanation for the elevated laboratory pattern, consider permanent discontinuation of study drug treatment.

11.7.6 Management Flow Chart

The following flow chart can be used to manage potential hepatotoxicity cases (Figure 11-3).

Figure 11-3. Management of Potential Hepatotoxicity



11.8 Appendix 8. Management of Adverse Events Including Xaluritamig Dose Modification

Table 11-3. Infusion-related Reaction

Grade	Description of Severity	Interruption/Delay	Specific Management	Restart Guidance
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.	N/A	Consider medication to control infusion reaction as deemed appropriate by the investigators according to local **SOC** and institutional guidelines. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.	N/A
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Immediate interruption/delay until event has improved to grade ≤ 1.		• Restart possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • **In case a delay is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance.** • Dose modification: Resume at the same dose or reduce **by one** dose **level** if clinically indicated.
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediate interruption/ delay until event has improved to grade ≤ 1.	Consider supportive therapy including steroids as clinically indicated. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.	• **Same a**s for grade 2 infusion related reaction, with the exception of mandatory dose modification: Reduce **by 1** dose **level**.
4	Life-threatening consequences; urgent intervention indicated.	N/A	**Same a**s for grade 3 infusion-related reaction.	• **Permanent discontinuation:** Immediately stop**/interrupt** the infusion (if applicable) and permanently discontinue xaluritamig therapy.

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IV = intravenous; N/A = not applicable; NSAIDs = non-steroidal anti-inflammatory drugs; **SOC = standard of care**.

Table 11-4. Cytokine Release Syndrome

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart Guidance
1	Fever (temperature ≥ 38 °C) without hypotension and hypoxia	N/A	• **Offer supportive care** with **antipyretics (eg**, acetaminophen/paracetamol), **IV hydration, and symptom management.** • **Consider managing as per G2 for subjects** with **persistent or refractory** fever**.**	• **Continue with next dose as planned.**
2	Fever (temperature ≥ 38 °C) with: • Hypotension not requiring vasopressor AND/OR • Hypoxia requiring low-flow ≤ 6 L/min nasal cannula or blow-by.	Immediately interrupt/ delay xaluritamig until event resolves.	• Administer **supportive care as per G1 plus IV fluid bolus and/or supplemental oxygen as needed.** • **Administer anti-IL6 therapy (eg, tocilizumab[b]** 8 mg/kg [max 800 mg] IV [or local equivalent]). Repeat after 8 hours, as needed, based on clinical assessment**, with a maximum of 4 doses total.** • **For persistent hypotension, add** dexamethasone[b] **10** mg BID **(or local equivalent)** for **24** hours **and reassess.** • **If no improvement within 24 hours of starting tocilizumab, manage as per G3.**	• Restart possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • **In case a delay is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance.** • Dose modification: - **If event** occurs **during step-up dosing (eg, in cycle 1), repeat prior dose or continue with dose escalation.** - **If event occurs during** target **dosing (eg,** in cycle **2 onwards), a 1 level** dose **reduction may be considered.** • Assessments: Follow guidance in **Section 6.2.1.1.1**.

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Table 11-4. Cytokine Release Syndrome

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart Guidance
3	Fever (temperature ≥ 38 °C) with: • Hypotension requiring a single vasopressor (excluding vasopressin) AND/OR • Hypoxia requiring high-flow (≤ 6 L/min) nasal cannula, facemask, nonrebreather mask, or Venturi mask	Immediately interrupt/delay xaluritamig until event improves to CRS grade 1.	• Administer supportive care as per G2 plus vasopressors as needed. • Admit to intensive care unit for close clinical and vital sign monitoring. Consider echocardiogram if not yet performed, to assess cardiac function and conduct hemodynamic monitoring. • Administer anti-IL6 therapy as per G2. • Administer dexamethasone[b] 10 mg (or local equivalent) every 6 hours and taper once symptoms improve. • If refractory, manage as per G4.	• Restart possible, if successfully managed and improved to ≤ grade 1 within 7 days. • In case a delay is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance. • Hospitalization: at least 24 to 48 hours per discretion of treating investigator. • Dose modification: - If event occurs during step-up dosing (eg. in cycle 1), repeat prior dose - If event occurs during target dosing (eg. in cycle 2 onwards), reduce by 1 dose level. • Assessments: Follow guidance **in Section 6.2.1.1.1** **Permanent discontinuation**: If there is no improvement to CRS grade ≤ 2 within 7 days or in case of recurrent grade 3 event.

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Table 11-4. Cytokine Release Syndrome

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart Guidance
4	Fever (temperature ≥ 38 °C) with: • Hypotension requiring multiple vasopressors (excluding vasopressin) AND/OR • Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).	N/A	• Admit to intensive care unit **if not already receiving ICU care.** • **Administer supportive care as per G3 plus mechanical ventilation as needed.** • **Administer anti-IL6 therapy as per G2.** • **Initiate high-dose corticosteroids (eg, methylprednisolone 500 mg** IV **BID** or local equivalent **for 3 days followed by tapering. If not improving, consider methylprednisolone 1000 mg IV BID or alternate therapy).**	**Permanently discontinue**

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BID = twice daily; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; EOI = end of infusion; **G = Group; ICU = Intensive Care Unit; IL6 = interleukin 6**; IV = intravenous; N/A = not applicable; **SOC = standard of care**.

Based on Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline https://ascopubs.org/doi/10.1200/JCO.21.01992

[a] Revised grading system for CRS (Lee et al, 2019).

[b] All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and **anti-IL6 therapy**.

Alternative guidelines may be used per local SOC provided that they include anti-IL6 therapy as part of the management of ≥ G2 CRS events. Consultation with the medical monitor for reviewing alternative guidelines is available if needed.

Table 11-5. Immune Effector Cell-associated Neurologic Syndrome

Grade	Description of Severity	Interruption/ Delay	Specific Management	Restart guidance
Neurological events meeting the definition of Immune Effector Cell-associated Neurologic Syndrome (ICANS) as described in the publication by Lee et al, 2019, please refer to the additional guidance and grading scale Section 11.11.				
1	Reference to Section 11.11 for grading and management guidelines	N/A	• **Supportive care (eg, IV hydration and aspiration procedures)** • **With concurrent CRS: consider anti-IL6 therapy (eg, tocilizumab 8 mg/kg [max 800 mg] IV) (or local equivalent). Repeat after 8 hours, as needed, based on clinical assessment. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to anti-IL6 therapy past the first dose**.	N/A
2	Reference to Section 11.11 for grading and management guidelines	N/A	• **Administer supportive care per G1** • **Without concurrent CRS: for high-risk patients (eg, seizure history) consider dexamethasone 10 mg (or local equivalent) x 2 doses and reassess. Repeat every 6 to 12 hours if no improvement. Begin tapering once symptoms improve to G1.** • **With concurrent CRS: consider admitting patient to intensive care unit if ICANS associated with ≥ G2 CRS. Administer anti-IL6 therapy per G1. If refractory to anti-IL6 therapy, initiate dexamethasone 10 mg (or local equivalent) every 6-12 hours. Begin tapering once symptoms improve to G1**.	N/A

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Table 11-5. Immune Effector Cell-associated Neurologic Syndrome

Grade	Description of Severity	Interruption/Delay	Specific Management	Restart guidance
3	Reference to Section 11.11 for grading and management guidelines.	Interruption/delay/ withholding of xaluritamig is required until the event improves to grade ≤ 1[b].	• **Admit to intensive care unit** • **Without concurrent CRS: administer dexamethasone 10 mg (or local equivalent) every 6 to 12 hours. Begin tapering once symptoms improve to G1.** • **With concurrent CRS: administer anti-IL6 therapy as per G2. If refractory to anti-IL6 therapy past first dose, initiate dexamethasone 10 mg (or local equivalent) every 6-12 hours. Begin tapering once symptoms improve to G1**.	• Restart possible if successfully managed and improvement to ≤ grade 1 or baseline in ≤ 14 days. • **In case a** delay **is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance**. • Dose modification: Resume at the same dose or reduce **one** dose **level** if clinically indicated. **Permanent discontinuation:** • Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days. • Grade 3 neurologic event reoccurs within 7 days of resuming xaluritamig.
4	Reference to Section 11.11 for grading and management guidelines.	Immediately stop any ongoing infusion	• **Admit to intensive care unit if not already receiving ICU care. Consider mechanical ventilation for airway protection.** • **Without concurrent CRS: initiate high-dose** corticosteroids **(eg. methylprednisolone 1000 mg IV BID or local equivalent) or alternate therapy. Consider alternate therapy. Begin tapering once symptoms improve to G1.** • **With concurrent CRS: administer anti-IL6 therapy as per G3 plus high-dose corticosteroids (eg,** methylprednisolone 1000 mg **IV BID or local equivalent**). **Begin tapering corticosteroids once symptoms improve to G1**.	Permanent**ly** discontinu**e**

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Table 11-5. Immune Effector Cell-associated Neurologic Syndrome

Grade	Description of Severity	Interruption/Delay	Specific Management	Restart guidance
Seizure	Reference Section 11.11 for grading and management guidelines	Interruption, withholding, delay of xaluritamig is required until the event improves to grade ≤ 1[b]	**Status epilepticus to be treated per institutional guidelines**.	• Do not resume xaluritamig until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved. **Permanent discontinuation:** • If a second seizure occurs after resuming xaluritamig.

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CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous; ICU = intensive care unit; N/A = not applicable; **SOC = standard of care**.
Based on **Management of** Immune-**Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline** **https://ascopubs.org/doi/10.1200/JCO.21.01992**
[b] Per CTCAE version 5.0
Alternative guidelines may be used per local SOC provided that they include anti-IL6 therapy as part of the management of ≥ G2 CRS events. Consultation with the medical monitor for reviewing alternative guidelines is available if needed.

Table 11-6. Neurological Events Not Meeting the Definition of ICANS

Grade	Interruption/Delay	Specific Management	Restart Guidance
≥ 2	Interruption/delay/ withholding until event has improved to grade ≤ 1	• Consider administration of corticosteroids[a] (and **anti-IL6 therapy [eg,** tocilizumab**]**[a] if associated with CRS)**.** • Following a seizure: Administer anti-seizure medication according to the local **SOC** and institutional guidelines	• Restart possible if successfully managed and improvement to ≤ grade 1 or baseline in ≤ 14 days. • **In case a** delay **is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance.** • Dose modification: Resume at the same dose or **undertake 1 level** dose **reduction** if clinically indicated. **Permanent Discontinuation:** • In case of grade 4 event • In case of **recurrent** grade ≥ 3 event despite dose reduction that does not improve to ≤ grade 1 in ≤ 14 days • In case of more than 1 seizure

CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; **IL6 = interleukin 6; SOC = standard of care**.
[a] All sites will ensure that CRS rescue medications are available on site, including corticosteroids and anti-IL6 therapy.

Table 11-7. Tumor Lysis Syndrome

Grade	Interruption/Delay	Specific Management	Restart Guidance
Present	Immediate interruption/delay until event has resolved.	TLS should be managed according to the local **SOC** and institutional guidelines and may include hydration and treatment with allopurinol and rasburicase.	• Restart possible if successfully managed and resolved in ≤ 14 days. • Consult with Amgen medical monitor first. • **In case a** delay **is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance.** • Dose modification: Resume at the same dose unless agreement by medical monitor to resume at a different dose. **Permanent discontinuation:** • In case of **recurrent** TLS event despite dose reduction.

SOC = standard of care; TLS = tumor lysis syndrome.

Table 11-8. Localized Inflammatory Events

Grade	Interruption/Delay	Specific Management	Restart Guidance
Localized inflammato**ry** events include but are not limited to myalgia, myofascitis, muscle weakness, arthralgia, **oropharyngeal pain, pharyngeal swelling and** soft tissue swelling including orbital oedema and genital oedema. **Vasculitis is a potential risk for xaluritamig that should be managed as a localized inflammatory event.** Note: Any **localized** inflammato**ry** event as a symptom of CRS (ie, onset within 48 hours of onset of CRS) should be managed per CRS guidelines. **Infectious causes, cardiac events (in case of chest pain), and other potentially serious non-treatment related etiologies should be ruled out before treating symptoms based on the guidelines below.**			
1	Delay **may be considered. See Table 11-9 and Table 11-10 for details**	• Initiate **NSAIDs (eg,** ibuprofen 400 mg every 8 hours **or local equivalent)** with gastric protection (eg, omeprazole 20 mg every 12 hours or local **equivalent**). • **In case of muscle pain, consider adding low dose muscle relaxant (eg, methocarbamol 750 mg BID [or local equivalent]) and additional analgesia (eg,** paracetamol **500 to** 1000 mg every **4-**6 hours **[or local equivalent])**. • **If symptoms worsen or do not improve, initiate** corticosteroids[a] **(eg**, dexamethasone 8 mg or prednisone 0.5 mg/kg **[or local equivalent]) once daily for 3 days or until symptoms resolve to grade ≤ 1 if earlier and then taper per local SOC**.	• **See Table 11-9 and Table 11-10. See also Section 6.2.1.1 for restart guidance.**
2	Interruption/delay required **until event has improved to grade ≤ 1 or baseline. See Table 11-9 and Table 11-10 for details.**	• **Initiate NSAIDs ± muscle relaxant/analgesia as per G1.** • Initiate corticosteroids[a] **(eg,** dexamethasone 8 to 12 mg or prednisone 0.5 to 1 mg/kg**) (or local equivalent) once daily for 3 days or until symptoms resolve to grade ≤ 1 if earlier and then** taper per local **SOC**.	• **For events occurring during step-up dosing (eg, in cycle 1), if subjects are continuing steroids for the treatment of adverse events, at a dose that is equivalent to (or higher than) 8 mg dexamethasone premedication, it is recommended to time the prescribed steroid dose as premedication for xaluritamig treatment**.

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Table 11-8. Localized Inflammatory Events

Grade	Interruption/Delay	Specific Management	Restart Guidance
2 (continued)		• **If associated with CRS and/or not responding to corticosteroids, administer anti-IL6 therapy (eg, tocilizumab at a dose of 8 mg/kg [max 800 mg] IV [or equivalent]). Administer up to 1 additional dose if no response as per local guidance (unless already administered within 28 days).** • **Consider additional diagnostic work up (eg, as outlined in Figure 11-4 footnote) and consultation with rheumatology**.	• Delay of next infusion and dose modification **(see Table 11-9 and Table 11-10). See also Section 6.2.1.1 for restart guidance**. • Symptoms must improve to grade ≤ 1 and remain stable for at least 1 cycle before **trial of** reescalation to **the** target dose. **Dose reductions below 0.3 mg are not allowed.**
≥ 3	Interruption/ delay required until event has improved to grade ≤ 1. **See Table 11-9 and Table 11-10 for details.**	• Initiate **NSAIDs ± muscle relaxant/analgesia as per G1**. • Initiate corticosteroids[a] (eg, dexamethasone **6 to 10** mg **BID** or prednisone 1 to 2 mg/kg **QD** [or local equivalent]) **for 3 days or until symptoms resolve to grade ≤ 1 if earlier and then** taper per local **SOC**.	• **For events occurring during step dosing (ie, in cycle 1), if subjects are continuing steroids for the treatment of adverse events, at a dose that is equivalent to (or higher than) 8 mg dexamethasone premedication, it is recommended to time the prescribed steroid dose as premedication for xaluritamig treatment**.

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Table 11-8. Localized Inflammatory Events

Grade	Interruption/Delay	Specific Management	Restart Guidance
≥ 3 (continued)		• If the **localized** inflammato**ry** event is associated with CRS **and/**or **not responding to** corticosteroids, **administer anti-IL6 therapy (eg, tocilizumab at a dose of 8 mg/kg [max 800 mg] IV [or equivalent]).** Administer **up to 1** additional **dose if no response as per local guidance (unless already administered within 28 days).** • **Consider additional diagnostic work up (eg, as outlined in Figure 11-4 footnote) and consultation with rheumatology**.	• **Delay of next infusion and** dose modification**: see Table 11-9 and Table 11-10. See also Section 6.2.1.1 for restart guidance.** • Symptoms must improve to grade ≤ 1 and remain stable for at least 1 cycle before trial of reescalation to the 1.0 or 1.5 mg target dose. Dose reductions below 0.3 mg are not allowed. **Permanently discontinuation:** • If **subject** experience**s** a recurrent grade 4 event or a single **grade 4** event that takes more than 14 days to recover to grade ≤ 1.

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BID = twice daily; CRS = cytokine release syndrome; IL6 = interleukin 6; IV = intravenous; N/A = not applicable; **NSAIDs = Non-Steroidal Anti-Inflammatory Drugs;** QD = once daily; **SOC = standard of care.**
[a] Refer to investigator brochure for additional information regarding preferred terms, incidence and severity of localized inflammatory events
Subjects with diabetes should be monitored for the blood glucose levels as per SOC while undergoing treatment with corticosteroids.
Other inflammatory events may be managed per the localized inflammatory event management guidance.

Table 11-9. Localized Inflammatory Event Dose Modification Guidelines – Before Target Dose (QW Step Dosing)

Event Status (at time of visit)	Next Dose (QW Step Dosing)[a]
Grade 1	• If the event persists prior to C1D8 or C1D15 dosing, C1D8 and C1D15 dosing may either continue as planned or be delayed until resolution to baseline. • If the event persists prior to C1D22 or C2D1 dosing, strongly consider delaying C1D22 and C2D1 dosing by one week each to maintain a minimum Q2W interval between C1D15, C1D22, and C2D1 (as applicable).
Grade 2	Delay subsequent dose until resolution to grade ≤ 1 or baseline, then: • Continue with dose escalation at next planned dose. • Alternatively, prior dose may be repeated at the investigator's discretion. • If event occurs prior to C1D22 or C2D1, both C1D22 and C2D1 should be delayed by at least one week each to maintain a minimum Q2W interval between C1D15, C1D22, and C2D1 (as applicable). • For recurrent grade 2 events: 1 level dose reduction[b,c] may be undertaken at the investigator's discretion.
Grade ≥ 3	Delay subsequent dose for at least 1 week and until resolution to grade ≤ 1 or baseline, then: • Repeat prior dose. If tolerated, continue with ongoing escalation. If prior dose is not tolerated, discuss with Amgen Medical Monitor. • If event occurs prior to C1D22 or C2D1, both C1D22 and C2D1 should be delayed by at least one week each to maintain a minimum Q2W interval between C1D15, C1D22, and C2D1 (as applicable). • If grade 4 event recovers to grade ≤ 1 or baseline within 72 hours, a 1 level dose reduction may be undertaken. If the symptoms do not resolve to grade ≤ 1 or baseline within 14 days, an additional 1 level dose reduction may be undertaken[b,c].

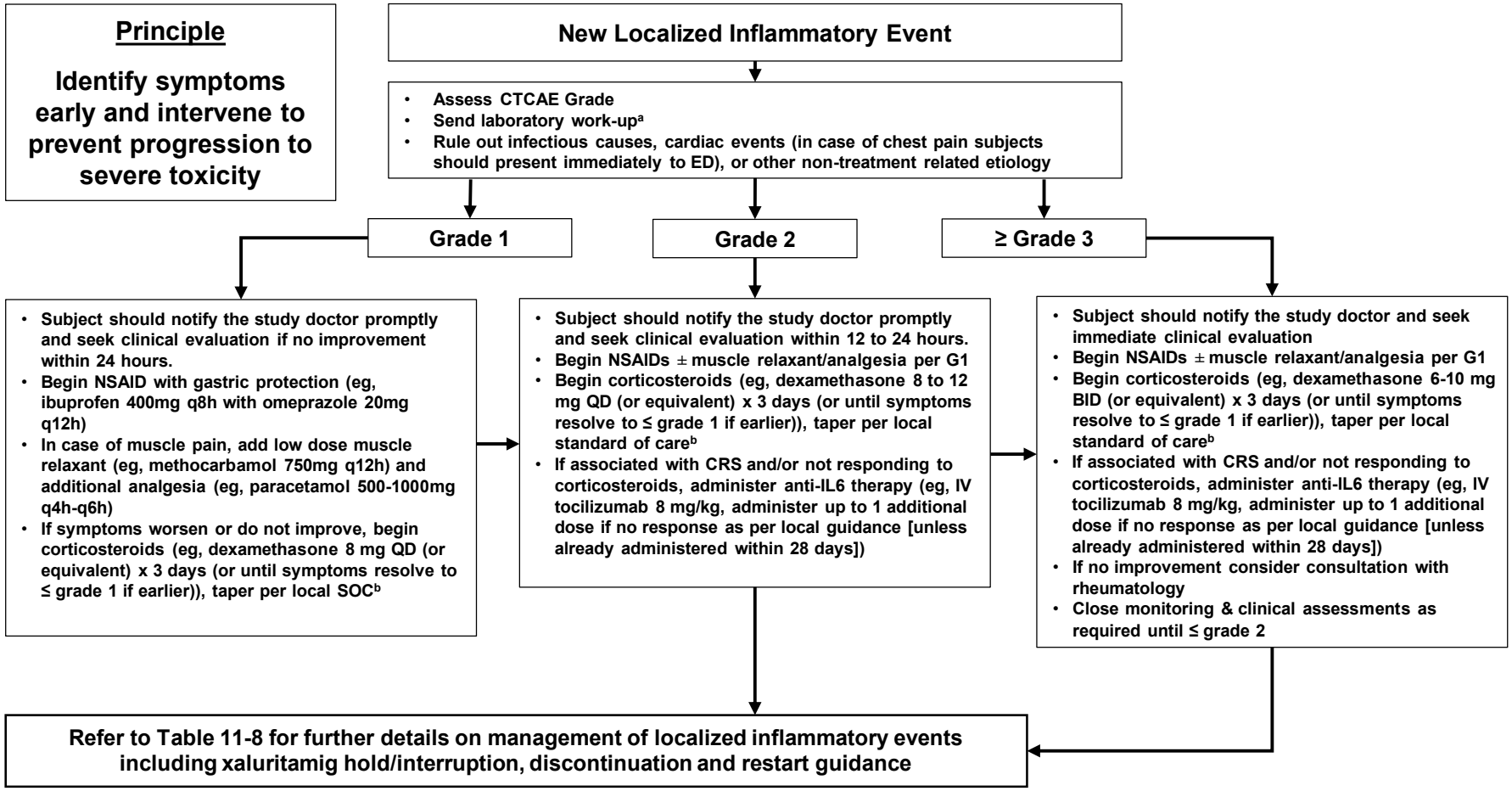
C = cycle; QW = weekly.
[a] Refer to Table 11-8 for full details on management and definitions of localized inflammatory events. Additional dose modification/interruption beyond this guidance may be undertaken at the investigator's discretion following discussion with the Amgen Medical Monitor.
[b] Symptoms must improve to grade ≤ 1 or baseline and remain stable for at least 1 cycle before re-escalation to target dose.
[c] Dose reductions below 0.3 mg are not permitted.

Table 11-10. Localized Inflammatory Event Dose Modification Guidelines – Following Target Dose (Q2W Schedule)

Event Status (at time of visit)	Next Dose (Q2W Schedule)[a]
Grade 1	• Consider delaying subsequent dose until the event has resolved to baseline.
Grade 2	• Delay subsequent dose until resolution to grade ≤ 1 or baseline. Alternatively, may continue dosing at investigator's discretion if significant clinical improvement with medical therapy. • Additionally, for recurrent or persistent grade 2 events: 1 level dose reduction may be considered at investigator's discretion.
Grade ≥ 3	• First grade 3 event: delay subsequent dose until grade ≤ 1 or baseline. Alternatively, may consider resuming with 1 level dose reduction[b,c] after resolution to grade 2 following significant clinical improvement with medical therapy. • Recurrent grade 3 event (within 2 months): delay subsequent dose until grade ≤ 1 or baseline, then resume with 1 level dose reduction[b,c]. Alternatively, may consider resuming with 1 level dose reduction after resolution to grade 2 following significant clinical improvement with medical therapy. • Recurrent grade 3 event with > 2 months since last occurrence: follow guidance for first grade 3 event or if the event is clinically significant, a 1 level dose reduction may be undertaken[b,c]. • If grade 4 event recovers to grade ≤ 1 or baseline within 72 hours, 1 level dose reduction may be undertaken. If the event takes longer than 14 days to resolve to grade ≤ 1 or baseline within, an additional 1 level dose reduction may be undertaken[b,c].

Q2W = every 2 weeks.
[a] Refer to Table 11-8 for full details on management and definitions of localized inflammatory events. Additional dose modification/interruption beyond this guidance may be undertaken at the investigator's discretion following discussion with the Amgen Medical Monitor.
[b] Symptoms must improve to grade ≤ 1 or baseline and remain stable for at least 1 cycle before re-escalation to target dose.
[c] Dose reductions below 0.3 mg are not permitted.

Figure 11-4. Xaluritamig Localized Inflammatory Event Algorithm



Ab = antibodies; BID = twice daily; CBC = complete blood count; CRS = cytokine release syndrome; CRP = C-reactive protein; CK = creatine kinase; CTCAE = Common Terminology Criteria for Adverse Events; ED = emergency department; ESR = Erythrocyte sedimentation rate; HMGCR = 3-hydroxy-3-methylglutaryl-CoA reductase; IL6 = interleukin 6; IV = intravenous; LRP4 = low-density lipoprotein receptor-related protein 4; MRI = magnetic resonance imaging; MuSK = Muscle-Specific Kinase; PO = orally; QD = once daily; q12h = every 12 hours; q24h = every 24 hours; SOC = standard of care.

This algorithm represents a visualization and interpretation of the guidance for adverse event management in Table 11-8 and serves only as an example to support management per investigators' discretion. Refer to Table 11-8 for terms defining localized inflammatory events.

[a] Laboratory work-up may include (if possible, prior to initiation of steroid therapy):

- **CBC with differential, comprehensive metabolic panel, ESR, CRP, cytokine panel, CK, aldolase, myoglobin (urine/serum), auto-antibodies (eg, myositis Ab 3, striated muscle Ab, MuSK Ab, anti-titin Ab, anti-LRP4 Ab, anti-HMGCR Ab)**

[b] Example steroid tapering options:

- **Dexamethasone 8 mg q24h x 3 days → dexamethasone 4 mg q24h x 3 days → dexamethasone 2 mg q24h x 3 days → dexamethasone 1 mg q24h x 3 days → STOP**
- **Prednisone 40 mg q24h x 3 days → prednisone 35 mg q24h x 3 days → prednisone 30 mg q24h x 3 days → prednisone 25 mg q24h x 3 days → prednisone 20 mg q24h x 3 days → prednisone 15 mg q24h x 3 days → prednisone 10 mg q24h x 3 days → prednisone 5 mg q24h x 3 days → STOP**
- **1 mg/kg IV methylprednisolone q12h x 3 days → 1 mg/kg q24h IV methylprednisolone x 3 days → 0.5 mg/kg q24h PO prednisone x 3 days → 0.33 mg/kg q24h PO prednisone x 3 days → 10 mg q24h PO prednisone x 3 days → 5 mg q24h PO prednisone x 3 days → STOP**

Table 11-11. Any Other Xaluritamig Related Events

Grade	Interruption/Delay	Specific Management	Restart Guidance
2		Toxicities should be managed depending on the clinical presentation and according to the local **SOC** and institutional guidelines.	• **In case a delay is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance.**
3	Interruption/delay/withholding required if deemed intolerable and/or clinically significant by the **subject** or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1.	Toxicities should be managed depending on the clinical presentation and according to the local **SOC** and institutional guidelines.	• Restart possible if successfully managed and improvement to ≤ grade 1 or baseline (grade ≤ 2 for rash, fatigue, and anemia) in ≤ 14 days. • **In case a** delay **is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance**. • Dose modification: Resume at the same dose or reduce to next lower dose if clinically indicated. **Permanently Discontinue:** • **In case of repeat grade ≥ 3 event despite dose reduction that does not improve to ≤ grade 1 in ≤ 14 days (exception of fatigue, myalgia, and anemia).**

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Table 11-11. Any Other Xaluritamig Related Events

Grade	Interruption/Delay	Specific Management	Restart Guidance
4	Interruption/delay/withholding required if deemed intolerable by the **subject** or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1.	Toxicities should be managed depending on the clinical presentation and according to the local **SOC** and institutional guidelines.	• Restart possible if not meeting criteria for permanent discontinuation successfully managed and improvement to ≤ grade 1 in ≤ 28 days. • **In case a** delay **is required for immediate management of adverse events, see Section 6.2.1.1 for restart guidance**. • Dose modification: Reduce to next lower dose (unless attributed lymphopenia or laboratory parameters of grade 4 not considered clinically relevant). Dose modification does not apply if **subject** meets criteria resulting in discontinuation of treatment (see Section 7.1). **Permanently Discontinue:** • **Immediately stop the infusion (if applicable) and permanently discontinue xaluritamig therapy (unless grade 4 fever, lymphopenia, or laboratory parameters of grade 4, not considered clinically relevant, and improve to grade ≤ 2 within 72 hours).** • **In case of reappearance of same event at grade 4.**

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SOC = standard of care.

11.9 Appendix 9. Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies TLS in grade 3 (present), grade 4 (life-threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 5.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this study, the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS and clinical TLS. Final event grade will be assigned according to CTCAE version 5.0.

Tumor lysis syndrome may occur in subjects with high tumor burden including liver metastases and extensive bone metastases. These subjects should be monitored carefully after their first dose with xaluritamig (cycle 1 day 1) and prophylactic measures for TLS may be considered. Based on the Cairo and Bishop system, laboratory TLS is defined as any 2 or more abnormal serum values present within 3 days before or 7 days after initiation of treatment in the setting of adequate hydration (with or without alkalinization) and use of a hypouricemic agent (see Table 11-14).

Table 11-14. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change from baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory tumor lysis syndrome.

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures.

11.10 Appendix 10. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as a US FDA Investigational New Drug safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 8.4.5 and Section 11.4.

Anticipated Serious Adverse Events for Study 20230005

MedDRA Preferred Term[a]
bone pain
blood calcium increased
dysuria
erectile dysfunction
hematuria
hypercalcemia
incontinence
pathological fracture
prostate cancer metastatic
prostate cancer
prostate induration
prostate tenderness
prostatic hemorrhage
prostatic mass
prostatic obstruction
prostatomegaly

[a] Exact Preferred Term according to MedDRA Version 26.1.

11.11 Appendix 11. Specific Guidance for Immune Effector Cell-Associated Neurotoxicity Syndrome

For this study, ICANS will be using the criteria referenced in the publication by Lee et al (2019). While the grading system has been developed in large part from chimeric antigen receptor T-cells therapies, symptoms of ICANS may be shared among immune effector cell-associated therapies such as BiTE® molecules. Although there may be a wide range of symptoms associated with ICANS, subjects may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

ICANS grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral oedema) not attributable to any other cause. Refer to the Immune Effector Cell-associated Encephalopathy (ICE) score below for grading of ICANS.

ICE Assessment Tool:

- Orientation: orientation to year, month, city, hospital: 4 points.
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points.
- Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point.
- Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point.
- Attention: ability to count backwards from 100 by 10: 1 point.

ICE scoring:

- 7 to 9, grade 1.
- 3 to 6, grade 2.
- 0 to 2, grade 3.
- 0 due to subject unarousable and unable to perform ICE. Assessment, grade 4.

Table 11-15. ASBMT Immune Effector Cell-Associated Neurotoxicity Syndrome Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (subject is unarousable and unable to perform ICE)
Depression level of consciousness[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging[d]	Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASBMT = American Society for Blood and Marrow Transplantation; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable.

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Intracranial haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.

Source: Lee et al, 2019.

11.12 Appendix 12. Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.

Clinical signs and symptoms of CRS are nonspecific and may include a combination of the following:

- Constitutional – Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
- Skin – Rash
- Gastrointestinal – Nausea, vomiting, diarrhea
- Respiratory – Tachypnea, hypoxemia
- Cardiovascular – Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
- Coagulation – Elevated D-dimer, hypofibrinogenemia ± bleeding
- Renal – Azotemia
- Hepatic – Transaminitis, hyperbilirubinemia

The symptoms associated with the CRS event do not meet the definition of an adverse event as defined in Section 11.4. Therefore, CRS **(or equivalent term)** should be documented on the Event CRF as the diagnosis. However, since it is important to document all symptoms related to a CRS event, a CRS Symptoms CRF will also be available to record the symptoms associated with each CRS event. If the severity of a CRS event changes from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF and fill out an associated CRS Symptoms CRF. If the symptoms worsen enough to impact the overall CRS grade, it is important to remember to record a new CRS event on the Event CRF with the appropriate grade. Temperature may normalize within a few hours of treatment, whereas the other components of CRS take longer to resolve. Once treatments are used to manage the fever, the subject is considered to still have CRS, even in the absence of fever, until all signs and symptoms leading to the diagnosis of CRS have resolved. Likewise, CRS can be downgraded in an afebrile subject treated with anticytokine therapy as their hemodynamic status and/or hypoxia improves. Typically, a subject with severe CRS whose fever, oxygen, and pressor requirements have resolved may be assumed to have resolved CRS unless there are alternative causes for the fever, hypoxia, and/or hypotension.

Table 11-16. Cytokine Release Syndrome (ASTCT; Lee et al, 2019)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
			With	
Hypotension	None	Not requiring vasopressors	Requiring a single vasopressor (not including vasopressin)	Requiring multiple vasopressors (not including vasopressin)
			And/or[b]	
Hypoxia	None	Requiring low-flow (≤ 6 L/minute) nasal cannula or blow-by	Requiring high-flow (> 6 L/min) nasal cannula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

Organ toxicities associated with CRS may be graded according to CTCAE version 5.0, but they do not influence CRS grading.

[a] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab **(or local equivalent)** or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

11.13 Appendix 13. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1 Eisenhauer et al, 2009) with Prostate Cancer Working Group 3 (PCWG3) Modifications (Scher et al, 2016)

11.13.1 PCWG3-modified RECIST v1.1

PCWG3-modified RECIST v1.1 criteria combine responses evaluated in skeletal disease areas (progression assessed using PCWG3) and soft tissue areas (response and progression assessed using modified RECIST v1.1).

Soft tissue response assessment is performed using modified RECIST v1.1 criteria and is based on quantitative evaluation of target, qualitative evaluation of non-target lesions, and the appearance of new lesions over time.

11.13.2 Modified RECIST v1.1 Criteria for Soft Tissue Assessment

11.13.2.1 Definitions:

11.13.2.1.1 Measurable Disease

The presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.13.2.1.1.1 Measurable Non-nodal Tumor Lesions

Non-nodal tumor lesions with clear borders that can be accurately measured in at least 1 dimension **with a minimum size of:**

- 10 mm **longest diameter** in CT **or** MRI scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.

11.13.2.1.1.2 Nodal Lesions

Lymph nodes are to be considered measurable if ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be **≤** 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.13.2.1.1.3 Special Considerations for measurable lesions:

- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above for non-nodal lesions. **However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.**
- **Bone lesions: Lytic bone lesions or mixed lytic-blastic bone lesions** with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above for non-nodal lesions.
- **Visible or palpable lesions can be considered measurable if ≥ 10 mm in longest diameter for non-nodal. Lesions should be measured radiologically if more accurate, if not then measured by calipers.**

11.13.2.1.2 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non measurable. (When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness).

Other examples of lesions usually considered to be non-measurable include:

- Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
- **The extraosseous soft tissue component of a bone lesion may be indicated as soft tissue non-target disease for the RECIST v1.1 if soft tissue component is non-measurable per RECIST v1.1.**
- Categorically, clusters of small lesions, bone lesions without a soft tissue component, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and leptomeningeal disease are non-measurable.

11.13.2.2 Methods of Measurement

All measurements should be taken and recorded in metric notation, using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the trial. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will be assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.13.2.2.1 CT/MRI

Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of intravenous (IV) contrast as well as timing of scanning. CT and MRI should be performed with ≤ 5 mm thick contiguous slices. The longest diameter of selected lesions should be measured in the plane in which the images were acquired. Ideally, the same scanner or at least type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

For any patients where CT contrast is contraindicated and premedication for contrast allergy is not medically appropriate, preference should be as follows:

- **First choice: CT chest non-contrast + MRI abdomen/pelvis with contrast**
- **Second choice: CT chest/abdomen/pelvis non-contrast**

- **Third choice: CT chest non-contrast + MRI abdomen/pelvis non-contrast**

Additionally, consideration should be given to the tumor type, anatomic locations of disease and the imaging modalities used in this and previous studies which may impact response interpretation.

Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable (NE) from that point forward.

11.13.2.2.2 PET-CT

The low dose or attenuation correction CT portion of a combined PET-CT is not **appropriate for** RECIST **v1.1** measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV contrast), then the CT portion of the PET-CT can be used for RECIST **v1.1** measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.13.2.2.3 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

11.13.2.3 Lesion Evaluation

11.13.2.3.1 Baseline Documentation of "Target" and "Non-target" Lesions

11.13.2.3.1.1 Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 25 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lymph nodes are considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for accurate repeated measurements. All other measurable lesions will be followed as non-target lesions.

An SOD (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported. The baseline SOD will be used as reference by which to characterize overall tumor response for all responses except PD. Progressive disease should be called based on comparison of timepoint SOD to SOD nadir (the smallest SOD on study including the baseline sum if that is the smallest on study).

11.13.2.3.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. These lesions should be followed as "present," "absent," "unequivocal progression," or "not evaluable" throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

11.13.2.4 Response Criteria

11.13.2.4.1 Evaluation of Target Lesions

Table 11-17. Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target non-nodal lesions. Any target lymph node must have reduction in short axis to < 10 mm, NOT total disappearance.
Partial Response (PR)	At least a 30% decrease in the sum of diameters **(SOD)** of target lesions, taking as reference the baseline **SOD**.
Progressive Disease (PD)	At least a 20% increase in the **SOD** of target lesions, taking as reference the **SOD nadir** (**the** smallest **SOD**) on study includ**ing** the baseline **SOD** if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. If a subject is missing lesion data at a disease assessment and yet **PD** criteria is met despite the missing data, the subject will be classified as **PD**.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Evaluable (NE)	When inadequate or no imaging/measurement is done at a particular time point, the subject's response is NE at that time point.
Not Applicable (NA)	**When no target lesions are present at baseline.**

11.13.2.4.2 Special Notes on the Assessment of Target Lesions

Target lesions that become "too small to measure"

While on study, all target lesions (nodal and non-nodal) recorded at baseline should have their measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT or MRI scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the non-lymph node lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT or MRI slice thickness (but should not be changed with varying CT or MRI slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an accurate measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment

When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum and identified as a fragment of the original lesion. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Target lesions that are being biopsied

It is strongly recommended not to perform a biopsy on target lesions. However, if a biopsy is performed on a target lesion, then that target lesion will be deemed NE at that and all subsequent time points.

11.13.2.4.3 Evaluation of Non-target Lesions

Table 11-18. Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-nodal non-target lesions and normalization of tumor marker level. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see **Section 11.13.2.4.4**). If a subject is missing lesion data at a disease assessment and yet unequivocal progression is met despite the missing data, the subject will be classified as PD.
Not Evaluable (NE)	When inadequate or no imaging is done at a particular time point, the subject's response is NE at that time point.
Not Applicable (NA)	**When no non-target lesions are present at baseline.**

11.13.2.4.4 Special Notes on the Assessment of Non-target Lesions

When the subject also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease (SD) or partial response (PR) in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for

measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

11.13.2.4.5 New Lesions

The term "new lesion" always refers to the presence of a new finding that is a malignant lesion. If a new lesion is identified via a modality other than CT or MRI, CT or MRI confirmation is recommended unless the new lesion is deemed unequivocally tumor. New findings that are not definitively tumor but may be benign (infection, inflammation, etc) are not selected as new lesions, until that time when the review is certain they represent malignant lesion.

- **If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If additional imaging confirms there is definitely a new lesion, then progression should be declared using the date of the initial scan.**
- **A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression, regardless of any response that may be seen in target or non-target lesions present from baseline.**

11.13.2.5 Tumor Response Assessment

11.13.2.5.1 Evaluation of Best Overall Response

The subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions and confirmation of response. Best overall response (BOR) will be based on all post-baseline disease assessments that occur before the initiation of subsequent anticancer treatment. At least 7 weeks from randomization must elapse without radiological disease progression to meet the minimum criteria for SD duration in order to assign a BOR of SD. In general, subjects not classifiable under the RECIST v1.1 response categories due to inadequate data or early death will be classified as NE for BOR but will be counted in the denominator of all response rate calculations.

11.13.2.5.2 Time Point Overall Response

Table 11-19. Time Point Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Subjects with Target (± Non-target) Disease			
CR	CR or NA	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR or Non-CR/Non-PD or NE or NA	No	PR
SD	CR or Non-CR/Non-PD or NE or NA	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
Subjects with Non-target Disease Only			
NA	CR	No	CR
NA	Non-CR/Non-PD	No	Non-CR/Non-PD[a]
NA	PD	Any	PD
NA	Any	Yes	PD
NA	NE	No	NE
Subjects without Target and Non-target Disease			
NA	**NA**	**NA**	**NED[b]**

CR = complete response**; NA = Not applicable;** NE = Not evaluable**; NED = no evidence of disease;** PD = progressive disease; PR = partial response; **RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1;** SD = stable disease**.**

[a] **Per RECIST v1.1, "Non-CR/Non-PD" is preferred over "SD" for Non-Target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.**

[b] **A time point response of NED will be treated as NE for the purposes of calculating Best Response.**

11.13.2.5.3 Confirmation Measurement/Duration of Response Confirmation

Confirmation of **complete response (**CR**)** and PR is not required**.**

11.13.2.5.4 Special Notes on Response Assessment

- **"Symptomatic deterioration" alone does not qualify as objective progression. If objective progression was not previously documented, then every effort should be made to document objective progression even after discontinuation of treatment.**
- **In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be further investigated by fine needle aspirate/biopsy or fluorodeoxyglucose (FDG)-positron emission tomography (PET), to confirm the CR status.**

- **If a lesion disappears and reappears at a subsequent timepoint it should continue to be measured. However, the subject's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the subject's tumor had reached a CR status and the lesion reappeared, then the subject would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria.**

11.13.2.5.5 Assessment Date Convention

It is acknowledged that an assessment may include several methods of evaluation performed over a period of several days within a window of time around an expected assessment date. The convention to be followed when assessing response or progression will be as follows:

- **The date of response (non-PD) will be recorded as the date of the latest radiographic evaluation included in the series for that assessment.**
- **The date of progression (PD) will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.**

11.13.3 PCWG3 Criteria for Bone Assessment

Bone response assessment is performed using PCWG3 criteria and is based on qualitative evaluation of bone lesions over time. PCWG3 measures progression of bone disease per the 2+2 rule.

11.13.3.1 Methods of Measurement

^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy is the standard modality for bone imaging to record and report presence or absence of bone metastases. All bone lesions should be reported and followed at subsequent scans.

IMPORTANT NOTE:

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, PET imaging with 18F-NaF, 18F-FDG, choline, or PSMA, bone marrow MRI (body MRI), and other modalities that are in use to image bone, are not acceptable for evaluating bone disease presence/absence.

Table 11-20. Bone Lesion Response Categories

No Evidence of Disease (NED)	**No bone lesion**
Non-PD	**At least one bone lesion present, but not PDu or PD**
Unconfirmed Progressive Disease (PDu)[a]	**Placeholder when PD is presumed per the 2+2 rule**
Progressive Disease (PD)	**Confirmed PD (from PDu per 2+2 rule)**
Not Evaluable (NE)	**When inadequate or no imaging is done at a particular time point, the subject's response is not evaluable (NE) at that time point**

[a] PDu is a temporary response: based on following (≥ 6 weeks apart) bone scan, PDu should be updated to PD or non-PD. If no later bone scan is available, PDu remains.

11.13.3.2 Tumor Response Assessment

11.13.3.2.1 Flare Window

The flare effect is a worsening of a bone scan associated with bone remodeling. This remodeling is characterized by an increase in size or radionuclide uptake intensity of existing lesions and/or appearance of new lesions due to reparative mineralization around the responding metastases. This phenomenon can occur in the first 12 weeks following initiation of therapy. New bone lesions are therefore assessed differently if they appear within or outside the flare window.

11.13.3.2.2 2+2 Rule: Within Flare Window

PD is confirmed when the following conditions are met:

- **First post-baseline bone scan (within flare window) shows ≥ 2 new bone lesions compared to baseline**

AND

- **Following bone scan (≥ 6 weeks apart) shows ≥ 2 additional new bone lesions with persistence of ≥ 2 lesions shown on first post-baseline scan.**

Response for first post-baseline bone scan showing ≥ 2 new lesions will be unconfirmed PD (PDu). If PD is confirmed per the rule above at follow-up bone scan, PDu is updated to PD and date of PD is declared at time of first post-baseline bone scan. If PD is not confirmed at the follow-up scan, PDu is updated to non-PD.

If only one or none of the bone lesions from the first post-baseline bone scan are persistent at the following scan or if the following bone scan doesn't show ≥ 2 additional new bone lesions, the lesions seen on the first post-baseline scan are considered flare and this scan becomes the new baseline for the 2+2 rule. Note that it is acceptable to have one or multiple NE responses for bone scans between PDu and confirmatory PD scans.

11.13.3.2.3 2+2 Rule: Outside of Flare Window

PD is confirmed when the following conditions are met:

- **A bone scan (out of flare window) shows ≥ 2 new bone lesions compared to baseline (or the new baseline).**

AND

- **Following bone scan (≥ 6 weeks apart) shows persistence of ≥ 2 of the lesions.**

Response for bone scan showing ≥ 2 new bone lesions, outside the flare window, compared to baseline (or the new baseline) will be PDu. Of note, the 2 new lesions triggering PDu do not need to appear in the same scan nor on two sequential scans. If PD is confirmed per the 2+2 rule at follow-up bone scan, PDu is updated to PD and date of PD is declared at time of first bone scan with appearance of 2 new lesions compared to baseline. If PD is not confirmed at the follow-up scan, PDu is updated to non-PD. Note that it is acceptable to have one or multiple NE responses for bone scans between PDu and confirmatory PD scans.

11.13.3.3 Missing Baseline Bone Scan

If a bone scan is missing at Baseline, the PCWG3 assessment can still be performed once there are two post-baseline scans received as follows:

- **First bone scan received will be NE as it cannot be determined whether bone disease visualized on the bone scan is new or has been present since baseline.**
- **Second post-baseline time point will be Non-PD or PDu as the second bone scan will be compared to the first.**
- **Progression can be confirmed at or after the third post-baseline scan per the 2+2 rule.**

11.13.3.4 Superscan

A superscan is defined as a bone scan demonstrating markedly increased diffuse skeletal uptake relative to soft tissue along with absent or faint activity in the genitourinary tract.

If a superscan is received at baseline, the reader will document the presence of a superscan, individual bone lesion annotations can be performed, but the number of bone lesions will be marked as > 20. Subsequent PCWG3 responses will be Non-PD unless criteria for PDu or PD are met.

If a superscan is received at any time point other than baseline, subject's PCWG3 timepoint response will be recorded as PDu. Subsequent superscan (≥ 6 weeks later) will be needed for PD confirmation.

If superscan is recorded at baseline and then unequivocal new bone lesions are identified at post-baseline time point, the standard PCWG3 reading process will be applied and the 2 new lesions will be followed.

If 2 new lesions are identified whether within or out of the flare window, and subsequent bone scan is a superscan, the PCWG3 response of PDu will be updated to PD.

11.14 Appendix 14. Patient-Reported Outcomes Questionnaire

11.14.1 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

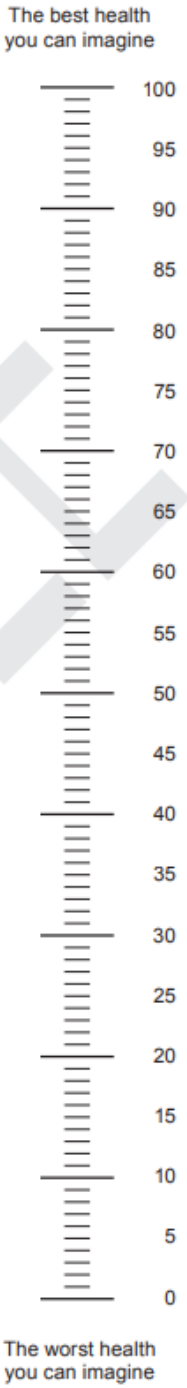
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



11.14.2 BPI-SF

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

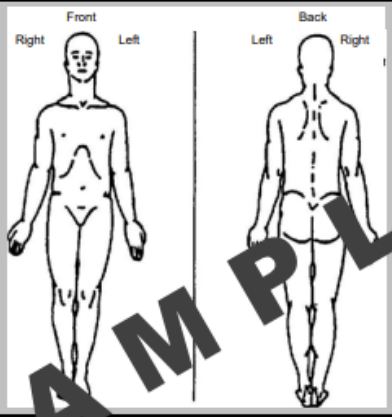
Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____
Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/___/____ Time: _____
Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8		10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4		6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3		5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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11.14.3 FACT-P

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please select one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please select one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please select one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

11.14.4 PRO-CTCAE

NCI- PRO-CTCAE® ITEMS-ENGLISH

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

9. PRO-CTCAE® Symptom Term: Nausea				
a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

16. PRO-CTCAE® Symptom Term: Diarrhea				
a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

19. PRO-CTCAE® Symptom Term: Shortness of breath				
a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

39. PRO-CTCAE® Symptom Term: Numbness & tingling				
a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

40. PRO-CTCAE® Symptom Term: Dizziness				
a. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

48. PRO-CTCAE® Symptom Term: General pain				
a. In the last 7 days, how OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

50. PRO-CTCAE® Symptom Term: Muscle pain				
a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

51. PRO-CTCAE® Symptom Term: Joint pain				
a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

53. PRO-CTCAE® Symptom Term: Fatigue				
a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

74. PRO-CTCAE® Symptom Term: Chills				
a. In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

11.15 Appendix 15. Performance Status According to Eastern Cooperative Oncology Group Scale

ECOG Performance Status Scale	
Grade	Descriptions
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, eg, light **housework**, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al, 1982

11.16 Appendix 16. Key Safety Risks of Cabazitaxel, Abiraterone Acetate, and Enzalutamide

Table 11-21. Key Safety Risks of Cabazitaxel

Key Risks	Description
Bone Marrow Suppression	Cabazitaxel is contraindicated in patients with neutrophils ≤ 1.5 x 10^9/L. Bone marrow suppression (particularly neutropenia) and its clinical consequences (febrile neutropenia, neutropenic infections, and death): Monitor blood counts frequently to determine if dosage modification or initiation of G-CSF is needed. Anemia has been observed in patients receiving cabazitaxel. Hemoglobin and hematocrit should be checked before treatment with cabazitaxel and if patients exhibit signs or symptoms of anemia or blood loss. Closely monitor patients with hemoglobin < 10 g/dL and appropriate measures should be taken as clinically indicated.
Increased Toxicities in Elderly Patients	Patients ≥ 65 years of age were more likely to experience fatal outcomes and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely.
Hypersensitivity	Severe hypersensitivity reactions can occur. Premedicate with corticosteroids and H2 antagonists. Discontinue infusion immediately if hypersensitivity is observed and treat as indicated.
Gastrointestinal Disorders	Nausea, vomiting, and diarrhea may occur. Mortality related to diarrhea has been reported. Rehydrate and treat with antiemetics and antidiarrheals as needed. If experiencing grade ≥ 3 diarrhea, dosage should be modified. Deaths have occurred due to gastrointestinal hemorrhage, perforation, and neutropenic enterocolitis. Delay or discontinue cabazitaxel and treat as indicated.
Renal Failure	Renal failure, including cases with fatal outcomes, has been reported. Identify cause and manage aggressively.
Urinary Disorders	Urinary disorders including cystitis: Cystitis, radiation cystitis, and hematuria may occur. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis. Interrupt or discontinue cabazitaxel and provide medical or surgical supportive care, as needed, in patients experiencing severe hemorrhagic cystitis.
Respiratory Disorders	Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome, including fatal outcomes, have been reported. Delay or discontinue cabazitaxel and treat as indicated.
Cardiac Arrhythmias	Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation.
Hepatic Impairment	Treatment with cabazitaxel is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN). Dose should be reduced for patients with mild (total bilirubin > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN), hepatic impairment.
Embryo-fetal Toxicity	Cabazitaxel can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception.
Impaired Fertility	**Cabazitaxel may impair fertility. Advise relevant subjects to consider sperm preservation options before initiating treatment with cabazitaxel.**

AST = aspartate aminotransferase; G-CSF = granulocyte-colony stimulating factor; ULN = upper limit of normal

Table 11-22. Key Safety Risks of Abiraterone Acetate

Safety Risk	Description
Hypokalemia, hypertension, fluid retention, and cardiovascular adverse reactions due to mineralocorticoid excess	Use abiraterone acetate with caution in patients with a history of cardiovascular disease. The safety of abiraterone acetate in patients with left ventricular ejection fraction (LVEF) < 50% or New York Heart Association (NYHA) Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.
Adrenocortical insufficiency	Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.
Hepatotoxicity	Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue abiraterone acetate.
Embryo-fetal toxicity	Based on animal reproductive studies and mechanism of action, abiraterone acetate can cause fetal harm and loss of pregnancy when administered to a pregnant female.
Musculoskeletal and connective tissue disorders	**Joint swelling or discomfort, muscle discomfort, and myopathy, including rhabdomyolysis have been observed in clinical trials and during post-approval use.**

Table 11-23. Key Safety Risks of Enzalutamide

Safety Risk	Description
Seizure	Seizure occurred in 0.4% of patients receiving enzalutamide in clinical studies. In these studies, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 604 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.
Posterior Reversible Encephalopathy Syndrome (PRES)	PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue enzalutamide in patients who develop PRES.
Hypersensitivity	Hypersensitivity reactions, including **o**edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in 4 randomized clinical studies.
Ischemic Heart Disease	Grade 3-4 ischemic events occurred in 1.2% of patients on the enzalutamide arm compared to 0.5% on the placebo arm. Ischemic events led to death in 0.4% of patients on the enzalutamide arm compared to 0.1% on the placebo arm. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia.
Falls and Fractures	Falls and fractures occurred in patients receiving enzalutamide, consider use of bone-targeted agents.

Safety Risk	Description
Embryo-Fetal Toxicity	Based on animal reproductive studies and mechanism of action, enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female.

11.17 Appendix 17. Safety Stopping Boundaries for Xaluritamig Arm

Table 11-24. Stopping Boundaries for Xaluritamig Arm

N	Stopping Boundary	N	Stopping Boundary	N	Stopping Boundary
30 to 33	≥ 9	167 to 171	≥ 39	310 to 313	≥ 69
34 to 38	≥ 10	172 to 176	≥ 40	314 to 318	≥ 70
39 to 42	≥ 11	177 to 180	≥ 41	319 to 323	≥ 71
43 to 47	≥ 12	181 to 185	≥ 42	324 to 328	≥ 72
48 to 51	≥ 13	186 to 190	≥ 43	329 to 332	≥ 73
52 to 55	≥ 14	191 to 195	≥ 44	333 to 337	≥ 74
56 to 60	≥ 15	196 to 199	≥ 45	338 to 342	≥ 75
61 to 64	≥ 16	200 to 204	≥ 46	343 to 347	≥ 76
65 to 69	≥ 17	205 to 209	≥ 47	348 to 352	≥ 77
70 to 74	≥ 18	210 to 213	≥ 48	353 to 356	≥ 78
75 to 78	≥ 19	214 to 218	≥ 49	357 to 361	≥ 79
79 to 83	≥ 20	219 to 223	≥ 50	362 to 366	≥ 80
84 to 87	≥ 21	224 to 228	≥ 51	367 to 371	≥ 81
88 to 92	≥ 22	229 to 232	≥ 52	372 to 375	≥ 82
93 to 96	≥ 23	233 to 237	≥ 53	376 to 380	≥ 83
97 to 101	≥ 24	238 to 242	≥ 54	381 to 385	≥ 84
102 to 106	≥ 25	243 to 247	≥ 55	386 to 390	≥ 85
107 to 110	≥ 26	248 to 251	≥ 56	391 to 395	≥ 86
111 to 115	≥ 27	252 to 256	≥ 57	396 to 399	≥ 87

N	Stopping Boundary	N	Stopping Boundary	N	Stopping Boundary
116 to 120	≥ 28	257 to 261	≥ 58	400 to 404	≥ 88
121 to 124	≥ 29	262 to 266	≥ 59	405 to 409	≥ 89
125 to 129	≥ 30	267 to 270	≥ 60	410 to 414	≥ 90
130 to 134	≥ 31	271 to 275	≥ 61	415 to 419	≥ 91
135 to 138	≥ 32	276 to 280	≥ 62	420 to 423	≥ 92
139 to 143	≥ 33	281 to 285	≥ 63	424 to 428	≥ 93
144 to 148	≥ 34	286 to 289	≥ 64	429 to 433	≥ 94
149 to 152	≥ 35	290 to 294	≥ 65	434 to 438	≥ 95
153 to 157	≥ 36	295 to 299	≥ 66	439 to 443	≥ 96
158 to 162	≥ 37	300 to 304	≥ 67	444 to 447	≥ 97
163 to 166	≥ 38	305 to 309	≥ 68	448 to 450	≥ 98

N = number of subjects treated with xaluritamig.

Stopping Boundary: recommend stopping the study if observing this number of subjects experienced grade 4 or higher treatment-related adverse events (excluding grade 4 lymphopenia/lymphocyte count decreases and other laboratory adverse events of grade 4 not considered clinically relevant).

Approval Signatures

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