**Janssen Research & Development ***

**Clinical Protocol**

**Protocol Title**
# A Phase 3 Randomized, Open-label Study of Pasritamig (JNJ-78278343), a T-cell-redirecting Agent Targeting Human Kallikrein 2, With Docetaxel Versus Docetaxel for Metastatic Castration-resistant Prostate Cancer

**KLK2-PASenger**

**Short Title: Pasritamig With Docetaxel vs Docetaxel in Metastatic Castration-resistant Prostate Cancer (mCRPC)**

**Protocol 78278343PCR3003; Phase 3**
**Version: Original**

**JNJ-78278343 (pasritamig)**

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**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## TABLES



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## ABBREVIATIONS

| | |
|---|---|
| ADL | activities of daily living |
| ADT | androgen deprivation therapy |
| AE | adverse event |
| AESI | adverse event of special interest |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| ARPI | androgen receptor pathway inhibition |
| ASMP | anticipated events safety monitoring plan |
| AST | aspartate transferase |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| ATC | Anatomical Therapeutic Chemical |
| AxMP | Auxiliary Medicinal Product (also known as NIMP) |
| BICR | blinded independent central review |
| BIPAP | bi-level positive airway pressure |
| BPI-SF | Brief Pain Inventory-Short Form |
| BRCA | BReast CAncer gene |
| BSC | best supportive care |
| C | cycle |
| CCL2 | chemokine (C-C motif) ligand 2 |
| CD | cluster of differentiation |
| CI | confidence interval |
| CIS | carcinoma in situ |
| CNS | central nervous system |
| COVID-19 | coronavirus 2019 |
| CPAP | continuous positive airway pressure |
| CrCl | creatinine clearance |
| CRF | case report form(s) (paper or electronic as appropriate for this study) |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor deoxyribonucleic acid |
| CYP17 | cytochrome P450c17 |
| CYP3A4 | cytochrome P450 3A4 |
| D | day |
| DA-LTE | Drug Access Long-term Extension |
| DIC | disseminated intravascular coagulation |
| DLL | delta-like ligand |
| DOR | duration of response |
| DNA | deoxyribonucleic acid |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| eDC | electronic data capture |
| EEA | European Economic Region |
| EEG | electroencephalogram |
| EGFR | estimated glomerular filtration rate |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| EORTC QLQ-PR25 | European Organisation for Research and Treatment of Quality of Life Questionnaire - Prostate |
| EOT | end of treatment |

| | |
|---|---|
| EpCAM | epithelial cell adhesion molecule |
| EQ-5D-5L | European Quality of Life 5 Dimensions 5 Level Version consisting of the EQ-5D descriptive system and the EQ-VAS |
| EU | European Union |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GnRH | gonadotropin releasing hormone |
| HAART | highly active antiretroviral therapy |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HK2 | human kallikrein 2 |
| HLA | human leukocyte antigen |
| HLH-MAS | hemophagocytic lymphohistiocytosis/macrophage activation syndrome |
| HR | hazard ratio |
| HRQoL | Health-Related Quality of life |
| HRT | hormonal replacement therapy |
| IB | Investigator's Brochure |
| ICANS | immune effector cell-associated neurotoxicity syndrome |
| ICE | immune effector cell-associated encephalopathy |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| ICP | intraductal carcinoma of the prostate |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IHC | immunohistochemistry |
| IL | interleukin |
| IMP | Investigational Medicinal Product |
| INR | International normalized ratio |
| IPPI | Investigational Product Preparation Instructions |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| JEISR | Janssen Electronic Inbound Safety Reporting |
| KLK-2 | human kallikrein 2 |
| LAM | lactational amenorrhea method |
| LDH | lactate dehydrogenase |
| LDR | legally designated representative |
| LFT | liver function test |
| LTE | long-term extension |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mCRPC | metastatic castrate-resistant prostate cancer |
| MDSC | Myeloid-derived suppressor cells |
| MoA | mechanism of action |
| MRI | magnetic resonance imaging |
| MRU | medical resource utilization |
| NA | not applicable |
| NCI | National Cancer Institute |

| | |
|---|---|
| NE | not evaluable |
| NIMP | Non-Investigational Medicinal Product |
| ORR | overall response rate |
| OS | overall survival |
| PARP | poly (ADP-ribose) polymerase inhibitors |
| PBMC | peripheral blood mononuclear cell |
| PCWG3 | Prostate Cancer Working Group 3 |
| PD | progressive disease |
| PD-1 | programmed cell death protein-1 |
| PFS | progression-free survival |
| PFS2 | progression-free survival on subsequent therapy |
| PI | package insert |
| PK | pharmacokinetic(s) |
| POCBP | partner of childbearing potential |
| PPK | population pharmacokinetics |
| PQC | product quality complaint |
| PRO | patient-reported outcomes |
| PSA | prostate-specific antigen |
| PSCA | prostate stem cell antigen |
| PSMA | prostate-specific membrane antigen |
| PT | prothrombin time |
| QoL | quality of life |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| rPFS | radiographic progression-free survival |
| RT-PCR | real-time polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management (eg, IVRS, IWRS) |
| SAC | safety advisory committee |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SCARS | severe cutaneous adverse reactions |
| SD | standard deviation |
| SGPT | serum glutamic oxaloacetic transaminase |
| SGOT | serum glutamic oxaloacetic transaminase test |
| SIPPM | Site Investigational Product and Procedures Manual |
| SMT | Safety Management Team |
| SoA | Schedule of Activities |
| $SpO_2$ | oxygen saturation |
| STEAP-1 | six-transmembrane epithelial antigen of the prostate-1 |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TGF-β | transforming growth factor-beta |
| TME | total mesorectal excision |
| TRAE | treatment-related adverse event |
| Treg | regulatory T-cells |
| TSP | time to symptomatic progression |
| TSRE | time to skeletal-related event |
| TST | time to subsequent therapy |
| ULN | upper limit of normal |
| US | United States |
| VI | bladder cytoscopy |
| WBC | white blood cell |

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**A Phase 3 Randomized, Open-label Study of Pasritamig (JNJ-78278343), a T-cell-redirecting Agent Targeting Human Kallikrein 2, With Docetaxel Versus Docetaxel for Metastatic Castration-resistant Prostate Cancer**

**IND:** 157066
**EU TRIAL NUMBER:** 2025-522713-29-00

**Pasritamig with Docetaxel vs Docetaxel in Metastatic Castration-resistant Prostate Cancer (mCRPC)**

Pasritamig (JNJ-78278343) is a bispecific antibody designed to direct T-cells to hK2 (encoded by the *KLK2* gene) on target cancer cells, leading to the activation of T-cell-mediated lysis of KLK2-bearing prostate tumor cells.

**OBJECTIVES**

The primary objective is to determine whether treatment with pasritamig+docetaxel prolongs rPFS compared with docetaxel in participants with mCRPC who have progressed on at least one ARPI. rPFS is defined as the time from randomization to the time of BICR-assessed radiographic progression by CT/MRI or bone scan per PCWG3 and RECIST v1.1, or death from any cause, whichever occurs first.

The key secondary objective is to demonstrate additional clinical benefit for participants with mCRPC who have progressed on at least one ARPI treated with pasritamig+docetaxel compared with docetaxel. Clinical benefit will be assessed by OS, time to symptomatic progression, time to subsequent therapy, and time to skeletal-related event.

Overall safety will be assessed.

**OVERALL DESIGN**

Key aspects of the trial design are summarized in table.

| | | | |
|---|---|---|---|
| **Study Model:** | randomized, open-label, 2 treatment arms | **Population Type:** | adult participants |
| **Comparator:** | docetaxel | **Population Diagnosis or Condition:** | mCRPC, progressed on at least one ARPI |
| **Study Treatment Assignment Method:** | 1:1 randomization, Stratification by sites of metastases (non-visceral, visceral-liver or visceral-other), LDH (normal vs abnormal at screening), ECOG (0 or 1 at screening), and prior PARP inhibitor use (yes or no) | **Population Age:** | ≥18 years of age |
| **Blinding** | open-label | **Site Distribution:** | multinational |
| **Substudies** | no | | |

Adult participants ≥18 years of age with mCRPC who have progressed on at least one ARPI will be randomized in a 1:1 ratio to receive the combination of pasritamig+docetaxel or docetaxel. This is an open-

label study that includes a Screening Phase, a Treatment Phase, an EOT visit, and a Follow-up Phase, which consists of Post-Treatment Follow-up and Survival Follow-up subphases. Following the Screening Phase (begins up to 28 days prior to randomization), the Treatment Phase will continue in both arms until the last dose of study treatment. Within 42 days (±7 days) of last dose of study treatment, participants will complete an EOT visit and continue to the Follow-up Phase. Participants who reach EOT but have not yet had a BICR-confirmed rPFS event or started subsequent therapy will enter the Post-Treatment Follow-up Phase, which includes continued in-person visits and disease assessments. Participants will enter the Survival Follow Up Phase following a BICR-confirmed rPFS event, start of subsequent anticancer therapy, or withdraw consent but still allow contact, whichever occurs first. Survival follow-up will continue every 12 weeks (±28 days) until death, loss to follow-up, or complete study withdrawal, whichever occurs first.

**STUDY TREATMENT AND DURATION**

Dosing of pasritamig consists of 2 step-up doses (3.5 mg and 18 mg) followed by the target dose of 300 mg once every 6 weeks by IV administration. For both treatment arms, up to 10 doses of docetaxel should be administered. In the experimental arm, participants continue to receive pasritamig after docetaxel completion/discontinuation and are evaluated for efficacy and safety until BICR-confirmed rPFS. If pasritamig is discontinued prior to 10 doses of docetaxel, participants can continue to receive docetaxel up to 10 doses or until criteria for docetaxel discontinuation are met (per investigator discretion). In the comparator arm, after docetaxel completion/discontinuation, participants will continue to be evaluated for efficacy until rPFS by BICR in the Post-Treatment Follow-up Phase. While receiving chemotherapy, participants in the comparator arm will take continuous prednisone (5 mg orally twice per day) per the docetaxel label.

**STATISTICAL METHODS**

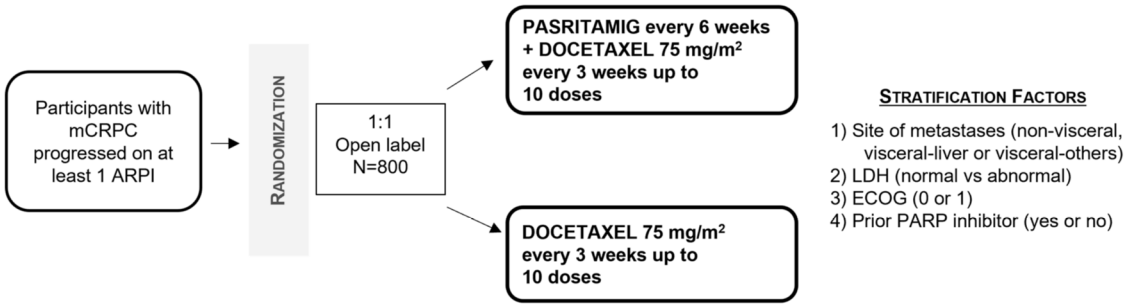
Approximately 800 participants with mCRPC who have progressed on at least one ARPI will be randomly assigned in a 1:1 ratio. The primary endpoint of rPFS will be assessed by BICR and is defined as the time from the date of randomization to the first date of radiographic disease progression, or death due to any cause, whichever occurs first. The sample size calculation assumes that pasritamig+docetaxel will result in a 32% reduction in the risk of progression or death over docetaxel (HR of 0.68, prolonging the median rPFS from 8.5 months with docetaxel alone compared to 12.5 months with pasritamig+docetaxel). Under the assumption that rPFS follows an exponential distribution, it is estimated that approximately 392 rPFS events will provide >96% power to detect a HR of 0.68 at a 2-tailed significance level of 0.05. Assuming variable enrollment rate the recruitment period spans 19 months, the rPFS primary analysis is expected 22 months after randomizing the first participant.

The safety parameters to be evaluated are the percentage and intensity of AEs, clinically significant changes in the participant's physical examination findings, vital signs measurements, and clinical laboratory results.

An Independent Data Monitoring Committee will be commissioned for this study.

## 1.2. Schema

**Figure 1: Schematic Overview of the Study**



## 1.3. Schedule of Activities (SoA)

**Table 1: Schedule of Activities: Pasritamig + Docetaxel Arm**

| Phase | Screening | Treatment Phase | | | | | | | EOT Visit[a] | Follow-up Phase | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Post-treatment Follow-up[b] | Survival Follow-up[c] | |
| **Period** | **≤28 d** | **Cycle 1 (8 weeks)** | | | | **Cycle 2 to Cycle 5 (6 weeks/cycle)** | | **Cycle 6 to EOT (6 weeks/cycle)** | | **Every 6 weeks** | **Every 12 weeks** | Cycle numbers correspond to pasritamig target dosing and each cycle contains 2 doses of docetaxel (refer to Figure 2). |
| **Visit Day** | | **1** | **8** | **15** | **36** | **1** | **22** | **1** | | | | |
| **Visit Window (days)** | | **±3** | | | | | | | **±7** | **+/-7** | **±28** | |
| **Screening/Administrative** | | | | | | | | | | | | |
| ICF, demographics, medical history, disease characteristics | X | | | | | | | | | | | Obtain ICF before any study-related procedures. |
| Inclusion/exclusion criteria | X | | | | | | | | | | | Laboratory values must meet inclusion criteria within 14 days prior to randomization. Imaging must be performed within 42 days prior to randomization. |
| **Randomization and Study Treatment Administration** | | | | | | | | | | | | |
| Randomization | X | | | | | | | | | | | Commence study treatment within 3 calendar days after randomization. |
| Pasritamig and pre-dose medications | | step-up dose 1 | step-up dose 2 | X | | X | | X | | | | First dose of pasritamig is Study Day 1. Refer to Section 6.9.1 for pre-dose medications, Table 7 for dose administration, and Section 7.1 for discontinuation. |
| Docetaxel and pre-dose medications | | | | X | X | X | X | | | | | Refer to Table 18 for docetaxel pre-dose medications. Dose modifications per local label and/or local practice guidelines. Refer to Section 6.6. Maximum of 10 doses, as tolerated. |
| **Efficacy Assessments** | | | | | | | | | | | | |
| CT or MRI (chest, abdomen, and pelvis) | X[d] | X<br>Every 8 weeks (±1week) for 18 months, then every 12 weeks (±1 week) until rPFS by BICR on CT/MRI or bone scan, start of subsequent therapy, or death, whichever occurs first. | | | | | | | | | | Imaging will be submitted to BICR. Unscheduled assessments can occur at any time, as needed. If study treatment is delayed, scheduled scans should occur at appropriate time window in relation to randomization. During follow-up, scans are collected only until radiographic progression. |
| $^{99m}$Tc bone scan | | | | | | | | | | | | |

| Phase | Screening | Treatment Phase | | | | | | | EOT Visit[a] | Follow-up Phase | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Post-treatment Follow-up[b] | Survival Follow-up[c] | |
| **Period** | **≤28 d** | **Cycle 1 (8 weeks)** | | | | **Cycle 2 to Cycle 5 (6 weeks/cycle)** | | **Cycle 6 to EOT (6 weeks/cycle)** | | **Every 6 weeks** | **Every 12 weeks** | Cycle numbers correspond to pasritamig target dosing and each cycle contains 2 doses of docetaxel (refer to Figure 2). |
| **Visit Day** | | **1** | **8** | **15** | **36** | **1** | **22** | **1** | | | | |
| **Visit Window (days)** | | **±3** | | | | | | | **±7** | **+/-7** | **±28** | |
| PRO assessments[e] | | X | X | X | X | X D1 of every 2 cycles (or every 12 weeks), starting from C2D1 | | | | | Every 12 weeks | BPI-SF, EORTC QLQ-C30, EORTC IL 46, EORTC QLQ-PR25, and EQ-5D-5L should be completed prior to any tests, procedures, drug administration, or other consultation. At EOT visit, if PRO was done within 6 weeks, no need to repeat. Only the EORTC QLQ-C30, EORTC QLQ-PR25, and EQ-5D-5L are to be completed in survival follow-up. |
| Survival status, symptomatic progression skeletal-related events, and next therapy | | X | | | | | | | | | | During follow-up, data may be obtained by telephone or chart review and at shorter intervals than every 12 weeks if required for study analysis. |
| **Safety Assessments** | | | | | | | | | | | | Perform prior to all study treatment administrations. |
| Physical examination | X | X | X | X | X | X | X | X | X | | | Complete physical examination at Screening. See Section 8.3.1. |
| Height | X | | | | | | | | | | | |
| Weight | X | X | | X | X | X | X | X | | | | |
| Vital signs | X | X[f] | X[f] | X[f] | X | X[f] | X | X | X | | | Temperature, heart rate, blood pressure, $SpO_2$. |
| Neurological examination (ICE tool) | X | *See Table 16* | | | | | | | | | | See Section 8.3.6. |
| 12-lead ECG | X | | | | | | | | | | | |
| ECOG performance status | X | X | X | X | X | X | X | X | X | | | |
| **Clinical Laboratory Tests** | | | | | | | | | | | | |
| Hematology, chemistry/ LFTs | X | X | X | X | X | X | X | X | X | | | Perform laboratory tests per Appendix 1 pre-dose on the same day of study treatment administration or up to 3 days prior. |
| Serum PSA | X | X | X | X | X | X | X | X | X | Every 6 weeks for 18 months, then every 12 weeks | | |
| Testosterone | X | | | | | | | | | | | |

| Phase | Screening | Treatment Phase | | | | | | | EOT Visit[a] | Follow-up Phase | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Post-treatment Follow-up[b] | Survival Follow-up[c] | |
| **Period** | **≤28 d** | **Cycle 1 (8 weeks)** | | | | **Cycle 2 to Cycle 5 (6 weeks/cycle)** | | **Cycle 6 to EOT (6 weeks/cycle)** | | **Every 6 weeks** | **Every 12 weeks** | Cycle numbers correspond to pasritamig target dosing and each cycle contains 2 doses of docetaxel (refer to Figure 2). |
| **Visit Day** | | **1** | **8** | **15** | **36** | **1** | **22** | **1** | | | | |
| **Visit Window (days)** | | **±3** | | | | | | | **±7** | **+/-7** | **±28** | |
| Coagulation, Serology (HBV, HCV) | X | | | | | | | | | | | Perform laboratory tests per Appendix 1 pre-dose on the same day of study treatment administration or up to 3 days prior. |
| **Ongoing Participant Review** | | | | | | | | | | | | |
| AEs and concomitant therapy | | *Collect continuously from informed consent until 42d after last dose of study treatment, or start of subsequent anticancer therapy, whichever occurs first. In follow-up, related SAEs should continue to be reported.* | | | | | | | | | | |
| **Medical Resource Utilization** | | | | | | | | | | | | |
| Medical Resource Utilization | | *Collected continuously after obtaining informed consent* | | | | | | | | | | |
| **Pharmacokinetics, Immunogenicity, and Biomarker Assessments (see Table 3)** | | | | | | | | | | | | |

a. EOT visit should be done within 42 days (±7 days) of last dose of study treatment or start of subsequent anticancer therapy, whichever occurs first (Section 8.1.4).
b. Post-treatment follow up is defined as the period after EOT but before progression or start of subsequent therapy, whichever occurs first. Includes visits in person, imaging assessments, PROs and PSA.
c. Survival follow up is defined as the period after BICR-confirmed radiographic progression (during treatment or post-treatment follow-up), start of subsequent therapy, or withdrawal of consent but allowing contact, whichever occurs first.
d. ≤42 d prior to randomization
e. PRO data collection will be discontinued when HR/difference in OS is statistically significant in a preplanned interim analysis. If the cycle is delayed, all assessments will be repeated on the day of actual administration, except PROs.
f. To be performed pre-dose before every dose. Pasritamig post-dose vital signs assessments should be performed every hour (±30 minutes) for at least the first 2 hours after step-up dose 1, step-up dose 2, and first 2 target doses (C1D15 and C2D1). Following the third target dose (C3D1), vitals can be monitored post-infusion if clinically indicated.

**Table 2: Schedule of Activities: Docetaxel Arm**

| Phase | Screening | Treatment Phase | | | | EOT Visit[a] | Follow-up Phase | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Post-treatment Follow-up[b] | Survival Follow-up[c] | |
| **Period** | **≤28 d** | **Cycle 1 (6 weeks)** | | **Cycle 2 to EOT (6 weeks/cycle)** | | | **Every 6 weeks** | **Every 12 weeks** | Each cycle contains 2 doses of docetaxel (refer to Figure 2). |
| **Visit Day** | | **1** | **22** | **1** | **22** | | | | |
| **Visit Window (days)** | | **±3** | | | | **±7** | **+/-7** | **±28** | |
| **Screening/Administrative** | | | | | | | | | |
| ICF, demographics, medical history, disease characteristics | X | | | | | | | | Obtain ICF before any study-related procedures. |
| Inclusion/exclusion criteria | X | | | | | | | | Laboratory values must meet inclusion criteria within 14 days prior to randomization. Imaging must be performed within 42 days prior to randomization. |
| **Randomization and Study Treatment Administration** | | | | | | | | | |
| Randomization | X | | | | | | | | Commence study treatment within 3 calendar days after randomization. |
| Docetaxel and pre-dose medications | | X | X | X | X | | | | Refer to Table 18 for docetaxel pre-dose medications. Dose modifications per local label and/or local practice guidelines. Refer to Section 6.6. Prednisone 5 mg orally twice daily will begin C1D1 and continue for at least 21 days after last docetaxel, then per investigator discretion. Maximum of 10 doses, as tolerated. |
| **Efficacy Assessments** | | | | | | | | | |
| CT or MRI (chest, abdomen, and pelvis)<br>$^{99m}$Tc bone scan | X[d] | X<br>Every 8 weeks (±1 week) for 18 months, then every 12 weeks (±1 week) until rPFS by BICR on CT/MRI or bone scan, start of subsequent therapy, or death, whichever occurs first. | | | | | | | Imaging will be submitted to BICR. Unscheduled assessments can occur at any time, as needed. If study treatment is delayed, scheduled scans should occur at appropriate time window in relation to randomization. During follow-up, scans are collected only until radiographic progression. |
| PRO assessments[d] | | X | X | X<br>D1 of every 2 cycles (or every 12 weeks), starting from C2D1 | | | | Every 12 weeks | BPI-SF, EORTC QLQ-C30, EORTC IL 46, EORTC QLQ-PR25, and EQ-5D-5L should be completed prior to any tests, procedures, drug administration, or other consultation. At EOT visit, if PRO was done within 6 weeks, no need to repeat. Only the EORTC QLQ-C30, EORTC QLQ-PR25, and EQ-5D-5L are to be completed in survival follow-up. |
| Survival status, symptomatic progression, skeletal-related events, and next therapy | | X | | | | | | | During follow-up, data may be obtained by telephone or chart review and at shorter intervals than every 12 weeks if required for study analysis. |

| Phase | Screening | Treatment Phase | | | | EOT Visit[a] | Follow-up Phase | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Post-treatment Follow-up[b] | Survival Follow-up[c] | |
| **Period** | **≤28 d** | **Cycle 1 (6 weeks)** | | **Cycle 2 to EOT (6 weeks/cycle)** | | | **Every 6 weeks** | **Every 12 weeks** | Each cycle contains 2 doses of docetaxel (refer to Figure 2). |
| **Visit Day** | | **1** | **22** | **1** | **22** | | | | |
| **Visit Window (days)** | | **±3** | | | | **±7** | **+/-7** | **±28** | |
| **Safety Assessments** | | | | | | | | | Perform prior to all study treatment administrations. |
| Physical examination | X | X | X | X | X | X | | | Complete physical examination at Screening. See Section 8.3.1. |
| Height | X | | | | | | | | |
| Weight | X | X | X | X | X | | | | See Table 7 and Table 8 for guidance on weight-based dose adjustments. |
| Vital signs | X | X | X | X | X | X | | | Temperature, heart rate, blood pressure, $SpO_2$. |
| Neurological examination (ICE tool) | X | *See Table 16* | | | | | | | See Section 8.3.6. |
| 12-lead ECG | X | | | | | | | | |
| ECOG performance status | X | X | X | X | X | X | | | |
| **Clinical Laboratory Tests** | | | | | | | | | |
| Hematology, chemistry/ LFTs | X | X | X | X | X | X | | | Perform laboratory tests per Appendix 1 pre-dose on the same day of study treatment administration or up to 3 days prior. |
| Serum PSA | X | X | X | X | X | X | Every 6 weeks for 18 months, then every 12 weeks | | |
| Testosterone | X | | | | | | | | |
| Coagulation, Serology (HBV, HCV) | X | | | | | | | | |
| **Ongoing Participant Review** | | | | | | | | | |
| AEs and concomitant therapy | | *Collect continuously from informed consent until 42d after last dose of study treatment, or start of subsequent anticancer therapy, whichever occurs first. In follow-up, related SAEs should continue to be reported.* | | | | | | | |
| **Medical Resource Utilization** | | | | | | | | | |
| Medical Resource Utilization | | *Collected continuously after obtaining informed consent* | | | | | | | |
| **Biomarker Assessments (see Table 4)** | | | | | | | | | |

a. EOT visit should be done within 42 days (±7 days) of last dose of study treatment or start of subsequent anticancer therapy, whichever occurs first (Section 8.1.4).
b. Post-treatment follow up is defined as the period after EOT but before progression or start of subsequent therapy, whichever occurs first. Includes visits in person, imaging assessments, PROs and PSA.
c. Survival follow up is defined as the period after BICR-confirmed radiographic progression (during treatment or post-treatment follow-up), start of subsequent therapy, or withdrawal of consent but allowing contact, whichever occurs first.
d. ≤42 d prior to randomization
e. PRO data collection will be discontinued when HR/difference in OS is statistically significant in a preplanned interim analysis. If the cycle is delayed, all assessments will be repeated on the day of actual administration, except PROs.

**Table 3: Collection Times for Pharmacokinetics, Immunogenicity and Biomarker Samples: Pasritamig + Docetaxel Arm**

| Study Day[a,b] | | Sampling Time[c] | Pharmacokinetics[d] | Immunogenicity[d] | Immunophenotyping (PBMC) | Serum biomarker | Plasma (ctDNA) | Metastatic biopsy (if available) |
|---|---|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | Pre-dose (0-4 h prior) | X | X | X | X | X | Archival[e] |
| | Day 8 | Pre-dose (0-4 h prior) | X | | | | | |
| | Day 15 | Pre-dose (0-4 h prior) | X | X | X | | | |
| | | End of infusion (0-30 min after) | X[f] | | | | | |
| Cycle 2 | Day 1 | Pre-dose (0-4 h prior) | X | X | X | X | X | Optional[g] |
| Cycle 3 | Day 1 | Pre-dose (0-4 h prior) | X | X | | | | |
| | | End of infusion (0-30 min after) | X[f] | | | | | |
| Cycle 4, 6, 8, 10 | Day 1 | Pre-dose (0-4 h prior) | Cycle 6, 10 only | Cycle 6, 10 only | Cycle 4, 8 only | Cycle 4 only | Cycle 4 only | |
| Cycle 14, 18 | Day 1 | Pre-dose (0-4 h prior) | X | X | | | | |
| EOT visit | | | X | X | X | X | X | Optional[g] |

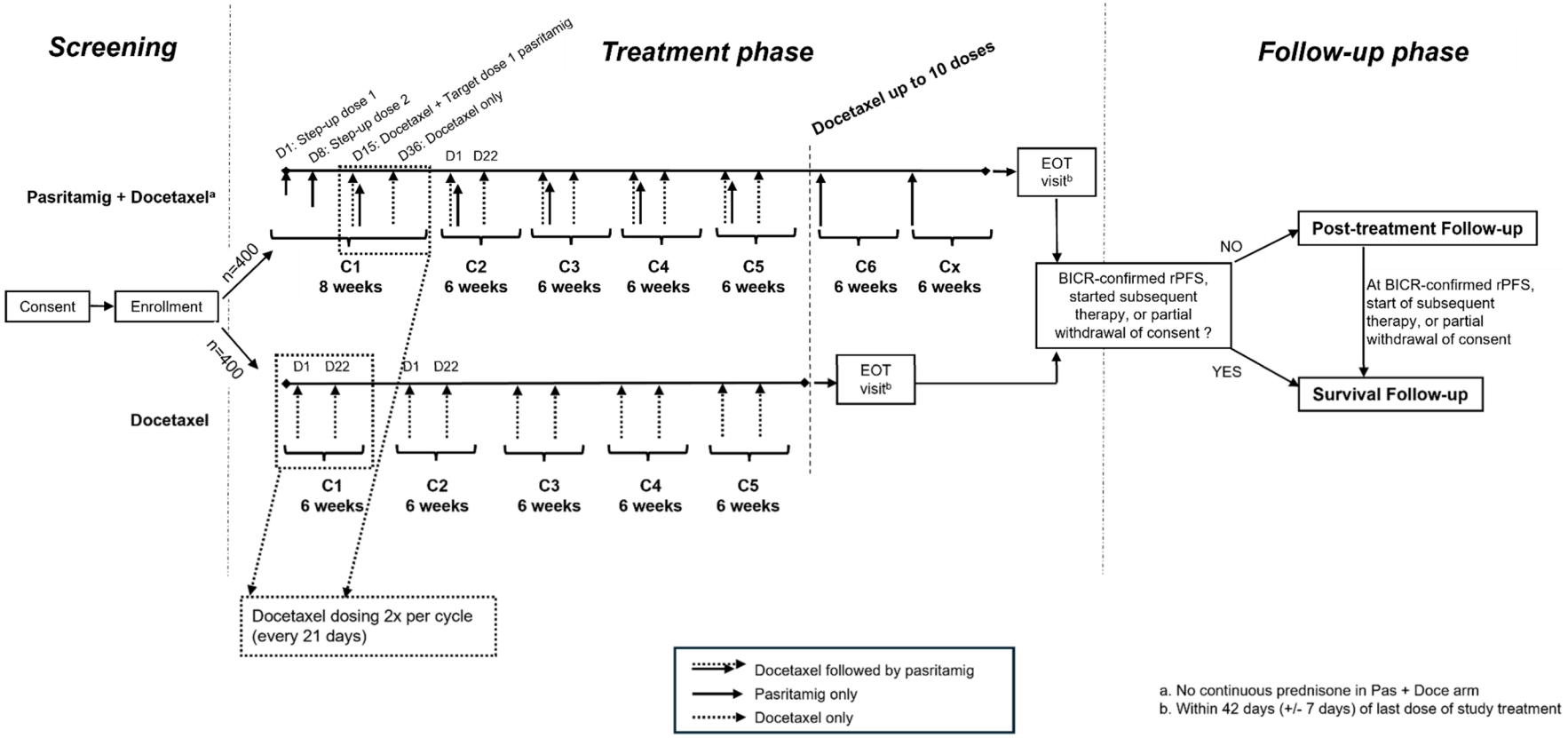
a. The samples should be collected on the same day as the clinical visit.
b. Cycle numbers correspond to pasritamig target dosing.
c. Timepoints are relative to the pasritamig administration.
d. At timepoints when both PK and immunogenicity samples are to be collected, aliquot(s) from PK samples will be used for immunogenicity assessments. No separate blood sample collection required.
e. If feasible, obtain available archival metastatic biopsies collected within 15 months prior to enrollment. Confirm their availability during screening and submit the biopsy material after C1D1.
f. PK samples collected at the end of infusion should be drawn from the contralateral arm where pasritamig is infused and after IV line is flushed.
g. Optional: Fresh biopsy of a metastatic lesion can be collected at any time point while the participant is on treatment starting at C2D1 and/or EOT from participants at select investigational sites. These biopsies can be collected from stable, new, regressing, or progressing lesions as clinically feasible and submitted for biomarker analysis.

**Table 4: Collection Times for Biomarker Samples: Docetaxel Arm**

| Study Day[a,b] | | Sampling Time | Immunophenotyping (PBMC)[c] | Serum Biomarker[c] | Plasma (ctDNA) | Metastatic Biopsy (if available) |
|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | Pre-dose (0-4 h prior) | X | X | X | Archival[d] |
| Cycle 2 | Day 1 | Pre-dose (0-4 h prior) | X | X | | |
| Cycle 4 | Day 1 | Pre-dose (0-4 h prior) | X | X | | |
| At disease progression | | | X | X | X[c] | |

a. The samples should be collected on the same day as the clinical visit.
b. Each cycle contains 2 doses of docetaxel.
c. Samples will be required from approximately 100 participants at selected investigational sites.
d. If feasible, obtain available archival metastatic biopsies collected within 15 months prior to enrollment. Confirm their availability during screening and submit the biopsy material after Cycle 1 Day 1 (C1D1).

**Figure 2: Study Treatment Dose Schedule**



## 2. INTRODUCTION

For the most comprehensive nonclinical and clinical information regarding pasritamig, refer to the latest version of the IB and Addenda for pasritamig.

The term “study treatment” throughout the protocol, refers to pasritamig+docetaxel or docetaxel with standard prednisone, as defined in Section 6.1.

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

### 2.1. Study Rationale

Despite significant advancements in therapies, mCRPC remains incurable and can cause considerable disease burden with high mortality and morbidity. The natural progression of mCRPC often involves worsening symptoms, such as skeletal-related events including bone pain, spinal cord compression, hypercalcemia, fracture, and functional debility which can be detrimental to the patient’s overall QoL. The goal of treatment is thus not only to improve survival but also to preserve patients’ QoL and alleviate cancer-related pain and symptoms.

**Taxane Chemotherapies in Prostate Cancer**

Taxane chemotherapy is a key treatment option for patients with mCRPC. Docetaxel is the first systemic therapy to demonstrate a survival benefit, establishing docetaxel as a standard of care for patients with mCRPC. In Study TAX 327, which compared treatment with docetaxel (75 mg/m$^2$ IV, once every 3 weeks) + prednisone to mitoxantrone (12 mg/m$^2$ IV, once every 3 weeks) + prednisone in participants with symptomatic mCRPC, participants in the docetaxel group had improved survival and rates of response as measured by pain status, serum PSA levels, and QoL (Tannock 2004). The HR for OS was 0.76 (95% CI: 0.62, 0.94; p=0.009) by the stratified log-rank test with a median survival of 16.5 months in the mitoxantrone group and 18.9 months in the docetaxel group. A 50% decrease in the serum PSA level (p<0.001 compared with mitoxantrone) was observed in at least 45% of participants; 35% (p=0.01) of participants had predefined reductions in pain; and 22% (p=0.009) of participants had improvements in QoL. However, in the era of novel androgen pathway inhibitors, docetaxel is often given later in the disease course after patients have progressed on an ARPI. In the post-ARPI setting, Study KEYNOTE 921 compared 10 or fewer cycles of docetaxel with either placebo or pembrolizumab. The median rPFS was 8.3 months in the placebo+docetaxel arm with a median OS of 19.0 months (Petrylak 2025).

Currently, docetaxel is recommended as a pre- or post-ARPI regimen, (NCCN 2025, EAU 2025), at a dose of 75 mg/m$^2$ IV once every 3 weeks for up to 10 cycles combined with prednisone 5 mg orally, twice a day. Prednisone can be omitted if there are contraindications or no major symptoms (EAU 2025).

Drug development efforts have focused on docetaxel as standard of care in trial design and regulatory approval. However, although new agents have been approved both in the pre-docetaxel (eg, sipuleucel-T, abiraterone acetate) and in the post-docetaxel setting (eg, cabazitaxel, abiraterone, enzalutamide) on the basis of improvements in OS, none of the drugs that have been

combined with docetaxel have yet demonstrated a survival benefit or gained regulatory approval (Antonarakis 2013; Petrylak 2025).

Given the relatively short PFS across available systemic therapies for mCRPC, including taxanes and radioligand therapy, an unmet medical need remains for more efficacious therapeutic options for this patient population.

**Rationale for Targeting KLK2 Using a CD3-Redirection Approach**

Bispecific T-cell engager therapies initially demonstrated clinical benefit in hematologic malignancies with blinatumomab (anti-CD19 x anti-CD3) in B-cell acute lymphoblastic leukemia and are now approved in solid tumors (eg, catumaxomab [EpCAM x anti-CD3] for malignant ascites, tarlatamab [anti-DLL3 x anti-CD3] for extensive stage small cell lung cancer, and tebentafusp [antiglycoprotein 100 x anti-CD3] for unresectable or metastatic uveal melanoma in patients positive for HLA-A*02:01). Currently, there are several targets for bispecific antibodies being explored in prostate cancer, including constructs targeting PSMA, PSCA, and STEAP-1.

Pasritamig is a humanized IgG1-based bispecific T-cell engager antibody designed to direct T-lymphocytes to hK2 (encoded by the *KLK2* gene and hereafter referred to as KLK2)-positive target cells. One arm of pasritamig binds to the CD3 receptor complex present on T-cells and the other arm binds to KLK2 present on target cells, leading to the activation of the T-cells and T-cell-mediated lysis of the KLK2-bearing cells.

Several lines of evidence indicate that KLK2 is a particularly attractive candidate for T-cell redirection therapy in the treatment of mCRPC:

- KLK2 is highly enriched in and specific to prostatic tissue and prostate cancer, with limited expression in normal non-prostate human tissues.
- KLK2 expression is mostly maintained throughout the progression of prostate adenocarcinoma, even in metastatic disease.
- The tumor microenvironment in prostate cancer may lack a sufficient immune presence to allow for efficient immune-mediated cytotoxicity. In these so called “cold” tumors, T-cell redirection may be a particularly important approach to enhance immunoreactivity in the tumor microenvironment.
- Although KLK2 is secreted, several preclinical studies demonstrate expression on the extracellular membrane that is available for antibody-mediated targeting.

## 2.2. Background

### 2.2.1. Nonclinical and Clinical Studies

For the most comprehensive nonclinical and clinical information regarding pasritamig, refer to the latest version of the IB and Addenda.

Pasritamig has been studied in a first-in-human, dose-escalation Phase 1 study to evaluate its safety, PK, pharmacodynamics, and preliminary antitumor activity in mCRPC, both as a single

agent (Study 78278343PCR1001) and in combination with taxane chemotherapy, ARPIs, and immunotherapy (Study 78278343PCR1003).

#### 2.2.1.1. Study 78278343PCR1001

An RP2D of 300 mg once every 6 weeks (target dose) by IV administration, with 2 step-up doses of 3.5 mg on Day 1 and 18 mg on Day 8, was selected and expanded.

In total, 33 participants treated who received the target dose were grouped together as the RP2D-efficacy population. A total of 42.4% achieved a PSA50 response and 36.4% had a confirmed PSA50 response. Median rPFS was 7.85 months. The most common treatment-related AEs at the RP2D dose level were fatigue (15.6%) and IRR (24.4%), all of which were Grade 2 or lower. No participants discontinued study treatment due to AEs and only 4 (8.9%) participants reported CRS, all of which were Grade 1 (Stein 2025).

#### 2.2.1.2. Study 78278343PCR1003: Pasritamig + Docetaxel Cohort

Participants with mCRPC received single agent pasritamig as step-up doses 3.5 mg on Day 1 and 18 mg on Day 8, then on Day 15 received docetaxel 75 mg/m$^2$ infusion followed by the target dose of pasritamig of 300 mg. Thereafter, docetaxel was administered every 3 weeks and pasritamig target dose was subsequently administered every 6 weeks.

At data cutoff 09 June 2025, 50 participants had received at least one dose of study treatment. Forty-nine of 50 (98%) participants reported TEAE and 48/50 (96%) reported TRAE. The most frequently reported (≥10%) TRAEs in Study PCR1003 were fatigue (54%), alopecia (40%), nausea (28%), diarrhea (26%), dysgeusia (18%), peripheral edema (18%), anemia (16%), stomatitis (14%), decreased appetite (12%), infusion-related reaction (12%), peripheral neuropathy (12%), and arthralgia (10%). These were mainly attributed to docetaxel. The reported rate of CRS or ICANS was 0/50 (0%) and no treatment-related deaths have been reported on study. There did not appear to be any potentiation effects in toxicity with the combination of pasritamig and docetaxel when compared with the docetaxel alone arm of KEYNOTE 921 (Petrylak 2025).

All participants were evaluable for PSA response as of 09 June 2025. Thirty-three (66.0%) participants achieved a PSA50 at any time and 17 (34.0%) participants achieved a PSA90 at any time. PSA declines occurred frequently with the step-up doses of pasritamig prior to receiving docetaxel. In other participants, there was a substantial drop in PSA upon receipt of the first combination dose of pasritamig + docetaxel. PSA50 response has been noted irrespective of prior exposure to chemotherapy or radioligand therapy. The PK of pasritamig when administered in combination with docetaxel was comparable to administration as monotherapy.

### 2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of pasritamig may be found in the IB.

Close clinical monitoring with frequent laboratory evaluations will be performed to assess participants for AEs. Special attention will also be given to potential immunological effects including, but not limited to, CRS, ICANS, or IRRs, as these have been observed with pasritamig.

The safety profile of docetaxel has been well established. Overlapping toxicities with pasritamig and docetaxel have been minimal in Study 78278343PCR1003. Per product label, docetaxel is given in conjunction with twice daily prednisone in the comparator arm, though concomitant use does not significantly impact the systemic exposure of docetaxel in patients with mCRPC, and there are no known or potential risks anticipated due to the lack of prednisone (Taxotere PI; Belderbos 2019). As the mechanism of action of pasritamig is via T-cell activation, continuous steroid exposure may inhibit its efficacy. Thus, oral daily prednisone will not be administered in the experimental arm (pasritamig+docetaxel) in this study. Though prednisone may potentially have some clinical efficacy, we consider this to be minimal and its omission should not negatively impact outcomes. Pre-dose medication for docetaxel will be administered per drug label in both arms to help mitigate infusion-related and delayed adverse reactions (see Section 6.9.1). The known or potential risks for study treatment and mitigation strategies are noted below:

| Potential Risks of Clinical Significance | Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Risks Due to Pasritamig** | | |
| Immunological effects:<br>• CRS<br>• Neurotoxicity including ICANS<br>• IRRs<br>• For participants with residual prostate or local tumor tissue, prostatitis is possible | As the specific mode of action of pasritamig is based on the binding and activation of T-cells and the release of cytotoxic cytokines in the tumor environment, AEs of CRS/IRRs/ICANS should be anticipated. CRS has been noted in the Phase 1 study in participants treated at the RP2D dose level and these events have all been low-grade. Cytokine-associated transient clinical laboratory abnormalities including lymphopenia and increased serum ALT and AST can be observed.<br>In addition to CRS and IRRs, pasritamig may lead to prostatitis based on its MoA in participants with residual prostate or local tumor tissue, though this has not been observed to date. | IV administration has been selected for the current Phase 3 study. Step-up dosing has been implemented to mitigate the risk of developing severe CRS. Guidance for pre-dose medications to manage these potential effects is provided in Section 6.9.1.<br>Management guidelines for potential toxicities (IRR, CRS, HLH/MAS, neurologic AEs, and prostatitis) are provided in Section 6.6.4. |
| **Risks Due to Docetaxel** | | |
| • Bone marrow suppression: neutropenia, febrile neutropenia, anemia, thrombocytopenia<br>• Hepatic impairment: increased ALP, ALT, bilirubin<br>• Neurologic reactions: neuropathy, paresthesia, dysgeusia, dysesthesia<br>• GI disorders: nausea, vomiting, diarrhea, constipation, mucositis<br>• Infection<br>• Myalgia<br>• Dyspnea<br>• Asthenia<br>• Anorexia<br>• Pain<br>• Fluid retention<br>• Severe cutaneous adverse reactions (SCARs)<br>• Alopecia<br>• Skin reactions<br>• Nail disorders<br>• Embryo-fetal toxicity | Per local product labeling | Management guidelines for potential toxicities are provided in the local product labeling.<br>See Table 12; Table 18. |

### 2.3.1. Benefits for Study Participation

Pasritamig may potentially lead to effective killing of target cells that express KLK2 such as those in mCRPC and could possibly result in improved efficacy measured by rPFS for participants with advanced disease and limited treatment options. Phase 1 data show that several participants across multiple active dose levels have achieved objective responses per RECIST v1.1 or remained on study for greater than a year with disease control, often with concurrent PSA responses.

### 2.3.2. Benefit-risk Assessment for Study Participation

While it is possible that treatment with pasritamig may cause adverse reactions, the Phase 1 data supports a low-risk safety profile, even at doses much higher than the current proposed RP2D dose level (refer to Section 4.3 for RP2D dose justification).

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with pasritamig are justified by the anticipated benefits that may be afforded to participants with mCRPC who have progressed on at least one ARPI.

### 2.3.3. Rationale for the Combination of Pasritamig with Docetaxel

Preclinical studies by Sano et al have demonstrated that the combination of CD3-redirectors with chemotherapy, including paclitaxel, enhances killing of non-inflamed tumors in a xenograft model compared with each individual therapy alone. This enhancement appeared to be both synergistic and reciprocal. Through its direct cytotoxic effect, paclitaxel contributed to the breakdown of tumor structure allowing for increased CD3-redirector distribution within the tumor. In turn, CD3-redirector stimulated the promotion and distribution of T-cells into the noninflamed tumor. Combining a CD3 TCE with chemotherapy may lead to the anticipated synergistic immunogenic cell death and result in enhanced outcomes (Sano 2022).

Combining pasritamig with docetaxel is hypothesized to enhance the efficacy of docetaxel and improve long-term disease control by actively engaging tumor targeting T-cells. Importantly, the addition of pasritamig may increase efficacy in patients who develop resistance to taxanes or who have primary refractory disease, by leveraging immune mechanisms. The combination approach may also benefit patients who discontinue docetaxel due to toxicity, allowing for pasritamig to be continued with continued clinical benefit, and limited adverse effects or negative impact on quality of life.

KLK2 represents a unique target for prostate cancer, providing specific targeting of prostate cancer cells while minimizing the risk of on-target/off-tumor toxicity. The safety profile of docetaxel is well established and given the distinct MoAs, overlapping toxicity should be limited when combined with pasritamig. The preliminary results from Study 78278343PCR1003 support the rationale for the combination of pasritamig and docetaxel (Section 2.2.1.2).

# 3. OBJECTIVES AND ENDPOINTS

**Table 5: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To determine whether treatment with pasritamig+docetaxel prolongs rPFS compared with docetaxel in participants with mCRPC who have progressed on at least one ARPI | rPFS (BICR-assessed per RECIST v1.1 and PCWG3) |
| **Key Secondary** | |
| To demonstrate additional clinical benefit for participants with mCRPC who have progressed on at least one ARPI treated with pasritamig+docetaxel compared with docetaxel | • OS<br>• Time to symptomatic progression<br>• Time to subsequent therapy<br>• Time to skeletal-related event |
| **Other Secondary** | |
| To further compare the clinical benefit of combination pasritamig+docetaxel to docetaxel | • Objective response rate<br>• Duration of response<br>• Time to PSA progression<br>• PSA response<br>• Duration of PSA response<br>• PFS2 |
| To characterize the safety profile of pasritamig+docetaxel | • Incidence and severity of AEs/SAEs<br>• Clinical laboratory test results |
| To evaluate the effect of treatment of pasritamig+docetaxel on HRQoL and participant experience | • Change from baseline in the HRQoL and symptom scales (BPI-SF, EORTC QLQ-C30, EORTC QLQ-PR25, EQ-5D VAS)<br>• Time to sustained worsening of pain (BPI-SF)<br>• Summarize EORTC IL 46 and the EQ-5D-5L |
| **Exploratory** | |
| • To assess the PK and immunogenicity of pasritamig<br>• To investigate biomarkers predictive of clinical response or resistance to pasritamig | • Serum concentration of pasritamig and incidence of anti-pasritamig antibodies<br>• Immunophenotyping, serum proteins (cytokines, etc), and circulating tumor DNA |

### ESTIMANDS

Study estimands are described in the Section 9.3.2.

### HYPOTHESIS

The hypothesis is that the combination of pasritamig+docetaxel will significantly improve rPFS compared with docetaxel in participants with mCRPC who have progressed on at least one ARPI.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a randomized, controlled, open-label international Phase 3 study in adult participants with mCRPC who have progressed on at least one ARPI. The KLK2-PASenger (78278343PCR3003)

study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of mCRPC. Approximately 800 participants will be randomly assigned in a 1:1 ratio to receive the combination of pasritamig+docetaxel vs docetaxel with standard prednisone. All participants must continue to receive background ADT during treatment or have had prior bilateral orchiectomy with castrate level testosterone (<50 ng/dL). Randomization will be stratified by sites of metastases (non-visceral, visceral-liver or visceral-other), LDH (normal vs abnormal at screening), ECOG (0 or 1 at screening), and prior PARP inhibitor use (yes or no).

The study will include a Screening Phase, a Treatment Phase, an EOT visit, and a Follow-up Phase, which consists of Post-Treatment Follow-up and Survival Follow-up subphases. The Screening Phase will begin up to 28 days prior to randomization. However, laboratory values must meet inclusion criteria within 14 days prior to randomization, except as noted in the SoA, (Table 1 and Table 2). Imaging can be performed within 42 days prior to randomization.

The Treatment Phase will extend from the start of study treatment until the last dose of study treatment (EOT). Participants in both arms should receive up to 10 doses of docetaxel (if tolerated) or until requirements for docetaxel discontinuation are met, per Table 12. After docetaxel completion/ discontinuation, participants in the experimental arm will continue to receive pasritamig. If pasritamig is discontinued prior to 10 doses of docetaxel, participants can continue to receive docetaxel up to 10 doses, or until criteria for docetaxel discontinuation are met (per investigator discretion). In the comparator arm, after completion/discontinuation of docetaxel, participants will complete the EOT visit. While receiving docetaxel, participants in the comparator arm will take continuous prednisone (5 mg orally twice per day) per the docetaxel label.

The EOT visit will occur within 42 days (±7 days) of the last dose of study treatment or start of subsequent anticancer therapy, whichever occurs first. Participants who reach EOT but have not yet had a BICR-confirmed rPFS event or started subsequent anticancer therapy, will enter the Post-treatment Follow-up Phase for evaluation of disease status and efficacy with in-person visits and assessments. Participants will enter the Survival Follow Up Phase following a BICR-confirmed rPFS event, start of subsequent anticancer therapy, or withdraw consent but still allow contact, whichever occurs first. Survival follow-up will continue every 12 weeks (±28 days) until death, loss to follow-up, or complete study withdrawal, whichever occurs first. During the Survival Follow-up Phase, data may be obtained by telephone or chart review.

Study treatment will be administered as described in Section 6.1 and will be discontinued following the criteria specified in Section 7. The frequency of study site visits and details of the procedures performed are outlined in the SoA (Table 1 and Table 2).

Planned interim and final analyses are described in Section 9.

An IDMC will be commissioned for the purposes of safety monitoring approximately every 6 months (or as needed) as defined in Section 10.2.7.

Efficacy, safety, PK, immunogenicity, PRO, biomarkers, PBMC, ctDNA, and serum protein will be assessed as indicated in the SoA (Table 1; Table 2; Table 3; Table 4).

A diagram of the study design is provided in Figure 1.

## 4.2. Scientific Rationale for Study Design

### 4.2.1. Blinding, Control, Study Phase/Periods, Treatment Groups

In the comparator arm, docetaxel will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active study treatment (ie, pasritamig). An open-label design is employed in this study to prevent participants randomized to the comparator arm from having to receive placebo (step-up and full dose) infusions corresponding to the infusion schedule of pasritamig, which would delay the initiation of active treatment. Prednisone will be administered with docetaxel in the comparator arm; however, prednisone will not be administered in the experimental arm. To maintain integrity of endpoint assessment, a BICR will be used to assess scans used for primary endpoint analysis (rPFS). Randomization will be used to minimize bias in the assignment of participants to the experimental arm (pasritamig+docetaxel) or comparator arm (docetaxel); to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms.

### 4.2.2. Biomarker Collection

Biomarker studies are designed to evaluate the clinical mechanisms of action, efficacy, and response to pasritamig and to identify potential subgroups of these participants that respond differently to pasritamig treatment.

The collected blood samples may be used for the following objectives: PBMCs for immunophenotyping and/or transcriptomics, serum for proteomics, and plasma for ctDNA analyses. Optional tumor biopsies may be collected from participants at select investigational sites for multi-omic assessment of tumor dependent mechanisms of response or resistance.
These studies will explore the following objectives:

- Assess pharmacodynamic biomarkers of immune-mediated anti-KLK2+ tumor activity of pasritamig+docetaxel, including T-cell phenotyping from PBMC and serum proteomic profiling.
- Identify tumor intrinsic and acquired biomarkers predictive of response or resistance to pasritamig+docetaxel, including but not limited to, changes in KLK2 expression; measuring soluble proteins associated with neuroendocrine differentiation; evaluating ctDNA for tumor burden, mutations (including baseline testing in BRCA1/2 unknown participants) and epigenomics-based transcriptional signatures.

Biomarker samples will be collected and tested in compliance with local regulations and may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

### 4.2.3. PK Assessments

Serum concentration-time data of pasritamig may help to assess the effect of participant baseline characteristics (demographics, laboratory variables, race, etc) as potential covariates affecting pasritamig serum exposure using nonlinear mixed-effects modeling.

If sufficient data are available, a PK/pharmacodynamic model may be explored to understand and characterize the relationship between serum concentrations of pasritamig and key efficacy, safety, and pharmacodynamics/biomarker data, to detect the influence of covariates, and to identify inter-individual variability in response.

### 4.2.4. MRU and PRO Evaluations

MRU data may be valuable in determining whether the treatment arms differ in terms of medical intervention needed for each arm of participants.

PRO data contribute to the totality of evidence and complement efficacy and safety findings to describe the participant experience, directly reported by the participant.

PRO and MRU data capture inputs required for cost-effectiveness modeling and help to communicate the value of treatment to patients, clinicians, regulators, and payers.

### 4.2.5. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand this information and provide their consent voluntarily will be enrolled. If applicable, the LDR must sign the ICF. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and patient preferences.

The primary ethical concern is that risks of pasritamig+docetaxel in this study population are not fully known. This study will evaluate the safety and clinical activity of this therapeutic combination. Participants will be closely monitored throughout the study for both safety and clinical benefit. All participants will undergo regular disease assessments to monitor the underlying disease and will discontinue if a favorable benefit-risk profile cannot be justified.

## 4.3. Justification for Dose

#### 4.3.1.1. Pasritamig

Dosing of pasritamig consists of 2 step-up doses (3.5 mg and 18 mg) followed by the target dose of 300 mg once every 6 weeks by IV administration.

The step-up and target doses of pasritamig for this study represent RP2D and were selected after review of the available nonclinical pharmacology, safety, efficacy, PK, and pharmacodynamics data from the monotherapy Study 78278343PCR1001 and Study 78278343PCR1003. Refer to Section 2.2.1.1, Section 2.2.1.2, and the latest version of the pasritamig IB and Addenda for further details.

#### 4.3.1.2. Docetaxel

Docetaxel will be administered at 75 mg/m$^2$ once every 3 weeks by IV administration per the approved label with a maximum of 10 doses.

The treatment label for docetaxel utilizes concomitant daily prednisone in mCRPC. Prednisone will be administered per the label in the comparator arm, but not in the experimental arm (see Section 2.3). Pre-dose medication will be administered in both arms per the label (see Section 6.9.1) to manage potential toxicities for both docetaxel and pasritamig.

### 4.4. End of Study Definition

The end of study/study completion is the last scheduled study assessment for the last participant in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

**Participant Study Completion Definition**

A participant is considered to have completed the study if the participant:

- died while on study OR
- remained on study at the time of the end of study (ie, did not meet the criteria for withdrawal from study, see Section 7.2).

## 5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days prior to randomization. Imaging can be performed within 42 days prior to randomization. Refer to Section 5.4, for conditions under which repetition of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. The investigator must consult with the appropriate Sponsor representative with any issues/questions related to entry criteria. Issues/questions must be resolved prior to participant enrollment into the study. Waivers are not allowed. For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

### 5.1. Inclusion Criteria

All potential participants must satisfy all the following inclusion criteria to be enrolled into the study. Participants must:

**Age**

1. Be ≥18 years of age at the time of informed consent or at least the legal age of majority in the jurisdiction in which the study is taking place.

**Disease Characteristics**

2. Have histologically confirmed adenocarcinoma of the prostate. Participants with primary (or documented evidence of conversion to) small cell carcinoma, carcinoid tumor, mixed NE carcinoma, large cell NE carcinoma, or sarcoma of the prostate are excluded.

3. Have disease that is metastatic at the time of the screening as determined by the investigator.

4. Have progressive disease defined as at least one of the following:
   - PSA level ≥2 ng/mL that has increased on at least 2 successive occasions at least 1 week apart.
   - Progressive disease or new lesion(s) in the lymph nodes, bones, or viscera as defined by RECIST v1.1 and/or in bone scan per PCWG3 while on medical or surgical castration.

**Prior Therapy Restrictions or Requirements**

5. Participants must receive ongoing ADT with a GnRH analog (agonist or antagonist) throughout the Treatment Phase or have had prior bilateral orchiectomy, and have serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening.

6. Have progressed on at least 1 novel ARPI but received no more than 2 different ARPI (eg, abiraterone acetate, apalutamide, enzalutamide, darolutamide) for any stage of disease. Must have discontinued ARPI before randomization into the study.

**Performance Status**

7. Have an ECOG performance status of 0 to 1 (Oken 1982).

**Renal Function**

8. Have an eGFR, calculated with the CKD-epi formula (at https://www.kidney.org/professionals/gfr_calculator), of >30 mL/min during the screening period. Participants with obstructive uropathy should have treatment prior to randomization (eg, foley catheter, nephrostomy tubes, etc).

**Hepatic Function**

9. Have the following laboratory values during the screening period:

| | ***Hepatic metastases*** | |
|---|---|---|
| | ***No known*** | ***Yes*** |
| AST | <1.5 x ULN | <3 x ULN |
| ALT | <1.5 x ULN | <3 x ULN |
| Total bilirubin | Normal, except in case of known congenital nonhemolytic indirect hyperbilirubinemias such as Gilbert's Syndrome: if total bilirubin is >1.5 × ULN, eligible if direct bilirubin is ≤1.5 × ULN | |

**Hematologic Values**

10. Have the following laboratory values during the screening period:
    - Hemoglobin ≥9.0 g/dL
    - Neutrophils ≥1.5 x $10^9$/L
    - Platelets ≥100 x $10^9$/L
    - **Note**, transfusion or growth factor usage within 14 days of randomization is not allowed.

**Sex and Contraceptive/Barrier Requirements**

13. Agree, while on study treatment and for 6 months after the last dose of study treatment, to:
    - Not donate gametes (ie, sperm) or freeze for future use for the purposes of assisted reproduction.
    - Wear an external condom, when transmission of sperm/ejaculate can occur.
    - If able to produce sperm and their partner is of childbearing potential, the partner must practice a highly effective method of contraception.

    See Appendix 3: Contraceptive and Barrier Guidance for details.

**Informed Consent**

14. Participant (or their legally designated representative) must sign an ICF.

15. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

## 5.2. Exclusion Criteria

Any potential participant who meets any of the following exclusion criteria will be excluded from participating in the study.

**Medical Conditions**

1. Known history of either brain or leptomeningeal prostate cancer metastases.
2. Patients with known BRCA 1/2 mutations (germline or somatic) who have not received treatment with a PARP inhibitor, unless not available or contraindicated.
3. Suspected or known allergies, hypersensitivity, or intolerance to pasritamig excipients (refer to the pasritamig IB and Addenda) or docetaxel excipients (Taxotere PI).
4. Not recovered from recent surgery.
5. Solid organ or bone marrow transplantation.
6. Active autoimmune disease within the 12 months prior to signing consent that requires systemic immunosuppressive medications (eg, chronic corticosteroid, methotrexate, or tacrolimus).

**Cardiovascular Dysfunction**

7. Any of the following within 6 months prior to first dose of study treatment:
   - severe or unstable angina,
   - myocardial infarction,
   - major thromboembolic events (eg, pulmonary embolism, cerebrovascular accident),
   - clinically significant ventricular arrhythmias or heart failure New York Heart Association functional classification Class II to IV.

   **Note:** Uncomplicated deep vein thrombosis is not considered exclusionary.

**Prior Malignancies**

8. Prior or concurrent second malignancy (other than the disease under study) because the natural history or treatment could interfere with study endpoints (see Appendix 5 on Allowed Recent Second or Prior Malignancies for details).

**Disease Characteristics**

9. Received cytotoxic chemotherapy for prostate cancer in any setting (eg, docetaxel, cabazitaxel, mitoxantrone, etc).

10. Received prior treatment with KLK-2-directed therapies.

11. Received prior treatment for prostate cancer with:
   - CD3 redirector therapies or
   - Radiopharmaceutical agents or
   - Immunotherapy agents for prostate cancer (eg, sipuleucel-T, PD-1 inhibitors, T-cell redirectors, costimulatory agents, etc) or
   - PARP inhibitors (other than for BRCA1/2 mutation) or
   - Any other investigational agent for the treatment of mCRPC.

**HIV Status**

12. Participants who are HIV-positive and meet any of the following:
   a) Detectable viral load (ie, $\geq$50 copies/mL) at screening.
   b) CD4+ count $\leq$300 cells/mm$^3$ at screening.
   c) AIDS-defining opportunistic infection within 6 months of screening.
   d) Receive treatment other than continued HAART. A change in HAART due to resistance/progression must occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

   **Note**: HAART that could interfere with study treatment is excluded (consult the Sponsor for a review of medications prior to enrollment).

**Viral Hepatitis Assessments**

13. Active hepatitis of infectious origin.

    a) Seropositive for hepatitis B: defined by a positive test for HBsAg. Participants with resolved infection (ie, participants who are HBsAg negative with positive antibodies to total hepatitis B core antigen [anti-HBc]) must be screened using RT-PCR measurement of HBV DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR (see Appendix 6).

    b) Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV) antibody.
    Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained at screening or within 3 months prior to first dose of study treatment.

    c) Other clinically active liver disease of infectious origin.

**Prior/Concomitant Therapy or Clinical Study Experience**

14. Received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study treatment. Non-live and non-replication-competent vaccines are allowed.

15. Received systemic glucocorticoids (doses >10 mg/day prednisone or equivalent) within 3 days prior to the first dose of study treatment. A single course of glucocorticoids is permitted as prophylaxis for imaging contrast (ie, for participants with allergies to contrast). If glucocorticoids were used to treat immune-related adverse events associated with prior therapy, ≥7 days must have elapsed since the last dose of corticosteroid.

16. Received external beam radiation therapy within 14 days prior to start of study treatment. However, if palliative focal radiation was used, the participant is eligible regardless of date of radiation.

**Other Exclusions**

17. Any condition which, in the opinion of the investigator, would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

    **Note**: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after randomization but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, the participant may still be eligible for participation in the study

based on the investigator's judgment. The Sponsor should be notified as soon as possible after administration of study treatment.

## 5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Carry a "wallet study card" for the duration of study participation. The participant must be provided with a "wallet study card" which must contain (a) study number, site number and participant's study ID number, (b) statement, in the local language(s), that the participant is participating in this clinical study, (c) investigator's name and 24-hour contact telephone number, (d) sponsor's name and 24-hour contact telephone number (for medical personnel only).
2. Agree to self-monitor for signs and symptoms of CRS (such as fever) and to seek immediate medical treatment.
3. Remain in a geographic area within 1 hour of access to emergency medical care during the first 48 hours after each treatment administration through the first 2 cycles, in case signs/symptoms related to CRS or neurologic symptoms including ICANS develop. This advice may be extended to later cycles if participants experience ≥ Grade 2 CRS or neurologic toxicity.
4. In the event of any neurologic symptoms, until they resolve, participants should refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery.

## 5.4. Screen Failures

**Mandatory Participant/Subject Identification and Enrollment Log Form**

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made.

**Participant/Subject Screening Log Form**

The investigator agrees to complete a participant/subject screening log tracking subjects from prescreening (as applicable) to randomization, to record reasons why screened participants were not enrolled, and to identify those participants that did not meet the eligibility criteria, to permit better understanding of participant population and enrollment at the site by the Sponsor. This study will use an RTSM system (eg, IWRS). The investigator will not generate screening logs directly from IWRS.

Individuals who do not meet all inclusion and exclusion criteria for participation in this study (and therefore considered a screen failure) may be rescreened one time at the discretion of the investigator. Retesting of abnormal screening laboratory values is allowed once during the screening period without requiring screen failure. The last laboratory result obtained prior to randomization will be used to determine eligibility. The measurements collected at the time closest to, but prior to, the start of study treatment administration will be defined as the baseline for safety assessment and treatment decision.

Rescreened participants must be assigned new participant numbers.

# 6. STUDY TREATMENT AND CONCOMITANT THERAPY

## 6.1. Study Treatments Administered

For this study, "study treatment" refers to pasritamig+docetaxel and docetaxel (Table 6).

**Table 6: Designation of Intervention(s)**

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Pasritamig<br>Docetaxel*<br>Prednisone**<br><br>Authorization status in the EU/EEA:<br><table><tr><td>Unauthorized</td><td>Docetaxel*</td></tr><tr><td>Unauthorized</td><td>Pasritamig</td></tr><tr><td>Authorized</td><td>Prednisone</td></tr></table><br>Authorized IMPs will be used in accordance with the terms of their marketing authorization.</td></tr>
<tr><td>Non-investigational Medicinal Product(s) (NIMP)/Auxiliary Medicinal Product(s) (AxMP)</td><td>Any GnRH analog (agonists or antagonists) under ATC code L02AE (such as leuprolide, goserelin, triptorelin, etc), or degarelix (ATC L02BX02), or relugolix (ATC L02BX04).<br>ADT<br><br>Technetium-99m ($^{99m}$Tc; radiotracer for bone scan)<br><br>Authorization status in the EU/EEA:<br><table><tr><td>Authorized<br>Authorized</td><td>ADT/ GnRH analog<br>$^{99m}$Tc</td></tr></table><br>Authorized NIMPs/AxMPs will be used in accordance with the terms of their marketing authorization.</td></tr>
<tr><td colspan="2">*Docetaxel is unauthorized IMP in the experimental arm (pasritamig+docetaxel); authorized IMP in the comparator arm (docetaxel).<br>**Prednisone is for the comparator arm of docetaxel.</td></tr>
</table>

Study treatment administration must be captured in the source documents and the CRF.

Pasritamig will be manufactured and provided under the responsibility of the Sponsor. Refer to the pasritamig IB and Addenda for a list of excipients.

All other study-specified medications are considered concomitant medications (see Section 6.9).

**Table 7: Description of Treatments: Pasritamig + Docetaxel arm**

| **Treatment Name** | Pasritamig (or JNJ-78278343) | Docetaxel |
|---|---|---|
| **Type** | Drug | Drug |
| **Dose Formulation** | Solution | Solution |
| **Unit Dose Strength(s)** | 18 mg/vial (5 mg/mL), 300 mg/vial (50 mg/mL) | 80 mg/vial (10 mg/mL), 80 mg/vial (20 mg/mL), 160 mg/vial (10 mg/mL) |
| **Dose Level(s)** | 1 step-up dose 3.5 mg, followed by 1 step-up dose 18 mg, followed by target dose of 300 mg once every 6 weeks until BICR confirmed rPFS. | 10 doses of 75 mg/m$^2$ once every 3 weeks, starting C1D15. The total dose should be recalculated when weight changes >10% from last calculated dose. |
| **Route of Administration** | IV infusion | IV infusion |
| **Administration instructions** | • Refer to IPPI for administration instructions.<br>• Pasritamig target dose should start at least 1 hour after completion of the docetaxel infusion.<br>• Pasritamig must NOT be administered as a bolus.<br>• Pasritamig: All step-up doses and the first target dose of pasritamig should be administered over a minimum duration of 1 hour.<br>• All subsequent doses may be administered over 30 minutes if no Grade ≥2 CRS or IRRs are observed.<br>• In the event of Grade 2 CRS or IRR, see corresponding Sections 6.6.4.1 and 6.6.4.2 for management instructions (eg, infusion rate change, interruption, or discontinuation).<br>• Participants who experience infusion-related Grade ≥2 CRS or IRR and subsequently tolerate at least 4 infusions without recurring Grade ≥2 CRS or IRR can be considered for shorter infusion durations after discussion with the Sponsor.<br>• In the event of AEs, refer to Section 6.6.1 for dose delay and dose reduction.<br>• In all cases of imminent surgery or major procedure requiring general anesthesia, it is recommended to interrupt dose administration and carefully monitor appropriate clinical laboratory data (eg, coagulation). Dose administration may be restarted when it is considered safe, according to the investigator's assessment. | • Docetaxel IV will be administered every 3 weeks prior to the pasritamig treatment dose.<br>• Administer as a 1-hour infusion.<br>• Refer to Table 18 for pre-dose medications for docetaxel.<br>• Continuous oral steroid will NOT be administered in this treatment arm.<br>• In the event of Grade 2 IRR, see corresponding Sections 6.6.4.1 and for management instructions (eg, infusion rate change, interruption, or discontinuation). |
| **Use** | Experimental | Experimental |
| **IMP** | Yes | Yes |
| **NIMP/AxMP** | No | No |
| **Sourcing** | Provided centrally by the Sponsor. | Provided centrally by the Sponsor. |
| **Packaging and Labeling** (Label info meets applicable regulatory requirements) | Single dose vial | Single dose vial |
| **Observation Period and Post-dose monitoring** | • Post-dose vital signs should be performed every hour (±30 minutes) for at least the first 2 hours post-dose for step-up dose 1, step-up 2, and first 2 target doses (C1D15 and C2D1). Following the third target dose (C3D1), vitals can be monitored post-infusion if clinically indicated.<br>• Following each dose, participants will be instructed to monitor for symptoms concerning for CRS. If temperature ≥38.0°C, shortness of breath, lightheadedness, confusion or any other neurologic symptoms, or generally feel unwell, they will be advised to seek immediate medical attention.<br>• Participant to remain within 1 hour of access to emergency medical care for at least 48 hours after each treatment administration through the first 2 cycles. | |

**Table 7: Description of Treatments: Pasritamig + Docetaxel arm**

| Treatment Name | Pasritamig (or JNJ-78278343) | Docetaxel |
|---|---|---|
| | • Participants will have a "wallet study card" to carry with them with pertinent information about the study treatment and study team contact information for the duration of study participation.<br>• Post-dose monitoring in the hospital or an appropriate healthcare setting is not required throughout this study unless certain toxicity criteria are met (refer to Section 6.6.4). If any of the specified toxicities occur, the participant will be hospitalized or observed in an appropriate healthcare setting for a minimum of 36 hours after the next study treatment administration to monitor for signs and symptoms. The duration of hospitalization or monitoring may be extended if determined to be necessary, in the opinion of the investigator or treating physician. | |

**Table 8: Description of Treatments: Docetaxel arm**

| Treatment Name | Docetaxel | Prednisone |
|---|---|---|
| **Type** | Drug | Drug |
| **Dose Formulation** | Solution | Tablet |
| **Unit Dose Strength(s)** | 80 mg/vial (10 mg/mL), 80 mg/vial (20 mg/mL), 160 mg/vial (10 mg/mL) | 5 mg |
| **Dose Level(s)** | 10 doses of 75 mg/m$^2$ once every 3 weeks starting C1D1. The total dose should be recalculated when weight changes >10% from last calculated dose. | 5 mg twice daily |
| **Route of Administration** | IV infusion | Oral |
| **Administration instructions** | • Administer as a 1-hour infusion.<br>• Refer to Table 18 for pre-dose medications for docetaxel.<br>• In the event of Grade 2 IRR, see corresponding Sections 6.6.4.1 and for management instructions (eg, infusion rate change, interruption, or discontinuation). | Starts with C1D1 with docetaxel. When docetaxel is completed, continue prednisone for at least 21 days after, then per provider discretion. |
| **Use** | Active comparator | Active comparator |
| **IMP** | Yes | Yes |
| **NIMP/AxMP** | No | No |
| **Sourcing** | Provided centrally by the Sponsor. | Provided centrally by the Sponsor. In some countries/territories, it can be provided locally by the study site, subsidiary, or designee. |
| **Packaging and Labeling** (Label info meets applicable regulatory requirements) | Single dose vial | Bottle |

## 6.2. Preparation/Handling/Storage/Accountability

Study treatment must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants in the study.

The study treatment administered to the participant must be documented on the treatment accountability form.

Refer to the study materials, such as IPPI, SIPPM or, if applicable, to the package insert, for all guidance on study treatment preparation, handling, storage, and disposal.

The investigator is responsible for ensuring that all study treatment received at the site is inventoried, accounted for throughout the study, stored and disposed of according to the Sponsor's instructions, in accordance with the protocol, study manuals and as indicated on the container label.

## 6.3. Assignment to Study Treatment

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 study arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by sites of metastases (non-visceral, visceral-liver or visceral-other; non-visceral includes metastatic either to bone, any lymph node, or both without clear evidence of metastasis to visceral organs at the time of screening and local-regional invasion [rectum, bladder]), LDH (normal vs abnormal at screening), ECOG (0 or 1 at screening), and prior PARP inhibitor use (yes or no). The RTSM system (eg, IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the participant. The requestor must use their own user identification and personal identification number when contacting the RTSM system and will then give the relevant participant details to uniquely identify the participant.

## 6.4. Blinding, Masking

As this is an open-label study, blinding procedures are not applicable.

## 6.5. Study Treatment Compliance

The study treatment may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Study treatment will be administered by qualified study site personnel and the details of each administration will be recorded in the CRF (including date, time of administration, and volume administered [where applicable]). Precautions associated with the use of the study treatment and prohibited concomitant medications will be reviewed with the participant.

Upon termination of the study, or at the request of the Sponsor or its designee, the pharmacist must return the study treatments to the Sponsor or its designee, after all treatment supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the Sponsor and the site. Additional details on study treatment compliance and accountability are provided in Section 6.2.

## 6.6. Dose Modification

Any dose adjustment must be overseen by medically qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present). Decisions regarding dose modification of the individual study treatments should be guided by the observed toxicity, the safety profile of each drug, the likelihood of causality to each agent, as well as each agent's potential contribution to any observed clinical benefit. Based on clinical experience from early phase studies, overlap in the anticipated toxicities of pasritamig and docetaxel is unlikely, and they are generally distinguishable – ie, hematologic toxicities and delayed/protracted hepatotoxicity are more likely associated with docetaxel, whereas CRS, and ICANS are more likely to be associated with pasritamig. Neutropenia, elevated liver enzymes, GI toxicity, and IRR may occur with both. As IRRs occur during treatment infusion, reactions should be attributable to the agent being infused at that time. In case a dose modification is necessary, the study treatment will be administered following the below guidelines.

### 6.6.1. Dose Modification of Pasritamig

The drug-related AE profile of pasritamig is largely driven by cytokine-mediated events, which are typically transient in nature and occur most frequently within the first 2 cycles. Dose delays (Table 9, Table 10, and Table 11) are the primary method for managing pasritamig-related AEs, though dose reductions can be incorporated if the toxicity is thought to be target mediated.

**Table 9: Dose Modification Guidelines for Toxicities Related to Pasritamig**

| Adverse Events | Pasritamig |
|---|---|
| **Hematological Adverse Event** | |
| Grade 3<br>- febrile neutropenia<br>- neutropenia with infection<br>- thrombocytopenia with bleeding<br>Grade 4 hematological AE (except lymphopenia) despite best supportive care. | **Withhold.**<br>Following recovery to Grade ≤2 or baseline, may continue the next administration of pasritamig at the same dose level or reduce by 1 dose level[b].<br>**Discontinue**[a], if reoccurring/ not manageable despite 2 prior dose reductions/ modifications and appropriate AE management (refer to Section 7.1). |
| **Non-hematological Drug-related Adverse Event** | |
| Grade ≥3 non-hematological drug-related AE (except clinically insignificant Grade 3 laboratory values)[c] | **Withhold.**<br>Following recovery to Grade ≤1 or baseline, may continue the next administration of pasritamig at the same dose level or reduce by 1 dose level[b].<br>**Discontinue**[a], if reoccurring/ not manageable despite 2 prior dose reductions/ modifications and appropriate AE management (refer to Section 7.1). |
| Grade 2 IRR, CRS, or ICANS | **Interrupt administration, if IRR**.<br>Following recovery to baseline, may continue the next administration of pasritamig at same dose (with slower rate of infusion if IRR). If these events occur during step-up dosage, the step-up dose schedule may continue.<br>Pre-dose medications should be given for next dose if CRS or IRR according to Table 17. |
| First occurrence of Grade 3 IRR, CRS, or ICANS. | **Stop administration, if IRR.**<br>Following recovery to baseline, may continue the next administration of pasritamig at the same dose level or reduce by 1 dose level[b]. Dose modification of pasritamig should be considered for participants who experience a first Grade 3 neurotoxicity event.<br>Pre-dose medications should be given for next dose if CRS or IRR according to Table 17. If no additional Grade ≥3 CRS or IRR occurs, subsequent doses may be re-escalated after consultation with the Sponsor. |
| Second occurrence of Grade 3 IRR, CRS, or ICANS, any occurrence of Grade 4 IRR, CRS, or ICANS, or any HLH/MAS. | **Discontinue**[a] study treatment. |

a. If the investigator feels that it is in the best interest of the participant to continue study treatment, study treatment may continue after discussion with the Sponsor.
b. Refer to Table 10 and Table 11 for dose reduction schedule and dosing. Dose re-escalation may be considered after discussion with the Sponsor.
c. Unless AE is controlled per institutional standard of care.

**Table 10: Dose Reduction Schedule for Pasritamig**

| Dose Reduction | Dose Level |
|---|---|
| Current dose | 300 mg |
| First dose reduction | 150 mg |
| Second dose reduction | 75 mg |

**Table 11: Guidelines for Restarting Pasritamig After Dose Delay**

| Last dose administered | Days since last dose administered | Action |
|---|---|---|
| Step-up dose 1 | ≤14 days | Proceed to step-up dose 2 (18 mg) |
| | >14 days | Restart pasritamig at step-up dose 1 (3.5 mg)[a] |
| Step-up dose 2 | ≤14 days | Proceed to target dose (300 mg) |
| | 15 to 42 days | Restart pasritamig at step-up dose 2 (18 mg)[a] |
| | >42 days | Restart pasritamig at step-up dose 1 (3.5 mg)[a] |
| Any dose treatment | ≤70 days | Continue pasritamig at last treatment dose |
| | >70 days | Restart pasritamig at step-up dose 1[a] after Sponsor approval |

a. See Table 17 for required pre-dose medications to be given for step-up dosage and target doses.

### 6.6.2. Dose Modification of Docetaxel

General guidance of dose modifications for docetaxel is provided in Table 12. Refer to the docetaxel package insert for detailed dose modification instructions. The total dose should be recalculated if the participant's weight changes >10% from the last calculated dose.

**Table 12: Dose Modification Guidelines for Docetaxel, Based on Toxicity**

| Toxicity | Dose Modification |
|---|---|
| **Hematologic** | |
| • Grade 2-3 neutropenia<br>• Platelets ≤100 x $10^9$/L | **Withhold**.<br>May resume once neutropenia resolves to Grade ≤1 and platelets ≥100 x $10^9$/L. |
| • Grade 3 neutropenia with fever<br>• Grade 4 neutropenia | **Withhold.**<br>May resume once neutropenia resolves to Grade ≤1 and fever has resolved, at a docetaxel dose of 60 mg/m$^2$. Dose may be increased per investigator discretion if symptoms/ toxicities are stable or improve.<br>If continued/ recurrent toxicity at the reduced dose level, treatment should be discontinued. |
| **Non-Hematologic** | |
| • Severe or cumulative cutaneous reactions<br>• Moderate neurosensory signs and/or symptoms | **Withhold.**<br>May resume once resolves or improves to baselines at a docetaxel dose of 60 mg/m$^2$. Dose may be increased per investigator discretion if symptoms/ toxicities are stable or improve.<br>If continued/ recurrent toxicity at the reduced dose level, treatment should be discontinued. |
| Grade 2 AST and/or ALT | **Withhold.**<br>May resume once resolves to Grade ≤1 or baseline. |
| Grade ≥ 3 AST and/or ALT | **Permanently discontinue docetaxel.** |
| Bilirubin >ULN | **Withhold.**<br>May resume once bilirubin < ULN (or baseline if Gilbert's). |
| Grade >3 neurosensory signs and/or symptoms | **Permanently discontinue docetaxel.** |
| Severe hypersensitivity | **Permanently discontinue docetaxel** if history of severe hypersensitivity reactions. |

### 6.6.3. Dose Delay Guidance

A participant for whom treatment was delayed should be assessed regularly to ensure adequate supportive care is being administered and for improvement of toxicity. Participants must meet retreatment criteria for docetaxel (per Section 6.6.2 based on product labeling and per local regulations and guidelines) and/or pasritamig (per Section 6.6.1), in accordance with protocol, prior to redosing with the respective agents. In the event that the AE may be attributed to both docetaxel and pasritamig in the experimental arm, upon restarting, docetaxel should be dose reduced first. See Appendix 12 for Dose Modification Schema.

**Comparator Arm**

**Docetaxel:** If docetaxel administration is delayed due to ongoing toxicities by more than 2 weeks (±3 days) from the scheduled date of administration (ie, >38 days since their last dose), then docetaxel should be discontinued per investigator discretion. If ≤38 days, dose may be administered once retreatment criteria are met with modifications per Section 6.6.2.

**Experimental Arm**

**Pasritamig + Docetaxel scheduled day:** If one or both drugs cannot be administered, delay both and re-evaluate approximately weekly for retreatment. If retreatment criteria are met within 2 weeks (±3 days) of last administered dose of docetaxel (ie, ≤38 days since their last dose), then both pasritamig and docetaxel can be administered on the same day. Schedule of subsequent doses should be adjusted based on the day of re-administration. If treatment criteria for pasritamig are not met within 38 days since last dose of docetaxel, then docetaxel should be restarted alone, and participant should continue to be re-evaluated for pasritamig per retreatment criteria. Schedule of subsequent doses should be adjusted based on the day of administration.

When retreatment criteria for pasritamig are met, refer to Table 11 for guidelines on restarting therapy after a dose delay and Section 7.1 for discontinuation of study treatment. Schedule of subsequent doses should be adjusted based on the day of re-administration.

**Docetaxel only scheduled day:** If docetaxel is delayed due to ongoing toxicities by more than 2 weeks (±3 days) from the scheduled date of administration (ie, >38 days since their last dose), then docetaxel should be discontinued per investigator discretion. If ≤38 days, dose may be administered once retreatment criteria are met with modifications according to Section 6.6.2. Schedule of subsequent doses should be adjusted based on the day of administration.

The Medical Monitor may be consulted if there are questions regarding restarting protocol treatment after dose delays.

### 6.6.4. Management Guidelines for Potential Toxicities

Best supportive care should be administered, as applicable. Appropriate resuscitation equipment and a qualified medical provider should be readily available during the administration of study treatment. Resources necessary for resuscitation include agents such as epinephrine and aerosolized bronchodilator; medical equipment such as oxygen, airway management equipment

and a defibrillator. Vital signs and laboratory parameters must be monitored per institutional guidelines until the toxicity has normalized.

In case of the occurrence of a Grade ≥2 study treatment-related neurologic toxicity including ICANS, a prior Grade ≥2 CRS, or a prior Grade ≥3 IRR that does not resolve to Grade ≤1 within 72 hours, the participant will need to be hospitalized or observed in an appropriate healthcare setting for a minimum of 36 hours after the next study treatment administration to monitor for signs and symptoms related to CRS, IRR, or neurologic toxicity. The duration of hospitalization or monitoring may be extended if determined to be necessary, in the opinion of the investigator or treating physician.

#### 6.6.4.1. Management of Infusion-Related Reactions (IRR)

Symptoms of IRR can include the following, but are not limited to: wheezing, flushing, hypoxemia, fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension, and etc). Participants who experience IRRs should have symptoms managed according to the recommendations provided in Table 13. See Table 15 for guidance on diagnosis of IRR vs CRS reaction.

All Grade ≥3 IRRs determined to be related to pasritamig treatment are considered AESIs and should be reported following the requirements as specified in Section 8.4.6.3.

Prophylactic medications must be administered according to Table 17 prior to the next administration of study treatment for cases of Grade ≥2 IRR.

**Table 13: Guidelines for Management of IRRs**

| Graded according to NCI-CTCAE 5.0 | Treatment/Drug |
|---|---|
| **Grade 2**<br>Mild or moderate reaction: requires therapy or interruption of administration but responds promptly to symptomatic treatment | **Interrupt administration, if still receiving infusion:** Start IV fluids; give diphenhydramine 50 mg IV (or equivalent) or paracetamol 500 to 1000 mg (acetaminophen) or both; consider glucocorticoids and bronchodilator therapy; monitor participant closely until recovery from symptoms.<br>**Complete administration, if applicable:** Following recovery from symptoms, administration may be restarted at a slower rate for administration (see IPPI for details). Monitor participant closely.<br>**Symptoms recur:** Stop study treatment administration; administer diphenhydramine 50 mg IV and monitor participant until resolution of symptoms. The amount of study treatment administered must be estimated and recorded on the CRF. Treatment rechallenge at next scheduled dose is at the discretion of investigator. |
| **Grade 3 or 4**<br>**Grade 3**: prolonged (eg, not rapidly responsive to symptomatic medication or brief interruption of administration); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)<br>**Grade 4**: life-threatening; urgent intervention indicated (eg, vasopressor or ventilator support indicated) | **Stop administration (if applicable)**: Start IV saline infusion. Recommend the following treatment and any other therapies deemed necessary to manage the event: bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent).<br>Investigators should follow institutional guidelines for the treatment of anaphylaxis.<br>Monitor until medically stable, per the investigator's medical judgment.<br>Refer to Table 9 for treatment rechallenge. |

#### 6.6.4.2. Management of Cytokine Release Syndrome (CRS)

As the specific mode of action of pasritamig is based on the binding and activation of T-cells and the release of soluble factors including cytokines into the tumor environment, AEs of CRS should be anticipated. Clinical symptoms indicative of CRS may include, but are not limited to, fever (with or without rigors), arthralgia, nausea, vomiting, tachypnea, hypoxia, tachycardia, hypotension, headache, confusion, tremor, delirium, dyspnea, pulmonary edema, and capillary leak. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, renal and hepatic failure, and DIC. Participants should be closely monitored for early signs and symptoms indicative of CRS. Study treatment administration should be interrupted immediately upon observation of clinical symptoms indicative of CRS. Trained clinical personnel should be prepared to intervene in the event of CRS, and the resources described in Table 14 should be available.

Laboratory testing to monitor for DIC, a manifestation of CRS, should be carried out in addition to daily monitoring of chemistry and hematology assessments (including ferritin and C-reactive protein when fever or other signs of potential CRS are present). Additionally, pulmonary, renal, and hepatic function will be monitored closely. Rarely, severe CRS can evolve into a presentation consistent with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) that may require additional therapy. In these cases, the following laboratory testing

should be performed: ferritin, lactate dehydrogenase, soluble CD25, and cytokines (such as interferon-gamma [IFN-γ] and interleukin [IL]-6), and serum levels of fibrinogen (Neelapu 2018).

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. Cultures and imaging should be considered, the clinical signs and symptoms should determine which tests are appropriate.

CRS and IRR can also have overlapping symptoms. Please see Table 15 for guidance on the diagnosis of IRR vs CRS reactions.

All Grade ≥3 CRS events and any HLH/MAS are considered AESIs and should be reported following the requirements as specified in Section 8.4.6.3.

**Guidelines for Grading CRS**

Toxicity grading for CRS based on the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines (see Table 14).

**Guidelines for the Treatment of CRS**

Guidelines for the management of CRS are provided in Table 14. At the first sign of CRS (such as fever), administration of study treatment should be interrupted (if possible), and the participant should be evaluated for hospitalization or observation in an appropriate healthcare setting, if not already hospitalized. In case of a CRS event, vital signs and oxygen saturation should be monitored until normalized, at a frequency of at least every 6 hours, during hospitalization or monitoring.

Recommendations for the clinical management of CRS include treatment with tocilizumab (Tocilizumab PI). Therefore, sites must ensure that tocilizumab is available prior to the administration of any dose of study treatment. Administration of tocilizumab should be based on symptoms rather than CRS grading; additionally, tocilizumab may be administered according to institutional standard of care guidelines.

Anakinra has been used for the treatment of HLH/MAS and more recently for CRS in CAR-T treatments at doses of 100 mg SC daily for 7 days (Bami 2020; Strati 2020). For cases of CRS that do not respond to tocilizumab, mAbs targeting cytokines (eg, anti-IL-1, anti- TNF-α) may be used based on institutional standards.

The use of myeloid growth factors, particularly GM-CSF, should be avoided during CRS.

The date and time of medication administration as well as the name and dosage regimen of medications used to manage CRS must be recorded in source documents and the CRF.

Prophylactic medications must be administered according to Table 17 prior to the next study treatment administration.

**Table 14: Guidelines for the Management of Cytokine Release Syndrome**

| CRS Grade[a] | Presenting Symptoms | Tocilizumab[b] | Corticosteroids |
|---|---|---|---|
| **Grade 1** | Temperature ≥38˚C[c] | May be considered.[f] | NA |
| **Grade 2** | Temperature ≥38˚C[c] with either:<br>Hypotension responsive to fluids and not requiring vasopressors.<br>OR<br>Oxygen requirement of low-flow nasal canula[e] or blow-by | Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).<br>Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental $O_2$.<br>Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. | Manage per guidance below if no improvement within 24 hours of starting tocilizumab. |
| **Grade 3** | Temperature ≥38˚C[c] with either:<br>Hypotension requiring one vasopressor with or without vasopressin.<br>OR<br>Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask | Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).<br>Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen.<br>Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. | If no improvement, administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (eg, 10 mg IV every 6 hours).<br>Continue corticosteroids use until the event is Grade ≤1, then taper over 3 days. |
| **Grade 4** | Temperature ≥38˚C[c] with either:<br>Hypotension requiring multiple vasopressors (excluding vasopressin).<br>OR<br>Oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) | Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).<br>Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen.<br>Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. | As above or administer methylprednisolone 1000 mg IV per day for 3 days per investigator discretion.<br>If no improvement or if condition worsens, consider alternate immunosuppressants[e]. |

Source: Modified based on Kymriah™ (tisagenlecleucel)

a. Grading is per Lee 2019 (ASTCT guidelines). CRS grade is determined by the most severe event. All other AEs should be graded using NCI-CTCAE Version 5.0.
b. Refer to tocilizumab prescribing information for details (Tocilizumab PI).
c. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or corticosteroids).
d. Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.
e. mAbs targeting cytokines anti-T-cell therapies may be considered based on institutional standards for unresponsive CRS.
f. Tocilizumab may be considered in participants with Grade 1 CRS who are at high risk of progressing to a higher grade CRS (eg, with comorbidities or high tumor burden), for whom a higher grade CRS would be clinically detrimental (eg, elderly), who are clinically progressing towards a higher grade CRS (eg, blood pressures decreasing, oxygen saturation decreasing), who have high-grade fever >24 hours not responding to supportive measures, or per institutional guidelines.

**Table 15: Differentiating between CRS, IRR, and ICANS**

| | IRR | CRS | ICANS |
|---|---|---|---|
| **Key Symptoms** | • Allergic/hypersensitivity (eg, chills, flushing, fatigue, itching, cough, urticaria)<br>• Bronchospasm<br>• Gastrointestinal issues like nausea and vomiting can also occur | • Fever (≥38°C)<br>• Hypotension<br>• Hypoxia | • Neurologic (eg, confusion, aphasia, altered levels of consciousness, headache)<br>• Seizures |
| **Onset** | During or immediately after infusion (within 2 hours after infusion completion) | Hours to days after infusion (usually develops later than IRR) | Typically, after CRS symptoms |
| **Fever** | Absent or mild | Present (≥38°C) | Can be present, but less specific than for CRS |
| **Main Drug Interventions** | • IV fluids<br>• Tylenol<br>• H1/H2 receptor antagonist<br>• Glucocorticoids<br>• Bronchodilators<br>• Epinephrine (recommended for Grade 3 or higher)<br>• Methylprednisolone (recommended for Grade 3 or higher) | • Supplemental $O_2$<br>• IV fluids<br>• Tocilizumab (recommended for Grade 2 or higher)<br>• Corticosteroids (recommended for Grade 2 or higher)<br>• Vasopressors (Grade 3 or higher) | • Manage CRS, if present<br>• Dexamethasone (recommended for Grade 2 or higher) |
| **Tocilizumab Response** | Not responsive | Typically responsive | Not typically responsive |
| **Pasritamig Phase 1 Reported AE at RP2D (Related TEAE)** | ~20% (all are Grade 1 and Grade 2). | <10% (all are Grade 1)<br>Median time of CRS onset is within 1 day, relative to most recent dose | None |

#### 6.6.4.3. Management of Neurologic Adverse Events

Severe or serious neurotoxicity, including ICANS, can occur with pasritamig treatment. Early recognition of neurotoxicity is critical to management. Therefore, participants should be monitored for neurotoxicity including, but not limited to, ICANS; speech disorders; convulsions; disturbances in consciousness, confusion or disorientation, and balance disorders. Participants should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible CNS abnormalities, such as new onset of headache or mental status changes. If neurotoxicity or ICANS events are suspected, the Sponsor's Medical Monitor must be consulted. Refer to Table 15 for guidance on the diagnosis of IRR, CRS, and ICANS.

Neurologic/psychiatric AEs that do not meet criteria for ICANS will be graded per NCI-CTCAE, Version 5.0 and managed per institutional standards. ICANS events will be graded per the ASTCT guidelines summarized in Table 16, which also includes management recommendations (Lee 2019).

Any Grade ≥3 pasritamig-related neurotoxicity and Grade ≥2 ICANS event, are considered AESIs and should be reported following the requirements as specified in Section 8.4.6.3.

**Table 16: ASTCT Grading and Recommended Management of ICANS**

| ICANS Grade[a] | Presenting Symptoms[b] | Concurrent CRS | No Concurrent CRS |
|---|---|---|---|
| **Grade 1** | ICE score 7-9[c] or depressed level of consciousness[d]: awakens spontaneously. | Management of CRS as appropriate per Table 14.<br>Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion. | Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion.<br>Consider dexamethasone[e]. |
| | | Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. | |
| **Grade 2** | ICE score-3-6[c] or depressed level of consciousness[d]: awakens to voice. | Administer tocilizumab per Table 14 for management of CRS.<br>If no improvement after starting tocilizumab, administer dexamethasone[e] 10 mg IV every 6 hours if not already taking other glucocorticoids. Continue dexamethasone[e] use until the event is Grade ≤1, then taper. | Administer dexamethasone[e] 10 mg IV every 6 hours.<br>Continue dexamethasone[e] use until the event is Grade ≤1, then taper. |
| | | Consider non-sedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. | |
| **Grade 3** | ICE score-0-2[c] or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either:<br>• any clinical seizure, focal or generalized, that resolves rapidly, or<br>• non-convulsive seizures on EEG that resolve with intervention, or increased ICP: focal/local edema on neuroimaging[d]. | Administer tocilizumab per Table 14 for management of CRS.<br>In addition, administer dexamethasone[e] 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone[e] use until the event is Grade ≤1, then taper. | Administer dexamethasone[e] 10 mg IV every 6 hours.<br>Continue dexamethasone[e] use until the event is Grade ≤1, then taper. |
| | | Consider non-sedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. | |
| **Grade 4** | ICE score-0[c] or depressed level of consciousness[d] either:<br>• participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or<br>• stupor or coma, or seizures, either:<br>• life-threatening prolonged seizure (>5 min), or<br>• repetitive clinical or electrical seizures without return to baseline in between,<br>or motor findings[f]:<br>• deep focal motor weakness such as hemiparesis or paraparesis,<br>or increased ICP/cerebral edema[g], with signs/symptoms such as:<br>• diffuse cerebral edema on neuroimaging, or<br>• decerebrate or decorticate posturing, or<br>• cranial nerve VI palsy, or<br>• papilledema, or<br>• Cushing's triad. | Administer tocilizumab per Table 14 for management of CRS.<br>Consider administration of methylprednisolone 1000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1000 mg IV per day for 2 or more days, per investigator discretion. | Consider administration of methylprednisolone 1000 mg IV per day for 3 days; if improves, then manage as above. |
| | | Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.<br>Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed.<br>In case of increased ICP/cerebral edema, refer to institutional guidelines. | |

a Grading per ASTCT guidelines (Lee 2019). ICANS severity is determined by the most severe event. All other neurologic AEs should be graded using NCI-CTCAE Version 5.0.

b Management is determined by the most severe event not attributable to any other cause.

c If the participant is arousable and able to perform mental status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention (ICE tool; see Table 19).

**Table 16: ASTCT Grading and Recommended Management of ICANS**

| ICANS Grade[a] | Presenting Symptoms[b] | Concurrent CRS | No Concurrent CRS |
|---|---|---|---|

d Attributable to no other cause.
e All references to dexamethasone administration are dexamethasone or equivalent.
f Tremor and myoclonus associated with immune effector cell therapies should be graded according to CTCAE v5.0, but these events do not influence ICANS grading.
g Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. Grade the event according to NCI-CTCAE v5.0.

Recovery of any grade neurotoxicity to baseline must occur before subsequent administration of study treatment. Dose modification of pasritamig may be considered for participants who experience a first Grade 3 neurotoxicity event. Participants who experience a second Grade 3 neurotoxicity or any Grade 4 neurotoxicity must permanently discontinue study treatment.

#### 6.6.4.4. Management and Prevention of Prostatitis

As KLK2 is also observed on normal prostate cells, any normal prostate cells are also expected to be targeted by pasritamig for participants with residual prostate or local tumor tissue. If prostatitis occurs, participants should be treated per institutional standards including catheterization and a urologic consultation as indicated.

### 6.7. Continued Access to Study Treatment

The LTE or DA-LTE phase may be initiated when site receives notification from the sponsor to initiate the start of the LTE or DA-LTE. Participants who are benefiting from the study treatment, as determined by their investigator, will be able to receive continued access via LTE (Section 10.10) and/or DA-LTE (Section 10.11) until 3 years after market authorization of pasritamig in the country the participant resides or the company ends the study. Local regulations on continued access will always take precedence.

Plan for continued access stated in this protocol may change if new information becomes available during the study or program.

### 6.8. Treatment of Overdose

For this study, any dose of pasritamig or docetaxel greater than >25% of the planned dose will be considered an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Sponsor's Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor's Medical Monitor, whether study treatment must be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until pasritamig or docetaxel can no longer be detected systemically (at least 80 days for pasritamig).
- Obtain a blood sample for PK analysis as soon as possible.
- Document the quantity of the excess dose in the CRF.

## 6.9. Prior and Concomitant Therapy

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the source document and CRF from the time of signing of the ICF until 42 days after the last dose of study treatment or until starting subsequent therapy for prostate cancer, whichever occurs first. This includes any concomitant therapies and any medications used to treat or support AEs or SAEs. Recorded information will include a description of the type of therapy, duration of use, dosage, route of administration, and indication. Concomitant therapies should also be recorded beyond the reporting period for related SAE's.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### 6.9.1. Required Pre-dose Medications

Participants must be premedicated prior to each study treatment administration as noted in Table 17 and Table 18. All pre-dose medications must be given within 2 hours prior to administration of pasritamig. Pre-dose medications for docetaxel are noted in Table 18. Additional pre-dose medications may also be used per investigator discretion.

**Table 17: Pre-dose Medication and Other Prophylactic Medications for Pasritamig**

| **Required Pre-dose Medications** | | | |
|---|---|---|---|
| **Medication** | **Dose** | **Route of Administration** | **Cycle/Day** |
| Glucocorticoid[a] | Dexamethasone (16 mg) or equivalent | IV or Oral | Required only for step-up doses and first target dose in Cycle 1 (C1D1, C1D8, C1D15).<br>Participants who receive 8 mg of dexamethasone before docetaxel should only receive 8 mg of dexamethasone before administration of pasritamig on the same day |
| Antihistamine | Diphenhydramine (50 mg) or equivalent | IV or Oral | Required only for step-up doses and first treatment dose in Cycle 1 (C1D1, C1D8 and C1D15). Optional for all other doses. |
| Antipyretic | Paracetamol/ acetaminophen 500 mg to 1000 mg (or equivalent) | IV or Oral | Required only for step-up doses and first treatment dose in Cycle 1 (C1D1, C1D8 and C1D15). Optional for all other doses. |
| **Required pre-dose medications for cases of *Grade ≥2 CRS or IRR*** | | | |
| • Treat with pre-dose medications as above.<br>• If no reactions are observed then administer half (ie, 8 mg) the glucocorticoid dose for the following study treatment administration.<br>• Glucocorticoids and other pre-dose medications may be omitted if no further Grade ≥2 CRS or IRR events occur after 2 consecutive study treatment administrations.<br>• For recurrent Grade 1 IRR, consider premedicating with antipyretic and antihistamine. | | | |

[a] See Appendix 8 for glucocorticoid conversion table and Appendix 9 for glucocorticoid premedication schema.

**Table 18: Pre-dose Medications for Docetaxel (Both Treatment Arms)**

| | Required Pre-dose Medications | | | |
|---|---|---|---|---|
| **Treatment Arm** | **Medication** | **Dose** | **Route of Administration** | **Cycle/Day** |
| Docetaxel | Dexamethasone or equivalent | 8 mg | Oral | -12hr, -3hr and -1hr prior to docetaxel administration |
| Pasritamig + Docetaxel[a] | Dexamethasone or equivalent | 8 mg twice daily | Oral | For 3 days starting 1 day prior to docetaxel administration.<br>Participants who receive 8 mg of dexamethasone before docetaxel should only receive 8 mg of dexamethasone before pasritamig on the same day |

[a] Continuous oral daily prednisone with docetaxel chemotherapy will only be administered for the comparator arm (docetaxel), not for the experimental arm (pasritamig+docetaxel) in this study.

### 6.9.2. Permitted Therapies and Treatments

The following concomitant medications or treatments are permitted in the study:

- Palliative radiation for existing lesions per institutional standards is permitted, will be counted as a TSP and/or TSRE and data should be captured on the CRF page. Radiotherapy to asymptomatic new lesions may be permitted in select cases after discussion with Sponsor. If palliative radiation is administered, any toxicities from radiation should resolve to Grade 1 or baseline or be adequately managed with supportive care before resuming treatment.
- Bone protective agents, such as denosumab and bisphosphonates, unless contraindicated. Participants should be on a stable dose, or at least have started one, prior to randomization if used.
- ADT: Continuous treatment with a GnRH analog (agonists or antagonists), if not previously surgically castrated, is mandatory for all participants. The choice of GnRH analog is at the discretion of the investigator.
- Growth factor support, erythropoietin-stimulating agents, and transfusions such as red blood cells and platelets are permitted to treat or prevent symptoms or signs of neutropenia, anemia, or thrombocytopenia according to local standards of care while on study. GM-CSF agents should be avoided during periods of highest risks for CRS. Participants must be without transfusions or growth factor support within 14 days of randomization.
- 5-alpha reductase inhibitors are permitted.

### 6.9.3. Prohibited or Restricted Medications

The following medications are prohibited or restricted during the study. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Any systemic anticancer therapy, including: other systemic agents that target androgen axis such as ARPI or CYP17 inhibitors (except for continued GnRH analog); immunotherapy; targeted therapy; radiopharmaceutical therapy (such as radium Ra-223 dichloride, strontium [89Sr], or samarium [153Sm]); radioligand therapy; cytotoxic chemotherapy; ketoconazole; or, experimental or investigational therapy (other than pasritamig).
- Only in the investigational arm with pasritamig: systemic glucocorticoid more than 10 mg daily of prednisone or equivalent other than for pre-dose medication/prophylaxis or management of AEs. Glucocorticoids may also be used as prophylaxis prior to administering imaging contrast material. No restriction in the comparator arm.
- Cyproterone acetate.
- In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, due to reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (eg, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor, per docetaxel local labeling and/or local practice guidelines.

## 7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Treatment

The participant should remain on study treatment until confirmed radiographic progression by BICR, or unless otherwise specified in criteria below. Study treatment should be continued for participants who have increasing PSA values in the absence of radiographic progression or unequivocal clinical progression. Although serial PSA values will be measured on this study, progression or change in PSA values is not considered a reliable measure of disease progression and should not be used as an indication alone to discontinue study treatment (Sandhu 2013).

Pasritamig or docetaxel (up to 10 doses) treatment beyond progression is allowed at the investigator's discretion if the participant has confirmed radiographic progression but not unequivocal clinical progression and alternate treatment is not initiated (refer to Section 8.2.2 for additional details).

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment. The participant should remain on study in the Follow-up Phase unless the participant specifically withdraws consent from the whole study. If the participant withdraws consent for only one of the study treatments in

the experimental arm (pasritamig or docetaxel), the other study treatment can be continued per investigator discretion.

- Investigator decision (as they believe it is in the best interest of the participant to discontinue study treatment).
- The participant received concurrent (non-protocol allowed) anticancer treatment.
- BICR confirmed radiographic disease progression per RECIST v1.1 or PCWG3 unless judged by the investigator to be in the best interest of the participant to continue study treatment after obtaining approval from the Sponsor's Medical Monitor.
- Intercurrent illness that prevents further administration of study treatments.
- If administration of pasritamig is interrupted consecutively for more than 100 days, study treatment must be permanently discontinued, unless otherwise agreed to by the Sponsor's Medical Monitor and the investigator based on evidence of clinical benefit.
- Grade 3 non-hematologic drug-related AE reoccurring despite 2 dose reductions and BSC, unless otherwise agreed to by the Sponsor's Medical Monitor and the investigator based on evidence of clinical benefit. Any Grade 4 non-hematologic drug-related AE except for laboratory findings that recover to Grade ≤1 within 14 days.
- Grade 4 hematologic drug-related AE (except lymphopenia) reoccurring despite 2 dose reductions and BSC, unless otherwise agreed to by the Sponsor's Medical Monitor and the investigator based on evidence of clinical benefit. During step-up dosage, participants with Grade 4 hematological drug-related AE (except Grade 4 lymphopenia) should be discontinued.
- Hy's Law criteria are met, as defined as: ALT or AST value ≥3x ULN, total bilirubin ≥2x ULN, and ALP ≤2x ULN, with no alternative etiology, except:
- For participants with baseline Grade 2 elevation of ALT or AST and/or Grade 2 elevation in total bilirubin, modified Hy's law criteria, are defined as: ALT or AST >3x baseline OR >8x ULN, whichever is lower, combined with total bilirubin >2x baseline AND >3x ULN, with no alternative etiology.
- Grade 3 IRR, CRS, or ICANS that reoccurs after 2 doses of study treatment.
- Grade 4 IRR, CRS, or ICANS.
- Any HLH/MAS.

Following treatment discontinuation, participants clinically able to return for evaluation should complete the EOT visit. The primary reason for treatment discontinuation must be documented in the source documents and CRF.

If a participant discontinues study treatment for any reason, the end-of-treatment assessments must be obtained and scheduled assessments per protocol should be continued until rPFS by BICR. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant.

Docetaxel is completed when a participant has received up to 10 doses or met any reasons for docetaxel discontinuation as per Table 12. Participants will be allowed to continue with pasritamig in the experimental arm. If any reason for pasritamig discontinuation is met as per Table 9,

participants can continue to receive docetaxel per investigator discretion in the experimental arm to the maximum of 10 doses.

## 7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent (different options described below)

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. When a participant withdraws consent as described on the ICF by the participant, further data collection will be limited to what the participant agrees to. The participant should (where applicable) be provided with an optional withdrawal informed consent, which presents the different study withdrawal options.

**Study Withdrawal Options**

There are multiple ways a participant can withdraw from the study partly or fully:

1. Participant can stop study treatment and continue study visits or phone calls.
2. Participant can stop study treatment and reduce the number of clinical visits or information that is being collected for the study.
3. Participant can stop study treatment and stop any further study visits and procedures but allow direct or indirect contact. This may include (as permitted by local law and regulations):
    a. Telephone/video calls, text messages, email, standard mail, fax, social media, or other contact with:
        - Participant
        - Relatives or identified support person of participant
        - Participant's physicians or other medical professional(s)

    **Note**: Details regarding these contacts must be properly documented in source records, including responses from participants.
    b. Review of any available medical records
    c. Insurance records
    d. Database searches
    e. Use of locator agencies
4. Participant can stop study treatment, stop any further study visits and procedures, and stop any direct or indirect contact. Public record searches and/or social media may still be used as permitted by local law.

Prior to a participant selecting option 4, the investigator must offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described in option 2 or 3 above. Potential reasons for which participants may want to withdraw from the study and options to address

participant's concerns are described in Appendix 13. Complete withdrawal of consent (option 4 above) must be an infrequent occurrence in clinical studies (Rodriguez 2015), therefore, prior to the start of the study the Sponsor and the investigator must discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

### 7.2.1. Withdrawal From the Use of Study Samples

**Withdrawal From the Optional Study Samples**

A participant who withdraws from the study or the optional study samples will have the following options regarding the optional study sample(s):

- The collected sample(s) will be retained and used in accordance with the participant's original separate informed consent for optional study samples.
- The participant may withdraw consent for optional study sample(s), in which case the tissue sample(s) will be returned, and no further testing will take place. To initiate the sample return process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the optional tissue samples and to request sample return. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample return.

**Withdrawal From the Use of Study Samples**

The participant can withdraw consent for use of study samples, including optional study samples (refer to Section 10.2.6). If consent is withdrawn, samples will be destroyed after they are no longer needed for the clinical study. However, tissue samples will be returned to the clinical site after they are no longer needed. Further details of sample retention can be found in the main ICF.

## 7.3. Lost to Follow Up

To reduce the chances of a participant being deemed lost to follow up, attempts should be made prior to study entry to obtain contact information from each participant, eg, telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site, despite all reasonable efforts documented in the participant's medical records. Reasonable effort includes, where possible, 3 telephone calls, emails or messaging apps, a certified letter to the participant's last known mailing address, or local equivalent methods.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

Site personnel will attempt to collect the overall survival status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. The site may engage a third party to search public sources for vital status information. If vital status

is determined as deceased, this will be documented. Sponsor personnel will not be involved in any attempts to collect vital status information.

# 8. STUDY ASSESSMENTS AND PROCEDURES

## 8.1. Administrative Procedures

### 8.1.1. Overview

The SoA summarizes the frequency and timing of all assessments applicable to this study.

All planned assessments, including clinical laboratory tests, must be completed and the results reviewed at each study visit. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO, vital signs, blood draw. Treatment decisions will be based on safety and disease assessments performed at the site. More frequent study visits may be performed, and clinical evaluations may be repeated more frequently, if clinically indicated.

Blood collections for PK should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed.

Repeat or unscheduled samples (eg, PK and biomarkers) may be taken for safety reasons or for technical issues with the samples. The total blood volume to be collected is within the limits considered to be acceptable based upon the recommendations by the Dana Farber/Harvard Cancer Center Guidance, which indicates a maximum of 10.5 mL/kg (52 kg person) or 550 mL, whichever is smaller, over any 8-week period.

### 8.1.2. Screening Phase

The Screening Phase begins when the first screening assessment is performed and within 28 days before randomization, except as noted in the SoA (Table 1; Table 2). ICFs must be signed before the first specific study-related activity is conducted.

Eligibility criteria (Section 5.1; Section 5.2) should be reviewed to ensure the participant meets all criteria. Lifestyle considerations (Section 5.3) should be reviewed with each participant at the time of informed consent.

Demographic information, including date of informed consent, version date of the protocol under which the participant signed consent, age, race, and ethnicity should be documented on the source document and CRF.

Disease characteristics and prior anticancer therapies should be documented on the CRF.

### 8.1.3. Treatment Phase

C1D1 of the Treatment Phase in both arms should occur within 3 calendar days from randomization. Participants will receive pasritamig+docetaxel (experimental arm) or docetaxel (comparator arm) as described in Section 4.1.

Prior to and after study treatment administration, vital signs (Section 8.3.2) will be monitored at intervals noted in the SoA (Table 1; Table 2). The participant will be evaluated for possible toxicities at each site visit. Toxicities should be managed as described throughout Section 6.6.4. Participants may continue to receive study treatment until any of the treatment discontinuation criteria outlined in Section 7.1 are met. Within 42 days (±7 days) of last dose of study treatment, or start of subsequent therapy, whichever occurs first, participants clinically able to return for evaluation should complete the EOT visit, and thereafter, enter the Follow-up Phase.

The frequency of study site visits and details of the procedures performed are outlined in the SoA.

The latest measurements taken before administration of the first study treatment will be defined as baseline values.

### 8.1.4. End of Treatment Visit

Once a participant receives the last dose of study treatment or prior to the start of subsequent anticancer therapy, whichever occurs first, an EOT visit will be triggered. The EOT visit is required for all participants, except for participants lost to follow-up, death, or withdrawal of consent for study participation. If a participant is unable to return to the site for the EOT visit or if the EOT visit occurs prior to Day 42 after the last treatment dose, participants should be contacted for AEs within the specified AE reporting period (Section 8.4.1).

### 8.1.5. Follow-up Phase

The Follow-up Phase starts after the EOT visit in both arms.

**Post-Treatment Follow-up:** Participants who reach EOT but have not yet had a BICR-confirmed rPFS event or started subsequent anticancer therapy, will enter the Post-Treatment Follow-up Phase for evaluation of disease status and efficacy with in-person visits and assessments. If a BICR-confirmed rPFS event occurs, subsequent anticancer therapy is started or participant partially withdraws consent during this phase, participant will enter the Survival Follow-up phase.

**Survival Follow-Up:** Participants will enter the Survival Follow Up Phase following a BICR-confirmed rPFS event, start of subsequent anticancer therapy, or withdraw consent but still allow contact, whichever occurs first. Survival follow-up will continue every 12 weeks (±28 days) until death, loss to follow-up, or complete study withdrawal, whichever occurs first.

During the Survival Follow-up Phase, data may be obtained by telephone or chart review.

If the participant has died, the date and cause of death will be collected and documented on the source document and CRF, if or when available. Related SAEs occurring during either Post-Treatment Follow-up or Survival Follow-up Phases should continue to be reported.

### 8.1.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the SoA (Table 1; Table 2) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided.

## 8.2. Efficacy Assessments

Efficacy assessments (for frequency, see SoA) include:

- radiographic disease assessments (CT scan or MRI [of chest, abdomen, and pelvis; Section 8.2.1] and whole-body bone scans [$^{99}$Tc; Section 8.2.1]) by BICR,
- electronic PROs (Section 8.2.5),
- serum PSA (Section 10.1),
- assessment of symptomatic progression (Section 8.2.2),
- survival status (Section 8.1.5).

Evaluation of rPFS will be assessed by BICR according to PCWG3 and RECIST v1.1 criteria (Scher 2016) and the results will be recorded in the source document and eCRF. Imaging screening scans and any unscheduled scans (for PSA rise) will be assessed by the investigator and BICR. The same modality (CT scan or MRI and [$^{99}$mTc]-bone scan) used at baseline should continue to be used throughout the study.

PRO assessments should be completed before (and not during) any tests, procedures, drug administration, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of PROs.

Unscheduled assessments should be considered, if clinically indicated, and results collected in the CRF.

### 8.2.1. Radiographic Image Assessment (CT, MRI)

Screening imaging will be assessed by investigator to determine eligibility and balance randomization based on the location of metastases (non-visceral, visceral-liver, or visceral-other). Baseline disease burden will be assessed using CT with IV contrast or MRI scans of the chest, abdomen, and pelvis, plus other areas of known disease involvement as appropriate. Participants who are intolerant of IV contrast agents may have CT scans performed with oral contrast and the reason for not using IV contrast should be documented in source documents.

MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT scan. In any case where an MRI is desirable, it must be the imaging technique used to assess disease at baseline and at all subsequent response evaluations for the same participant. Brain MRI is required only if clinically indicated. CT scan of the head can be used if MRI is contraindicated.

Subsequent efficacy evaluations during the study will include radiographic imaging of all disease sites documented at baseline.

### 8.2.2. Assessment of Symptomatic Progression

If symptomatic deterioration occurs without documentation of radiographic progression, then the clinical findings used to make this determination must be specified in the CRF as 'symptomatic progression' and documented in the source documents. Every effort should be made to document progression via radiographic confirmation by BICR even after discontinuation of treatment for symptomatic deterioration.

### 8.2.3. Assessment of Bone Lesions

Progression of bone disease will be evaluated according to PCWG3 criteria and must be confirmed by a subsequent scan ≥6 weeks later.

The first post-treatment scan at Week 8 of this study should be used as the reference scan to which all subsequent scans are compared with, to determine progression.

Bone progression is defined as one of the following:

1. First post-treatment scan at Week 8 is observed to have ≥2 new bone lesions compared with baseline scan. A confirmatory scan performed ≥6 weeks later is required and would fall into 1 of the 2 categories below:
    a. If confirmatory scan (which is performed ≥6 weeks later) shows ≥2 new lesions compared with the first post-treatment scan (ie, a total of ≥4 new lesions compared with baseline scan), then bone scan progression will be considered at the time of the first post-treatment scan (at Week 8).
    b. Confirmatory scan that does not show ≥2 new lesions compared with the first post-treatment scan will not be considered bone scan progression at that time. The first post-treatment scan (at Week 8) will be considered as the reference scan to which subsequent scans are compared.
2. Post-treatment scan does not show ≥2 new bone lesions compared with baseline scan. The first scan timepoint that shows ≥2 new lesions compared with the first post-treatment scan (at Week 8) will be considered as the bone scan progression timepoint if these new lesions are confirmed (as above) by a subsequent scan ≥6 weeks later.

### 8.2.4. Treatment After Initial Disease Progression

For the experimental arm only, where there is radiographic progression by BICR without clinical progression, but the treating physician believes that continuation of study treatment is in the best interest of the participant, the participant may be allowed to continue to receive study treatment. The criteria to continue study treatment after radiographic progression by BICR include, but are not limited to:

- Continuation of treatment is in the best interest of the participant, per the investigator.
- Participant has no symptoms or signs indicating clinically significant progression of disease.
- Participant has no decline in ECOG performance status.

- Participant has no symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord depression).

Participants should continue to follow all on-treatment requirements and evaluations per SoA.

Re-consent is required in participants who are planned to continue study treatment beyond disease progression (Section 10.2.3). Participants should continue to follow all on-treatment requirements and evaluations per SoA.

### 8.2.5. Electronic Patient-reported Outcomes

The participant's symptoms, functioning, and general well-being will be captured using the following PRO instruments: BPI-SF, EORTC QLQ-C30, EORTC IL 46, EORTC QLQ-PR25, and EQ-5D-5L.

The PRO instrument will be provided in the local language in accordance with local guidelines, where available. The PRO instrument may be submitted to regulators and to IRB/IEC when applicable. PRO and AE data will not be reconciled with one another. If PRO was done as scheduled per SoA during Treatment Phase, but study treatment infusion was delayed on the same day, PRO should not be repeated on the actual day of study treatment infusion.

**Brief Pain Inventory – Short Form (BPI-SF)**

The BPI-SF was developed to measure both intensity or severity of pain and pain interference with daily life dimensions. It consists of a both-sides-of-the-body diagram, 4 pain severity items, one item each about pain medication use and relief, and 7 items about pain interference with activities of daily living (Charles 2009). The BPI Short Form measures pain intensity via 4 questions, ie, "pain at its worst in the last 24 hours", "pain at its least in the last 24 hours", "pain on the average", and "pain you have right now". The BPI-SF assesses how much pain has interfered with the following 7 activities: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

**EORTC Quality of Life Questionnaire-Cancer Module (EORTC QLQ-C30) Version 3**

The EORTC QLQ-C30 - Version 3 is a self-administered, 30-item questionnaire measuring the HRQoL of participants with cancer. The recall period for most items is the past week. EORTC QLQ-C30 includes 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status / quality of life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Responses to items 1-28 are rated on a 4-point Likert response scale ranging from 1 "Not at all" to 4 "Very much". Two global health status items are rated on a 7-point numeric rating scale from 1 "Very Poor" to 7 "Excellent". The EORTC QLQ-C30 can generally be completed in 4-5 minutes.

**EORTC Quality of Life Questionnaire–Prostate (EORTC QLQ-PR25)**

The EORTC QLQ-PR25 was developed collaboratively between the EORTC Quality of Life and Genitourinary Cancer groups (van Andel 2008). This self-completed instrument was specifically designed for prostate cancer patients and includes 25 items that cover 6 dimensions: (1) PR URI

(urinary symptoms, 8 items), (2) PR BOW (bowel symptoms, 4 items), (3) PR HTR (hormonal treatment-related symptoms, 6 items), (4) PR AID (incontinence aid, 1 item), (5) PR SAC (sexually active, 2 items); and (6) PR SFU (sexual function, 4 items). Note that one item ("Has wearing an incontinence aid been a problem for you?") is conditional upon wearing an incontinence aid. Similarly, the 4 PR SFU items are conditional upon being sexually active over the last 4 weeks. The EORTC QLQ-PR25 can be completed in 3 to 4 minutes.

**EORTC Additional Item from the Item Library**

The EORTC Item Library was originally created as a database of all the EORTC QoL items and their translations. In its current form, Item Library is an online platform composed of more than 1,000 individual items from over 70 EORTC measures (Phase 3 completed, following the EORTC QLG Module Development Guidelines), some of which have been translated into over 120 languages. The aim of the Item Library is to facilitate flexible, timely measurement of symptoms, complementing the use of fully validated quality of life instruments (Kulís 2018). In this study, participants will be asked to complete the following item: EORTC IL 46 (Treatment Side Effect Bother). The item is scored using a 1-4 numerical rating scale where 1="not at all" and 4="very much". This question can be completed in less than 1 minute.

**European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) and Visual Analog Scale (VAS)**

The EQ-5D-5L is a self-administered, standardized measure of health status in a wide range of health conditions and treatments. It provides a descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care. The recall period for all items is 'Today'.

The EQ-5D descriptive system comprises 5 items across the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L uses a 5-point Likert response scale ranging from "No problems" to "Extreme problems". The EQ-5D health states defined by the EQ- 5D descriptive system can be converted into a single index value using country-specific value sets. The index value facilitates the calculation of quality-adjusted life years that are used to inform economic evaluations of health care interventions. The EQ-5D also includes a visual analog scale (EQ-VAS) that has endpoints labeled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Participants are asked to indicate how they rate their own health by indicating the point on the EQ-VAS which best represents their own health on that day. The EQ-5D-5L can generally be completed in under 2 minutes.

## 8.3. Safety Assessments

Timing of assessments are specified in the SoA (Table 1; Table 2).

Adverse events will be reported and followed by the investigator as specified in Section 8.4.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA.

### 8.3.1. Physical Examinations

A complete physical examination will be conducted at screening. During the Treatment Phase, symptom- and disease-directed physical examinations should be performed at each study visit and prior to all study treatment administrations and include an evaluation of organ systems previously noted to be abnormal or involved, and of clinically relevant abnormalities in any organ.

### 8.3.2. Vital Signs

Temperature, heart rate, blood pressure, and $SpO_2$ will be assessed per the SoA. Heart rate and blood pressure will be assessed with an automated device; if not available, manual techniques are allowed.

### 8.3.3. Electrocardiograms

Collection of ECGs will be obtained as indicated in the SoA (Table 1; Table 2).

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

Additional cardiovascular assessments should be performed as clinically appropriate to ensure participant safety. The clinical investigator must review the ECG results, including ECG morphology, for immediate management. The results that support AE reporting should be entered into the CRF. Abnormalities noted at screening should be included in the medical history.

### 8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, coagulation, and serology will be collected locally as noted in Section 10.1 (refer to the SoA for sampling schedules; Table 1; Table 2). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the CRF. The laboratory results must be entered into the CRF with local laboratory reference ranges per guidelines. The laboratory reports must be filed with the source documents.

### 8.3.5. ECOG

The ECOG performance status scale will be used to grade changes in the participant's daily living activities (Oken 1982). The ECOG performance status assessment should be performed pre-dose.

### 8.3.6. ICE Score

The ICE tool presented in Table 19 will be used prior to the first step-up dose of study treatment (on C1D1) to establish baseline neurologic status and then as clinically indicated. If ICANS is suspected, additional assessments should be performed to assess severity per the ASTCT grading scale (Table 16).

**Table 19: Immune Effector Cell-associated Encephalopathy (ICE) Tool**

| Category | Points |
|---|---|
| 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 backward from 100 by 10 | 1 point |

Scoring is as follows (see also 6.6.4.3 for additional details regarding ICANS severity grading):

- 10; no impairment
- 7 to 9; Grade 1 ICANS
- 3 to 6; Grade 2 ICANS
- 0 to 2; Grade 3 ICANS
- 0 due to participant unarousable and unable to perform ICE assessment; Grade 4 ICANS.

Source: Lee 2019

## 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of study participants and patients, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures to ensure appropriate *safety* reporting; *and this study is to be* conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally designated representative).

The Sponsor assumes responsibility for appropriate reporting of the Safety Information, including SUSARs, to the Regulatory Authorities/IECs/IRBs in each respective country/territory, as applicable.

### 8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and special reporting situations, whether serious or non-serious, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures, must be recorded using medical terminology in the source document and on the appropriate pages of the CRF and appropriate forms. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy (see Section 8.4.3). All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained.

All AEs, special reporting situations and SAEs that occur until 42 days after the EOT or until the start of new subsequent anticancer therapy for prostate cancer, whichever is earlier, must be reported and recorded on the appropriate pages in the CRF or on specific forms. Related SAEs occurring in the Follow-up Phase should continue to be reported.

AEs will be graded according to the NCI-CTCAE Version 5.0 and ASTCT criteria for CRS and ICANS. Participants with Grade 3 or higher toxicity or unresolved AEs will continue to be assessed until recovery to Grade ≤1 or baseline, the event is deemed irreversible, the end of the study, or a maximum of 6 months, whichever comes first.

Information regarding SAEs (initial and any follow up) will be transmitted to the Sponsor immediately, but no later than 24 hours of their knowledge of the event, using the study-specific SAE Form with the complete (eg, causality, narrative) information available in the medical records that has been already assessed by a study site physician, and transmitted via CRF through JEISR.

### 8.4.2. Definitions and Classifications

#### 8.4.2.1. All Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding from a diagnostic procedure or laboratory assay), symptom, or disease that is new in onset or aggravated in severity or frequency from baseline and temporally associated with the use of such product (as defined by ICH).

The investigator is obligated to take all necessary steps to elucidate the nature and causality of the AE as fully as possible.

#### 8.4.2.2. Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
  The cause of death of a participant in a study within 42 days after the EOT visit, whether or not the event is expected or associated with the study treatment, is considered an SAE. However, death attributed to progression of disease should not be considered an AE or SAE. For details, see Section 8.4.3.]
- Is life-threatening
  The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, except:
  - Hospitalization attributed to progression of disease; for details, see Section 8.4.2.2.

- Hospitalizations for planned observations related to any component of treatment administration, unless an SAE event occurs during observation period (ie, CRS, IRR etc).
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, convenience for participant, etc).
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

**Note:** Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is indicating suicidal ideation or behavior
- Is Medically Important Exercise medical judgment to decide on reporting as SAE of other events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

*SAE recording and reporting*

All SAEs that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves, stabilizes or returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, or participant is lost to follow-up).

### 8.4.3. Attribution of Causality

The causal relationship between study treatment administration and the AE is assessed by the investigator and documented in the Medical Records. This assessment must consider factors such as characteristics of participant and event, temporal relationship, pharmacologic plausibility and confounding clinical factors. Data on challenge can help the assessment (did the event improve when the study treatment was withdrawn in the absence of any other intervention and what happened when participant restarted the study treatment). The following must be used for all AEs:

- **Related:** There is a reasonable causal relationship.
- **Not Related:** There is not a reasonable causal relationship.

### 8.4.4. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE Version 5.0. Any AE or SAE not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to adverse event.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL=activities of daily living
Notes: A semi-colon indicates 'or' within the description of the grade.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

### 8.4.5. Special Reporting Situations

Safety events of interest pertaining to the study treatment in this study that require expedited reporting and may trigger safety evaluation include, but are not limited to:

- Overdose of study treatment
- Suspected abuse/misuse of study treatment
- Accidental or occupational exposure to study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

Participant-specific special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF. Reporting should occur as for other AE and SAE (Section 8.4.1).

### 8.4.6. Procedures

#### 8.4.6.1. Anticipated Events

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in Appendix 7.

#### 8.4.6.2. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Progression of disease should not be considered nor should be reported as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (refer to Section 8.4 and Section 8.4.7). Similarly, death due to disease progression should not be reported as an SAE, instead signs and symptoms resulting from disease progression should be reported if they fulfill the serious adverse event definition.

#### 8.4.6.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it.

The communication requirements for AESIs are detailed in the table below. Any AESI should be followed until recovery to baseline or until there is no further improvement.

| AESI | Definition | Data collection and rapid communication requirements |
|---|---|---|
| *IRRs* | *Grade ≥3; refer to Section 6.6.4.1 for full definition.* | Grade ≥3 event is always serious, report as SAE. |
| *CRS* | *Grade ≥3; refer to Section 6.6.4.2 for full definition.* | Grade ≥3 event is always serious, report as SAE. |
| *HLH/MAS events* | *Refer to Section 6.6.4.2 for full definition.* | Event is always serious, report as SAE. |
| *ICANS* | *Grade ≥2; refer to Section 6.6.4.3 for full definition.* | Grade ≥2 event is always serious, report as SAE. |
| *Any other pasritamig-related neurotoxicity* | *Grade ≥3; refer to Section 6.6.4.3 for full definition.* | Grade ≥3 event is always serious, report as SAE. |

### 8.4.7. Product Quality Complaint Handling

**Definition**

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it

includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

**Procedures**

All initial PQCs must be reported to the Sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the Sponsor.

### 8.4.8. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

## 8.5. Pregnancy Information

### 8.5.1. Participants Whose Partners Become Pregnant

All initial reports must be made to the Sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Outcome of the reported pregnancy and any postnatal sequelae in the infant will be required. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as SAEs.

## 8.6. Pharmacokinetics

### 8.6.1. Evaluations

Serum samples will be used to evaluate the PK of pasritamig as indicated in Table 3 of the SoA. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity, or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

### 8.6.2. Pharmacokinetic Parameters

Sparse samples collected for PK of pasritamig will be analyzed. Individual serum concentrations by timepoints including descriptive statistics will be summarized if feasible.

If data allow PPK analysis of serum concentration-time data of pasritamig may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (eg, demographics, laboratory variables, race, etc) may be tested as potential covariates affecting

PK parameters. If the PPK analysis is conducted, details will be given in a PPK analysis plan and the results of the analysis will be presented in a separate report.

## 8.7. Biomarkers

The biomarker assessments are designed to: 1) assess pharmacodynamic biomarkers of T-cell dependent antitumor activity in this population of mCRPC patients; 2) Identify both tumor and immune-mediated mechanisms of response and resistance through multi-omic profiling of PBMC, serum and ctDNA.

### Tumor Tissue and Circulating Tumor DNA

Metastatic tumor biopsies of a stable, new, regressing, and/or progressing lesion collected while on study treatment (after Cycle 2, Day 1) and/or at EOT as indicated in Table 3, may be used to assess tumor antigen expression, including but not limited to, KLK2 and neuroendocrine associated proteins, and immune infiltrate and functionality by IHC. Furthermore, tissue may be used for DNA/RNA based evaluations to assess impact of genetic mutations and transcriptional signatures as biomarkers for response or resistance to therapy. Fresh metastatic tumor biopsy sample collections are optional and may be limited to participants at select investigational sites. Available archival biopsies from metastatic sites collected within 15 months from screening are requested from all participants in both treatment and comparator arms if feasible (Table 3 and Table 4), and may be used for the same purposes as outlined above for fresh biopsies.

DNA fragments are shed into the blood during normal cell turnover, including dying cancer cells. Prostate cancer cells have lower cell turnover than other tumor types, and more sensitive methylation-based approaches may be utilized to measure tumor fraction, as well as other genetic variant panel-based profiling assays. ctDNA will be isolated from plasma samples collected at baseline, on treatment and at the EOT visit according to Table 3 and Table 4.

Baseline ctDNA samples may be analyzed for tumor fraction as a surrogate for tumor burden to determine how this parameter correlates to treatment response. Further tumor fraction quantitation from the on-treatment and end-of-treatment samples may be used to assess kinetics and/or clearance of ctDNA in relation to response or resistance. Genomic profiling of ctDNA may provide insight into gene specific mutations and alterations that associate with pasritamig response. Specifically, profiling of baseline samples of participants with unknown BRCA1/2 mutation status will be conducted to confirm the presence or absence of the mutation. Additionally, sensitive chromatin epigenetics (methylation/acetylation) based ctDNA assays may be leveraged to assess changes in activity at the gene level to understand intrinsic and acquired mechanisms of resistance.

### Circulating Biomarkers

Blood samples for circulating biomarkers should be collected pre-dose as specified in the SoA (Table 3 and Table 4). Sample collections/procedures are subject to modification or termination contingent upon emerging data.

Peripheral immune cell fitness and antitumor immune responses may be assessed using PBMCs isolated from the blood using methods including, but not limited to, immunophenotyping and RNA sequencing. Assessments of T-cell activation, proliferation, exhaustion, cytotoxicity, etc will be assessed by cell phenotyping and serum proteomics to understand potential variations in the antitumor immune response and associations of immune-related factors with response or resistance.

Serum soluble factors including, but not limited to, cytokines, chemokines, and tumor antigens such as KLK2 and neuroendocrine associated proteins, may be measured prior to, while on, and following treatment. Monitoring soluble tumor antigens and their association with clinical activity may give insight into resistance mechanisms associated with the loss of cell surface expression of KLK2 or the transition of tumor cells to more aggressive, neuroendocrine types.

Sample collection and testing will comply with local regulations.

Additional biomarkers (DNA, RNA, and protein) relevant to cancer biology may also be assessed in blood and tissue samples collected on study to better understand the disease and mechanisms of response or resistance to treatment.

**Stopping Decision**

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

**Additional Collections**

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study treatment(s) or diseases being investigated.

## 8.8. Immunogenicity Assessments

Antibodies to pasritamig will be evaluated in serum samples collected from all participants according to Table 3 of the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, and for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

## 8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. The data collected may be used to conduct exploratory economic analyses, eg, on hospitalizations and health care visits.

# 9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the Sponsor or under its authority. A general description of the statistical methods to be used is outlined below; for more detail see the SAP, which will be finalized prior to database lock.

## 9.1. Statistical Hypotheses

The hypothesis is that pasritamig+docetaxel will demonstrate improved rPFS, compared with docetaxel in participants with mCRPC who have progressed on at least one ARPI.

A similar hypothesis holds for the secondary endpoints OS, TSP, TSRE, and TST.

## 9.2. Participant Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| Analysis Sets | Description |
|---|---|
| Enrolled Analysis Set | All participants who sign the ICF and are not screen failures |
| Full Analysis Set | All randomized participants (classified according to their assigned treatment arm, regardless of the actual treatment received) |
| Safety Analysis Set | All randomized participants who receive at least 1 dose of study treatment |
| Pharmacokinetic Analysis Set | All participants who receive at least 1 dose of pasritamig and have at least 1 evaluable concentration measurement of pasritamig |
| Immunogenicity Analysis Set | All participants who receive at least 1 dose of pasritamig and have at least 1 post-treatment immunogenicity sample collected |

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

All tests will be conducted at a 2-sided alpha level of 0.05 and 95% CIs will be provided, unless stated otherwise. Continuous variables will be summarized using number of participants, mean, SD, median, minimum, and maximum. Discrete variables will be summarized with frequency and percentage. The Kaplan-Meier product limit method will be used to estimate time-to-event variables. All efficacy analyses will be performed using the Full Analysis Set and all safety analyses will be carried out on the Safety Analysis Set.

All PRO data will be summarized over time by the treatment arm. Changes from baseline PRO scale scores will be analyzed using a repeated measures fixed effects model. The fixed effects will

include baseline score, intervention group and cycle number as categorical variables, and intervention group-by-cycle interaction. Participant is included as a random effect.

The safety parameters to be evaluated are the percentage and intensity of AEs, clinically significant changes in the participant's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study treatment and reasons for discontinuation of study treatment will be tabulated.

### 9.3.2. Primary Endpoint/Estimand

The primary endpoint is rPFS assessed by BICR and is defined as the time from the date of randomization to the first date of radiographic disease progression, or death due to any cause, whichever occurs first. The evidence of disease progression is defined by:

- Progression of soft tissue lesions measured by CT or MRI as defined in RECIST v1.1.
- Progression of bone lesions observed by bone scan and based on PCWG3. Under these criteria, any bone progression must be confirmed by a subsequent scan ≥6 weeks later. The first post-treatment scan should be used as the baseline to which all subsequent scans are compared to determine progression. Bone progression is defined in Section 8.2.3.

Participants without radiographic progression or death will be censored at the last disease assessment if they never start subsequent anticancer therapy or censored at the last disease assessment date prior to the start of the subsequent systemic anticancer therapy if they started subsequent anticancer therapy.

**Estimand**

The primary scientific question of interest is: What is the effect of pasritamig+docetaxel versus docetaxel on rPFS?

The primary estimand is defined by the following 5 components (ICH E9 [R1] 2017):

**Study Treatment:**

- **Experimental:** pasritamig+docetaxel
- **Comparator:** docetaxel

**Population:** Participants ≥18 years of age with mCRPC who have progressed on at least one ARPI as defined by the inclusion/exclusion criteria to reflect the target participant population.

**Variable:** rPFS

**Summary Measure (Population-level Summary):** Hazard Ratio of pasritamig+docetaxel vs docetaxel

**Intercurrent Events and Their Corresponding Strategies:**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Initiation of subsequent systemic anticancer therapy prior to the documented disease progression or death | **Hypothetical strategy:** participants are censored at the last disease assessment showing no evidence of PD before the use of subsequent anticancer therapy |
| Missing ≥2 consecutive planned disease assessment visits immediately before the documented disease progression or death | **Hypothetical strategy:** participants are censored on the date of the last evaluable disease assessment before the missed/unevaluable scans |
| Discontinuation of study treatment for toxicity or other reasons | **Treatment policy strategy:** use time to disease progression or death, regardless of whether study treatment discontinuation occurred |

### 9.3.3. Secondary Endpoints/Estimands

After the primary endpoint achieves statistical significance, the 2-sided 0.05 alpha will be passed and split between OS and other key secondary endpoints of TSRE, TSP, and TST, defined below and will be split between them (details in the SAP).

#### 9.3.3.1. Overall Survival

OS is defined as the time from the date of randomization to the date of death due to any cause. Participants alive at the time of analysis will be censored on the last date the participant was known to be alive.

**Estimand** for OS

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 9.3.2 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: OS.

**Intercurrent Events for OS and Their Corresponding Strategies:**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Initiation of subsequent therapy | **Treatment policy strategy:** Use time to death, regardless of whether subsequent therapy was initiated |
| Treatment discontinuation | **Treatment policy strategy:** Use time to death, regardless of whether treatment was discontinued |
| Administration of prohibited or restricted medications | **Treatment policy strategy:** Use time to death, regardless of whether prohibited or restricted medications were administered |

#### 9.3.3.2. Time to Symptomatic Progression

TSP is defined as the time from the date of randomization to the date of the first occurrence of any of the following:

- The use of external beam radiation for skeletal or pelvic symptoms. Note: radiation planned prior to randomization will not be considered as symptomatic progression.
- The need for tumor-related orthopedic surgical intervention.
- Other cancer-related procedures (eg, nephrostomy insertion, bladder catheter insertion, or surgery for tumor symptoms).

- Cancer-related morbid events (ie, fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events).
- Initiation of a new systemic anticancer therapy because of cancer symptoms.

Participants who do not experience any of the events described above will be censored on the date on which they were last known to be event-free.

Prostatitis due to drug reaction that needs treatments such as catheterization should not count as a symptomatic progression event.

**Estimand** for TSP

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 9.3.2 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: TSP.

**Intercurrent Events for TSP and Their Corresponding Strategies:**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Initiation of subsequent systemic anticancer therapy because of cancer symptoms | **Composite strategy:** Initiation of new systemic anticancer therapy due to cancer symptoms is considered an event for this endpoint. |
| Initiation of subsequent systemic anticancer therapy due to reasons other than cancer symptoms (eg, AE) | **Treatment policy strategy:** Use time to symptomatic progression. |
| Treatment discontinuation | **Treatment policy strategy:** Use time to symptomatic progression, regardless of whether study treatment discontinuation occurred. |

#### 9.3.3.3. Time to Subsequent Therapy

TST is defined as time from randomization to the initiation of any subsequent systemic anticancer therapy. Participants who do not receive a subsequent therapy will be censored at the last known alive date.

**Estimand** for TST

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 9.3.2 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: TST.

**Intercurrent Events for TST and Their Corresponding Strategies:**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Treatment discontinuation | **Treatment policy strategy**: use time to initiation of new antineoplastic therapy, regardless of whether study treatment was discontinued |

#### 9.3.3.4. Time to Skeletal-related Event

TSRE is defined as the time from the date of randomization to the date of first occurrence of any of the following:

- The use of external beam radiation therapy to relieve skeletal symptoms.
- The need for tumor-related orthopedic surgical intervention.
- The occurrence of new bone fractures (cancer-related; vertebral or non-vertebral).
- The occurrence of tumor-related spinal cord compression.

Participants who do not experience any of the events described above will be censored on the date on which they were last known to be event-free

**Estimand** for TSRE

The 5 components of estimand are defined similarly to that of the primary endpoint in Section 9.3.2 with scientific question of interest, variable, and population-level summary addressing the respective endpoint: time to skeletal-related event.

**Intercurrent Events for TSRE and Their Corresponding Strategies:**

| Intercurrent Events | Strategy for Addressing Intercurrent Events and Its Description |
|---|---|
| Initiation of subsequent therapy | **Treatment policy strategy:** Use time to skeletal-related event, regardless of whether subsequent therapy was initiated |
| Treatment discontinuation | **Treatment policy strategy**: use time to skeletal-related event, regardless of whether study treatment was discontinued |

### 9.3.4. Other Secondary Endpoints/Estimands

The other secondary endpoints are (details will be provided in the SAP):

- ORR
- DOR
- PFS2
- Time to PSA Progression
- PSA response rate
- Duration of PSA response
- PROs (Section 9.3.5)

### 9.3.5. Patient-Reported Outcome

Full details of the statistical analyses will be provided in the SAP.

Compliance will be reported by PRO instrument and all PRO scores will be summarized descriptively at each time point. Mean changes from baseline (BPI-SF, EORTC QLQ-C30, EORTC QLQ-PR25, EQ-5D VAS) will be calculated for each subscale by fitting a mixed-effects model and time to sustained worsening (BPI-SF) of pain symptoms will be calculated using Kaplan-Meier methods. For EQ-5D-5L and IL-46 scores, item frequency count and percentage of each reporting level over time will be provided.

### 9.3.6. Safety Analyses

All safety analyses will be based on the Safety Analysis Set and based on the actual treatment received, unless otherwise specified.

For continuous safety variables, descriptive statistics by treatment group may include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment group using frequency counts and percentages.

**Adverse Events**

The verbatim terms in the CRF to identify AEs will be coded using the MedDRA. Any new or worsening AE occurring at or after the initial administration of study treatment through the day of last dose plus 42 days or prior to the start of subsequent anticancer therapy, whichever is earlier, *or* any follow-up AE (linked to an existing TEAE) with onset date and time beyond 42 days after the EOT visit but prior to the start of subsequent therapy *or* any AE that is considered treatment-related regardless of the start date of the event, is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, discontinue treatment due to an AE, or experience a severe or an SAE.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized.

**Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point as appropriate. Parameters with predefined toxicity grades will be summarized. Change from baseline to the worst grade experienced by the participant during the study treatment will be provided as shift tables.

**Electrocardiogram**

The baseline ECG will be summarized using descriptive statistics.

**Vital Signs**

Vital signs including temperature, heart rate, blood pressure (systolic and diastolic), and $SpO_2$ will be summarized over time, using descriptive statistics or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

**Physical Examinations**

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

### 9.3.7. Other Analyses

The following data will be analyzed as specified in the SAP, and may be presented in a separate report:

- Pharmacokinetic data
- Biomarker data
- Immunogenicity data
- Pharmacodynamic data
- Medical resource utilization

## 9.4. Interim Analysis

There will be a single analysis for the primary endpoint of rPFS. Two interim analyses and one final analysis are planned for the secondary endpoints of OS, TSRE, and TSP. The first interim analysis for the secondary endpoints will coincide with the rPFS primary analysis for. The second interim analysis will take place when 328 (IF=80%) OS events occur. The final analysis will be performed when 409 OS events have occurred. Additionally, the key secondary endpoint of TST will be evaluated during the primary rPFS analysis and again during the second interim analysis for OS.

To preserve the overall familywise type I error rate at the 2-sided 0.05 level, a hierarchical multiple testing procedure incorporating group sequential methods will be applied. After the primary endpoint is statistically significant, the 2-sided 0.05 alpha will be split between OS and other key secondary endpoints of TSP, TST, and TSRE. These 3 key secondary endpoints are tested in a hierarchical order, starting with TSP, followed by TST, and then TSRE.

To control the familywise error rate at the 2-sided 0.05 level, alpha spending functions will be applied. For OS Hwang, Shih and DeCani spending function with gamma=-4 and for TSP, TST, and TSRE Kim-DeMets spending function with rho=2 will be applied. The actual alpha spent at the time of interim analysis will be based on the total number of events observed at interim analysis for each of the secondary endpoints. Details will be provided in the statistical analysis plan (SAP).

## 9.5. Sample Size Determination

An overall type I error of 5% is planned for this study. Approximately 800 eligible participants will be randomized in a 1:1 ratio to receive either pasritamig+docetaxel or docetaxel.

The sample size calculation is based on the assumption that the pasritamig+docetaxel will result in a 32% reduction in the risk of disease progression or death over docetaxel (HR of 0.68, prolonging the median rPFS from 8.5 months in the comparator arm [docetaxel] to 12.5 months in the experimental arm [pasritamig+docetaxel]). Under the assumption that rPFS follows an exponential distribution, it is estimated that approximately 392 rPFS events will provide >96% power to detect a HR of 0.68 at a 2-tailed significance level of 0.05. Assuming that the recruitment period spans 19 months over 3 intervals (0-6, by 12 months, by 19 months) with 19%, 57%, and 100% participant enrollment, with an annual drop-out rate of 5% in the experimental arm and 10%

in the comparator arm, the rPFS primary analysis is expected to occur approximately 22 months after the first participant is randomized.

This study aims to achieve adequate statistical power (85%) to detect a HR of 0.74 for the key secondary endpoint of OS. This HR reflects an anticipated improvement in median OS from 23 months in the comparator arm [docetaxel] to 31.08 months in the experimental arm [pasritamig+docetaxel], representing an increase of 8 months. To achieve this level of power, approximately 409 events will be required for the final analysis.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed according to the SoA.

Local laboratory will be used for all protocol-required laboratory assessments, except for tumor marker (PSA) starting at C1D1.

1. Central laboratory will be used for tumor marker (PSA) assessment starting at C1D1 and for all samples collected in Table 3 and Table 4 (PK, immunogenicity, and biomarker samples). Local PSA is permitted if central PSA is not available. Sites must ensure local PSA results are entered in the CRF. Central laboratory PSA results are not required prior to dosing.

**Protocol-Required Laboratory Assessments**

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | • Platelet count<br>• Hemoglobin<br>• White Blood Cell (WBC) count<br>• Absolute Neutrophil count (ANC)<br>• Lymphocytes<br>• Monocytes |
| Clinical Chemistry | • Sodium<br>• Potassium<br>• Blood urea nitrogen (BUN)<br>• Creatinine [*will be used for eGFR/CrCl calculation*]<br>• AST/SGOT<br>• ALT/SGPT<br>• Total bilirubin[a]<br>• Alkaline phosphatase<br>• Albumin<br>• LDH |
| Coagulation | • Coagulation: PT/INR and aPTT |
| Tumor markers | • PSA |
| Other Laboratory Tests (Screening only) | • Serology: HBsAg, HBsAb, HBcAb, hepatitis B DNA, HCV antibody, and hepatitis C RNA<br>• Total testosterone |

[a] Direct bilirubin if congenital nonhemolytic hyperbilirubinemia such as Gilbert's disease

## 10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

### 10.2.1. Regulatory and Ethical Considerations

- **The investigator is responsible** for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country- or territory-specific requirements.
- **Regulatory Approval/Notification**: This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.
- **Protocol Amendments**: No modification to this protocol will occur without a formal amendment issued by the sponsor and signed and dated by the investigator. Amendments can't be implemented without prior approval by IEC/IRB and relevant competent authority, except to eliminate immediate hazards to the participants (promptly submit amendment to the IEC/IRB and relevant competent authority). Documentation of amendment approvals must be provided to the sponsor.
- **Departure from the Protocol**: In situations where a departure from the protocol is unavoidable during the study, the investigator or delegate will contact the appropriate sponsor representative listed in the Contact Information page(s) to discuss the situation and agree on an appropriate course of action prior to such departure, except in emergency situations. The departure and its rationale must be recorded in source documents and be reflected in the CRF data.
- **Required Prestudy Documentation**: Documentation that must be provided to the sponsor before shipment of study treatment to the study site are specified in the appropriate documents such as the Clinical Trial Agreement. Additional documentation might need to be provided prior to enrolment of the first participant.
- **Independent Ethics Committee or Institutional Review Board**: Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of all documents as required by local regulations. Required documents are specified in the appropriate documents such as the Clinical Trial Agreement. This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, which should be submitted promptly, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this dated approval, with clear identification of the IEC/IRB and the documents approved.
  During the study the investigator (or Sponsor where required) will send documents and updates to the IEC/IRB for their review and approval, where appropriate, as specified in the appropriate documents such as the Clinical Trial Agreement.
  At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.
  At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).
- **Country/Territory Selection**: This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the

developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.5.

- **Other Ethical Considerations**:

For study-specific ethical design considerations, refer to Section 4.2.5.

### 10.2.2. Financial Disclosure

During the study and for 1 year after completion of the study, investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations. Refer to appropriate documents such as the Clinical Trial Agreement for details.

### 10.2.3. Informed Consent Process

Each participant give consent according to local requirements after the nature of the study has been fully explained and a response to all questions regarding the study was given. The ICF(s) must be signed before any study-related activity.

Informed consent may be obtained remotely per local guidelines.

The consent must be appropriately recorded by means of the participant's personally dated signature; the authorized person obtaining the consent must also sign the ICF. After consent, a copy of the ICF must be given to the participant. The medical records must include a statement that consent was obtained as required.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the assessment window as defined in the SoA.

Where local regulations require, a separate ICF may be used for the specific component(s), such as DNA analysis, of the study.

When applicable, during the study, participants must be re-consented to the most current version of the ICF(s).

Re-consent is required in a participant who is planned to continue study treatment beyond disease progression.

### 10.2.4. Recruitment Strategy

Refer to Recruitment and Informed Consent Procedure Template for details.

### 10.2.5. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant data that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects, including notification to appropriate authorities in accordance with applicable law.

### 10.2.6. Storage, Use, Transfer, and Retention of Data and Samples

- Study samples will be coded [or anonymized] at all times in accordance with the informed consent; no personal identifiers will be used.
- Investigator and study site will only store, use, transfer and retain data and (optional) study samples, in accordance with the informed consent, applicable law, and any written agreement with the Sponsor. Other than what is specified in this written agreement with sponsor, study site and investigator shall not conduct or facilitate any research not required by the protocol (i) on participants, or (ii) on samples or data collected from study participants during the study, if the research relates to pasritamig.
- Sponsor may store, use, transfer or retain the data and (optional) study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.
- The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer disks or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the Sponsor at the time the study is completed, terminated or discontinued.
- If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the Sponsor.

### 10.2.7. Committees Structure

**Independent Data Monitoring Committee**

An IDMC will be established to monitor study data and to ensure the continuing safety of the participants enrolled in this study. The composition, detailed objectives and procedures will be documented in its charter.

### 10.2.8. Use of Information, Registration of Study and Publication

- All information, including but not limited to information regarding pasritamig, supplied by the Sponsor to the study site or investigator and not previously published, and any data generated as a result of this study, are considered confidential and the sole property of the Sponsor. Study site and investigator shall not use nor disclose this information except as needed for the conduct of the study, and then only on like terms of confidentiality and non-use.
- Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between Sponsor and study site or investigator.
- The Sponsor will register the study and publish the study results in compliance with applicable law. The disclosure of the study results will be performed after the end of study. The Sponsor will generally support publication of multicenter studies only in their entirety.
- Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

- For studies conducted in the EU under Regulation EU 536/2014 appropriate provisions for interim analyses should always be described in the protocol. Use one of the options below as appropriate. Other options might be considered in specific situations.

The summary of the results from the interim analysis as described in Section 9.4, will be submitted to the EU database within one year of the intermediate data analysis date.

### 10.2.9. Data Quality Assurance, Monitoring and Audits

- Data quality will be ensured by selection of qualified investigators and study sites, review of protocol procedures and guidelines for CRF completion with the investigator and study site personnel before the study, and periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's database. Review and verification of CRF data may occur, as appropriate.
- Written instructions will be provided for collection, handling, storage, and shipment of samples.
- The Sponsor will use monitoring techniques such as central, remote, or on-site monitoring to monitor this study as frequently as necessary. It is expected that during remote contacts, study site personnel will be available to provide an update on the study.
- Representatives of the Sponsor's clinical quality assurance department may conduct an on-site audit of the study in compliance with regulatory guidelines and company policy. Study site personnel must be available for consultation. These audits will require access to all study records, including source documents. Participant privacy must, however, be respected.
- Similar auditing procedures may also be conducted by agents of any regulatory body; the investigator must immediately notify the Sponsor if they were contacted concerning such inspection.

### 10.2.10. Source Documents and Case Report Form Completion

- For each participant, the Sponsor provides CRFs in electronic format for recording, in English, of all data relating to the study by the investigator or authorized study site personnel. Worksheets, which are considered part of participant’s source documents, may be used for the capture of some data to facilitate completion of the CRF. The CRF must be completed as soon as possible after a participant visit. The investigator must verify that all data entries in the CRF are accurate and make corrections as appropriate. Study-specific data will be transmitted in a secure manner to the sponsor. If necessary, queries will be generated in the eDC tool.
- All participative measurements (eg, pain scale information or other questionnaires) will be completed, whenever possible, by the same assessor who made the initial baseline determinations.
- Source documents, on paper to be filed or using any eSource system to be maintained at the study site, provide evidence for the existence of the participant and substantiate the integrity of all study data collected, with at minimum the level of detail as commonly recorded at the study site.
- The author of an entry in the source documents must be identifiable.

- Specific details required as source data for the study and source data collection methods will be reviewed with the study staff before the study and will be described in the monitoring guidelines (or other equivalent document). This will include the list of any data recorded directly into the CRF that will be considered source data.

### 10.2.11. Study and Site Start and Closure

**Study Start Date** is defined as the date the first participant is screened.

**Study/Site Termination**

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

## 10.3. Appendix 3: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures (Section 5.1). In case a pregnancy occurs while on study treatment, pregnancy information will be collected and reported as noted in Section 8.5.

**Definitions**

***Participants of Childbearing Potential***

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

***Participants Not of Childbearing Potential***

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- permanent absence of reproductive potential (for the purpose of this study)
  - Has undergone a procedure that precludes reproductive potential.
  - Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active where pregnancy can occur), a participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

If applicable, study participants should be counselled about donation and cryopreservation of gametes prior to starting study treatment.

**Examples of Contraceptives**

| **EXAMPLES OF HIGHLY EFFECTIVE METHODS OF CONTRACEPTIVES[a]:** |
|---|
| **USER INDEPENDENT Highly Effective Methods[a]** |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation |
| • Intrauterine device (IUD) |
| • Intrauterine hormone-releasing system (IUS) |
| • Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation) |
| • Azoospermic partner *(vasectomized or due to medical cause)*<br>*(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)* |
| **USER DEPENDENT Highly Effective Methods[a]** |
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]: oral, injectable, transdermal or intravaginal |
| • Progestogen-only hormone contraception associated with inhibition of ovulation[b]: oral or injectable |
| • Sexual abstinence from intercourse where pregnancy could occur<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse where the possibility of pregnancy exists during the entire period of risk associated with exposure to the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)[a]** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Condom with or without spermicide (don't use multiple condoms together because of risk for failure due to friction) |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of external condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| • Withdrawal (coitus-interruptus) |
| • Spermicides alone |
| • Lactational amenorrhea method (LAM) |
| a. Highly Effective Methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.<br>b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment. A participant using oral contraceptives must use an additional contraceptive method. |

## 10.4. Appendix 4: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies

It is recognized that major disruptions may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The Sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study treatment will be followed.

If, as a result of the major disruption scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "Major Disruption-related" in the CRF.

## 10.5. Appendix 5: Allowed Recent Second or Prior Malignancies

### Allowed Recent Second or Prior Malignancies

i. Any malignancy that was not progressing nor requiring treatment change in the last 12 months [and not considered at high risk of recurrence requiring systemic therapy].

ii. Malignancies treated within the last 12 months and considered at very low risk for recurrence:

a) Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low-grade, <3 cm, no CIS).

b) Skin cancer (non-melanoma or melanoma).

c) Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, localized breast cancer and receiving antihormonal agents.

iii. Other malignancy that is considered at minimal risk of recurrence.

In the event of any questions, consult with the Sponsor's Medical Monitor prior to enrolling a participant.

## 10.6. Appendix 6: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine participant eligibility (see Section 5.2) for the study:

- Individuals who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Individuals who test **negative** for surface antigen (HBsAg-) and **positive** for core antibody (anti-HBc+) ***and*** **either positive or negative** for surface antibody (anti-HBs+ or anti-HBs-) must undergo further testing for the presence of HBV DNA.
    1. If the HBV DNA test is **negative**, the participant is eligible for this protocol. However, testing for the presence of HBV DNA should be performed every 3 months in addition to the ALT/AST laboratories according to the SoA while receiving study treatment until EOT. HBV DNA should be continued every 3 months along with ALT/AST monthly [in the follow-up period, if one exists, up to 12 months] or before the start of new anticancer treatment. If there is evidence of HBV reactivation, hold study treatment, if applicable, and initiate treatment for HBV infection as appropriate per institutional guidance.
    2. If the HBV DNA test is **positive**, the individual is ***NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the individual is ***NOT eligible*** for this protocol.
- Individuals who test **positive only** for **surface antibody** (anti-HBs+) and have a known history of prior HBV vaccination ***are eligible*** for this protocol.
- Individuals who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.

| **Eligibility Based on Hepatitis B Virus Test Results** | | | | |
|---|---|---|---|---|
| | **Hepatitis B test result** | | | |
| **Action** | Hepatitis B surface antigen (HBsAg) | Hepatitis B surface antibody (anti-HBs) | Hepatitis B core antibody (anti-HBc total) | Hepatitis B DNA |
| **Exclude** | positive | negative *or* positive | negative *or* positive | NA |
| | negative | negative *or* positive | positive | positive |
| | | | | |
| **Include** | negative | negative | negative | NA |
| | negative | negative *or* positive | positive | negative |
| | negative | positive | negative | NA |

NA: Not applicable or no need to test. A negative test (or antibodies/DNA below the level of quantification) is denoted as "negative"; a positive test (or presence of antibodies/DNA above laboratory thresholds) is denoted as "positive".

Modified from source: https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf. Accessed 11 March 2020.

## 10.7. Appendix 7: Anticipated Events

**Purpose [for US Submissions Only]**

This appendix applies only to the reporting of anticipated events by the Sponsor to the US FDA, and US-based Investigators and IECs/IRBs, in accordance with the FDA's guidance. The intent is to minimize the submission of a multitude of uninformative IND safety reports to these recipients.

**Definition of an Anticipated Event**

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen.

**Background**

The FDA acknowledges that certain SAEs can be anticipated to occur commonly in the study population regardless of drug exposure. Although these anticipated SAEs may meet the definition of unexpected (ie, SUSARs), because they are not listed in the IB, they do not warrant expedited reporting as individual cases, or even in aggregate if the incidence is consistent with the expected background rates in the study population.

**Analysis and Reporting of Anticipated Events**

All AEs and SAEs will be recorded and reported by the investigator to the Sponsor as described in Section 8.4.

The SAC is an established safety committee, independent of the study team. To meet US safety reporting, the SAC will periodically perform aggregate analysis of anticipated events per the ASMP, which details the statistical analysis, the frequency of review and thresholds to trigger an aggregate analysis of anticipated events.

If an anticipated event is determined to occur more frequently in the experimental arm(s) of the study and there is a reasonable possibility that the anticipated event could be drug-related, the Sponsor will prepare an aggregate safety report for FDA and US-based IRBs/ECs and Investigators.

**Anticipated Events for the Study**

The below list includes adverse events that are commonly anticipated for the disease stage, study population and background treatment, for which the Sponsor does not plan to report individual cases, regardless of the assessment of causality. This list is limited to those events for which an individual occurrence, or even an aggregate incidence consistent with the background rate in the study population, is inconsequential in the developing safety profile of the study treatment.

For the purposes of this study, the following events will be considered anticipated events:

| Disease-specific Events | ADT Events |
|---|---|
| erectile dysfunction | depression |
| hematospermia | gynecomastia |
| hematuria | libido decreased |
| incontinence | osteoporosis |
| lymphoedema | sexual dysfunction |
| nocturia | testicular atrophy |
| painful ejaculation | bone pain |
| pathologic fracture | |
| pollakiuria | |
| prostatic specific antigen increased | |
| spinal cord compression | |
| ureteral obstruction | |
| urethral obstruction | |
| urinary flow decreased | |
| urinary hesitation | |
| urinary tract obstruction | |

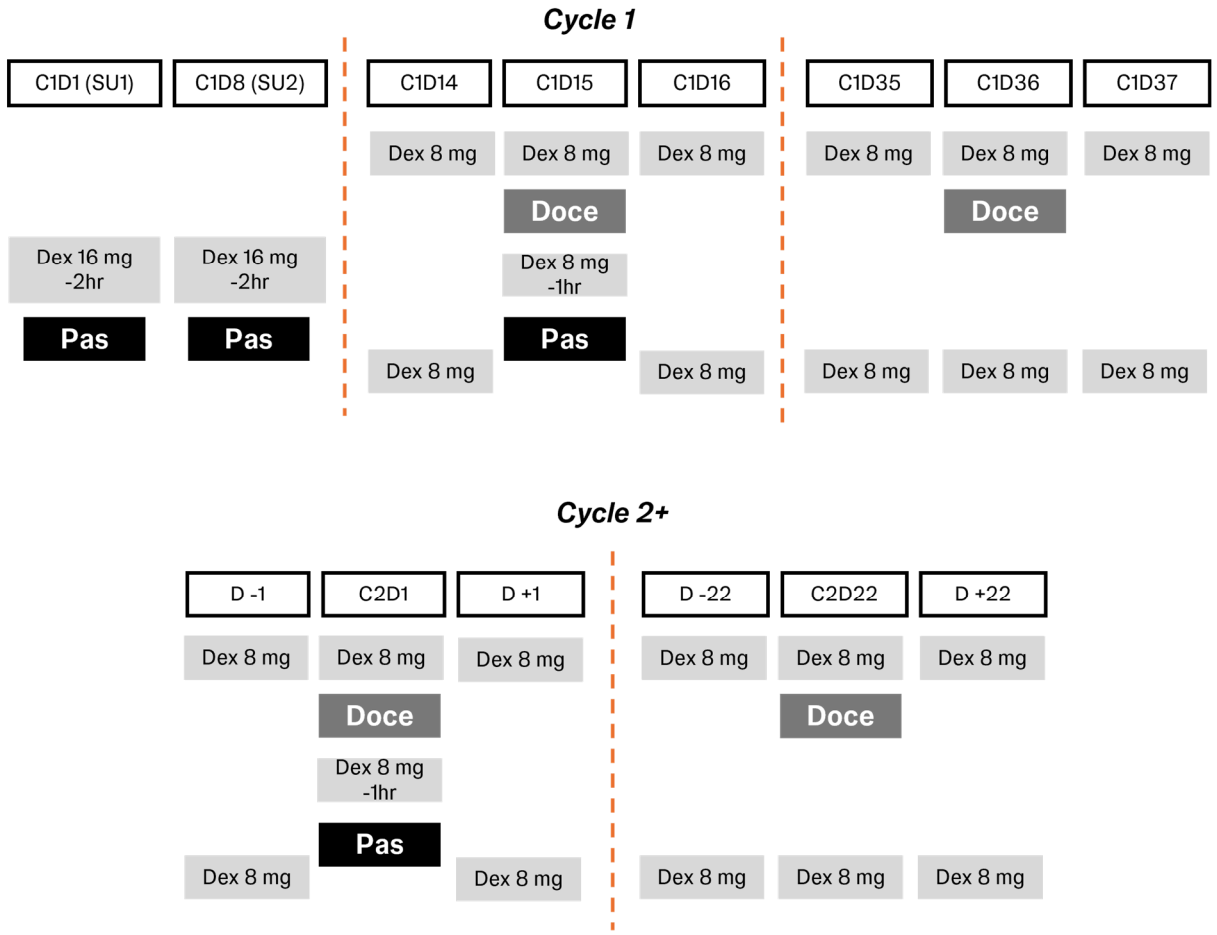
## 10.8. Appendix 8: Conversion Table for Glucocorticoid Dose

| Glucocorticoid | Approximate Equivalent Dose (mg) | Half-life (Biologic) (hours) |
|---|---|---|
| Short-Acting | | |
| Cortisone | 25 | 8-12 |
| Hydrocortisone | 30 | 8-12 |
| Intermediate-Acting | | |
| Methylprednisolone | 4 | 18-36 |
| Prednisolone | 5 | 18-36 |
| Prednisone | 5 | 18-36 |
| Triamcinolone | 4 | 18-36 |
| Long-Acting | | |
| Betamethasone | 0.6-0.75 | 36-54 |
| Dexamethasone | 0.75 | 36-54 |

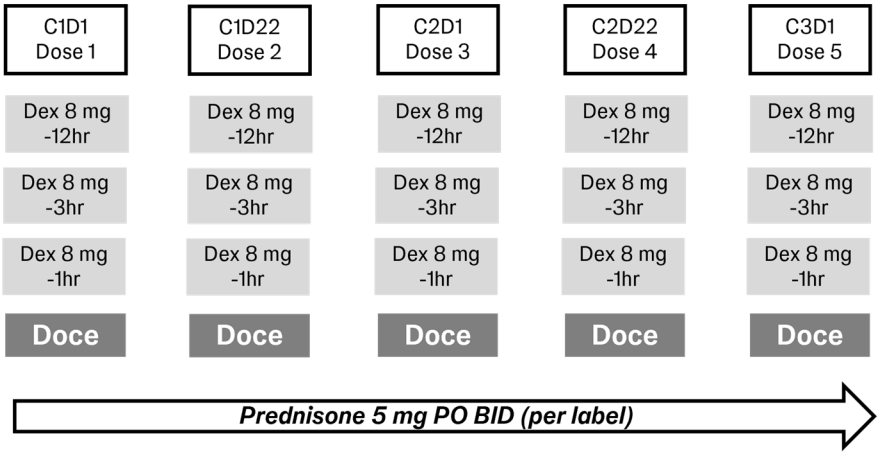
Source: http://globalrph.com/medcalcs/corticosteroid-converter-based-on-anti-inflammatory-potency/. Accessed 04 April 2024.

## 10.9. Appendix 9: Glucocorticoid Premedication Schema

**Experimental arm: Pasritamig + Docetaxel**




**Comparator arm: Docetaxel**




BID = Twice daily, Dex = Dexamethasone, Doce = Docetaxel, Pas = Pasritamig, PO = Orally, SU1 = Step-up dose 1, SU2 = Step-up dose 2

## 10.10. Appendix 10: Long-term Extension Phase With Crossover

The LTE Phase will be initiated when the site receives notification from the sponsor to start LTE. During this phase and if the Sponsor decides to allow study participant to cross over, participants from the comparator arm might cross over to the experimental study treatment arm. The purpose of this LTE Phase is to provide continued treatment to participants, while limiting data collection burden. This phase will continue until the discontinuation criteria described in Section 7.1 are met, or until notification by the Sponsor that participants will be moved to the DA-LTE Phase (Section 10.11).

- Participants who were randomized to receive pasritamig+docetaxel and are still on study treatment (ie, who are in Treatment Phase of the experimental arm) will continue to receive pasritamig until they reach a reason for discontinuation of treatment (see Section 7) or until further notification by the Sponsor of a different means for continued supply of study treatment, whichever occurs first.
- For participants randomized to receive the comparator (docetaxel) and are still in the Treatment Phase, the investigator may choose to cross the participant over to start pasritamig treatment if the participant meets the eligibility criteria below. Since all participants are already expected to have completed 10 doses of docetaxel, the participant will receive pasritamig alone. Investigators can also choose to maintain the participant on docetaxel in which case participants will transition to the Follow-up Phase and continue to be in follow-up per the below Time and Events Schedule (LTE) (Table 20).
- Participants who have already ended study treatment altogether and are in the Follow-up Phase in the main study will continue to be in follow-up per Table 20.

The EOT visit for the open-label Treatment Phase should occur within 3 months of the Sponsor's notification to proceed into the LTE.

### Eligibility Criteria for Participants who Cross Over to Open-label Pasritamig

Participants who are identified as candidates for crossover to experimental arm with pasritamig alone should meet the eligibility criteria below within 28 days prior to initiating pasritamig. If a participant does not meet these eligibility criteria, the participant will transition to the Follow-up Phase.

1. Still participating in the Treatment Phase of the study
2. Willing and able to provide informed consent to receive pasritamig
3. ECOG performance status Grade 0 or 1

Adequate organ function as outlined in the Sections 5.1 and 5.2.

### Study Treatment Administration

#### *Androgen Deprivation Therapy Administration*

ADT should be continued according to the standard of care.

***Open-label Study Treatment***

Pasritamig should continue to be administered as described in Section 6.1 (Table 7) and Section 6.9.1.

***Dose Modifications and Management Guidelines for Potential Toxicities:***

Refer to Section 6.6 and Section 6.6.4 of the protocol.

***Prohibitions and Restrictions***

Refer to Section 6.9.3 of the protocol.

***Study Procedures for the Long-term Extension***

Participants who meet the eligibility criteria as outlined above will be permitted to crossover to pasritamig. Cycle 1 Day 1 of the LTE should follow the last cycle in the Treatment Phase for those crossing over to pasritamig from docetaxel. Participants who enter LTE continuing the same study treatment they received in the Treatment Phase (ie, pasritamig) will continue with cycles numbered sequentially from the last cycle received while in the main study (ie, if the last cycle in the Treatment Phase was Cycle 11, the first LTE cycle will be Cycle 12).

All participants continuing in the LTE should follow the SoA (Long-term Extension) provided in Table 20.

Blood samples for safety laboratory tests should be collected from a local laboratory as specified in the SoA (Long-term Extension) (Table 20). The investigator should review the laboratory report, document this review, and record any clinically relevant changes in the AE section of the CRF.

**Table 20: Time and Events Schedule (LTE)**

| Procedures | Participants crossing over to open-label pasritamig after receiving docetaxel in the Treatment Phase | | | | Participants continuing pasritamig after already receiving pasritamig+ docetaxel in the Treatment Phase | | Participants off study treatment |
|---|---|---|---|---|---|---|---|
| **Screening** | | | | | | | |
| Informed consent for the LTE Phase | X | | | | X | | |
| Eligibility | X | | | | | | |
| **Period** | **Cycle 1 of LTE (8 weeks)** | | | **Cycle ≥2 of LTE (6 weeks)** | **Cycle X[b] of LTE (6 weeks)** | | |
| **Cycle Day[a]** | **1** | **8** | **15** | **1** | **1** | **22[h]** | |
| **Study Treatment Dispensing** | | | | | | | |
| Pasritamig[c] | Step-up dose 1[c] | Step-up dose 2[c] | X[c] | X | X | | |
| **Visit frequency** | | | | | | | |
| Participant should visit the study site | X | X | X | X | X | | X |
| **Clinical Laboratory** | | | | | | | |
| Safety laboratory assessments[d] | X | X | X | X | X | | |
| **Safety** | | | | | | | |
| Physical examination and vital signs[e] | X | X | X | X | X | | |
| AE/SAE | Continuously[f] | | | | | | |
| Survival[g] | | | | | | | X |
| **Efficacy** | | | | | | | |
| Efficacy assessments | Per local practice | | | | | | |

a. All cycles are 6 weeks except for Cycle 1 of LTE which will be 8 weeks.
b. "X" pertains to whichever cycle number is applicable to participant at start of LTE.
c. Refer to Table 7 on dose administration instructions and Table 9 for a list of pre-medications and instructions and requirements on premedication administration. A visit window of ±3 days for each scheduled treatment (including step-up doses) is allowed.
d. See Section 10.1 for a list of protocol-required laboratory tests. All laboratory assessments should be obtained per local practice. Hematology and chemistry assessments should be performed pre-dose.
e. Vital signs to be performed pre-dose before every dose. Post-dose vital signs assessments should be performed every hour (±30 minutes) for at least the first 2 hours post-dose for step-up dose, step-up dose 2, and first target dose (C1D15) and the second target dose (C2D1). Following the third target dose, vitals can be monitored post-infusion, if clinically indicated.
f. Continuous during this period and until 42 days after termination of study treatment or until starting subsequent treatment for prostate cancer, whichever occurs first. During follow-up, related SAEs will be collected and reported within 24h of notification of the event according to Section 8.4.
g. Every 3 months until notified by the Sponsor to stop collection. May be obtained by telephone or chart review

## 10.11. Appendix 11: Drug Access Long-term Extension Phase

The Drug Access Long-term Extension (DA-LTE) Phase will be initiated at the time when (1) the study reached its final analysis, or (2) LTE Phase with crossover is complete. Investigators should monitor and assess the participants for disease status (response, progression, survival) and safety according to routine practice and local label requirements. This phase will continue until the discontinuation criteria described in Section 7.1 are met or as described in Section 6.7.

Data collection will be limited to SAEs, which will be reported as specified in the relevant section on the appropriate SAE Form. No other safety nor any efficacy data are to be collected during the DA-LTE; no analyses other than routine periodic safety review encompassing reported SAEs are planned for the DA-LTE.

Participants entering DA-LTE who were randomized to receive pasritamig + docetaxel or crossed over to open-label pasritamig in LTE and are still on study treatment will continue to receive pasritamig. Participants assigned to docetaxel will be discontinued from the study upon the start of the DA-LTE.

Participants who had discontinued study treatment and are in the Follow-up Phase will be discontinued from the study upon the start of the DA-LTE, and all data collection will cease.

Participants who elect not to continue in the DA-LTE Phase will be discontinued from the study within approximately 3 months from the initiation of the DA-LTE Phase at the site.

**Study Treatment Administration**

***Androgen Deprivation Therapy Administration***

ADT should be continued per local practice.

***Open-label Study Treatment***

Pasritamig should continue to be administered as described in Section 6.1 (Table 7) and Section 6.9.1of the protocol.

***Dose Modifications and Management Guidelines for Potential Toxicities:***

Refer to Section 6.6 and Section 6.6.4 of the protocol.

***Prohibitions and Restrictions***

Refer to Section 6.9.3 of the protocol.

**Study Procedures for the Drug Access Long-term Extension**

All participants continuing in the DA-LTE should follow the schedule of procedures provided in the Time and Events Schedule (DA-LTE) in this appendix (Table 21).

### Case Report Form Completion

No data will be collected in the eCRF during this treatment period. However, documentation of assessments performed should be done in the participant file/source notes.

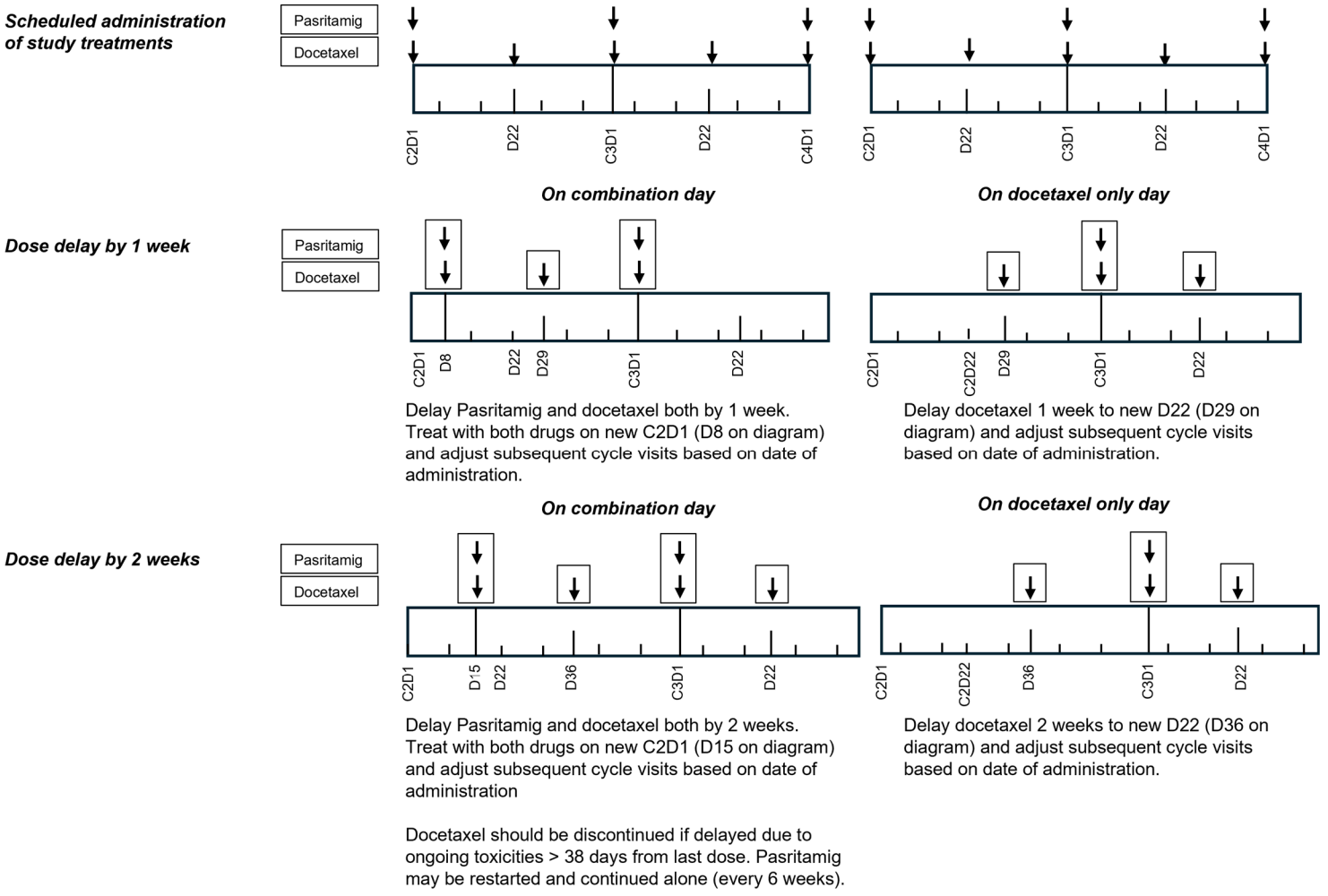
Section 10.2.10 of the main protocol will remain in effect, but follow the Time and Events Schedule and list of assessments in the Time and Events Schedule (DA-LTE) (Table 21).

**Table 21: Time and Events Schedule (DA-LTE)**

| Procedures | Continuing to Receive Pasritamig |
|---|---|
| **Informed Consent** | |
| Informed consent for the DA-LTE Phase | Participants must sign informed consent prior to entering DA-LTE Phase. |
| **Study Treatment Dispensing** | |
| Pasritamig | Dosing administration once every 6 weeks for pasritamig as described in Section 6.1. |
| Study treatment accountability | Drug accountability will be done in IWRS. |
| **Clinical Laboratory (Local Laboratory)** | |
| Hematology and blood chemistry | Should be collected pre-dose prior to administering pasritamig. No data will be collected. |
| **Safety** | |
| SAEs | Collection of SAEs as described in Section 8.4.<br>Pregnancy reporting should continue as described in Section 8.5. |
| **Efficacy** | |
| Efficacy assessments | Per local practice. No data are collected. |

## 10.12. Appendix 12: Dose Modification / Dose Delay Example Schema

The examples below are for explanatory purposes, the principles apply to any dose delay in the experimental arm on a combination dosing day or a docetaxel only dosing day in cycle 1-5.



## 10.13. Appendix 13: Participant Retention Challenges/Options

The examples below describe potential reasons participants may want to withdraw from the study and ways to address them. If other retention issues come up, contact the sponsor for discussion.

| Potential Withdrawal Reason | Options to Address Concern |
|---|---|
| Adverse events | • Inform participant upfront about potential adverse events and how to manage them.<br>• Encourage participant to reference participant-specific resources/ materials (wallet card, participant study guide, caregiver guide).<br>• Check in frequently on how the participant is feeling.<br>• Encourage participant to contact site with new or worsening symptoms. |
| Frequency of visits | • Inform participants about flexibility in scheduling visits (visits windows, advanced appointment scheduling, availability of travel support, and follow-up visits by telephone or chart review).<br>• Discuss any potential scheduling conflicts or if frequently missed visits.<br>• Inform the participant about the importance of continuing through the follow-up period.<br>• This will be particularly important for participants in the comparator arm who have completed/discontinued docetaxel and are continuing in the Post-treatment Follow-up Phase. Visit windows have been included specifically to allow greater flexibility during this phase. |
| Wants to discontinue study treatment permanently | • Determine reason why participant wants to discontinue treatment and whether the concern can be addressed (contact sponsor if cannot be addressed locally).<br>• If the specific concern cannot be addressed: offer the option to start the follow-up period and re-iterate the importance of the follow-up period (subsequent anticancer therapy can be started during the follow-up period). |
| Objects to a specific assessment | • Educate on importance of assessments – laboratory assessments, biomarker testing, imaging, biopsy (if indicated) in monitoring disease and response.<br>• While every effort should be made to complete all protocol-defined assessments, agreements with sponsor can be made for participants at risk of discontinuation. |
| Wants to discontinue follow-up visits | • Discuss importance of the follow-up period and inform about the flexibility in scheduling the visits, with alternative options available.<br>• If participant is not willing to continue follow-up visits, offer the option for site to get routine visit records from treating physician. |
| Concerns about data privacy regarding collection of pharmacokinetic, immunogenicity or biomarker samples | • Advise participant that they may opt-out of continued use and storage of coded study samples if desired. |

## 10.14. Appendix 14: Protocol Amendment History

This is an original protocol.

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## INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Victor M. Villalobos, MD, PhD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

# Signature

| User | Date | Reason |
| --- | --- | --- |
| Villalobos Victor 1079563 | 15-Sep-2025 18:10:02 (GMT) | Document Approval |