A Phase 1 Trial of Valemetostat Plus Darolutamide in Metastatic Castration-Resistant Prostate Cancer

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SUMMARY

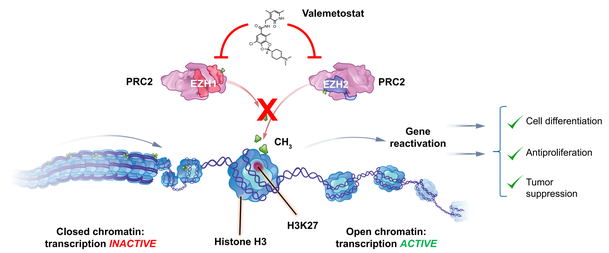
- Metastatic castration-resistant prostate cancer (mCRPC) is a universally lethal disease with poor prognosis that invariably develops resistance to androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs), with limited benefit to standard-of-care approaches[1]
- Valemetostat is a dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1 with promising tolerability and disease control in genitourinary malignancies when combined with immune checkpoint inhibition[2,3]; darolutamide is a potent ARPI with demonstrated efficacy and tolerability in castration-resistant and hormone-sensitive prostate cancer (PC)[4,5]
- In PC, EZH2 drives ARPI resistance by reprograming androgen receptor (AR) output,[6] and the inhibition of EZH2/EZH1 by valemetostat is proposed to resensitize tumors to darolutamide and prevent potential compensatory mechanisms due to EZH1 activity[7,8]
- DS3201-343 is a multicenter, open-label, phase 1 study evaluating the safety and tolerability, preliminary efficacy, and pharmacokinetic (PK)/pharmacodynamic profile of valemetostat in combination with darolutamide in patients with progressive mCRPC previously treated with an ARPI
- This trial is actively enrolling patients in Australia, China, Europe, Japan, and the United States

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INTRODUCTION

- PC is a leading cause of cancer-related death in men, with 2.9 million global cases expected by 2050[9]
- Patients initially respond to ADT and ARPIs but progress to castration-resistant prostate cancer (CRPC), characterized by:
  - Poor prognosis[1]
  - Median overall survival (OS) of ≤ 3 years[1]
  - Persistent AR activity linked to epigenetic reprogramming (particularly via EZH1 and EZH2, components of the polycomb repressive complex 2 [PRC2], which trimethylates histone H3 lysine 27 [H3K27me3])[10,11]
- In PC, EZH2 sustains ARPI resistance via canonical PRC2-mediated gene repression and noncanonical AR transcriptional coregulation[6]
  - EZH2 dysregulation also drives lineage plasticity, promoting neuroendocrine differentiation and leading to ARPI resistance[12,13]
- Valemetostat is a potent oral dual inhibitor of EZH2 and EZH1 that maximally suppresses H3K27me3 (**Figure 1**) and demonstrates promising tolerability and early signals of disease control when combined with ipilimumab in advanced genitourinary malignancies, including aggressive variant PC[2,3]

Figure 1. Mechanism of action of valemetostat



CH_3, trimethyl group.

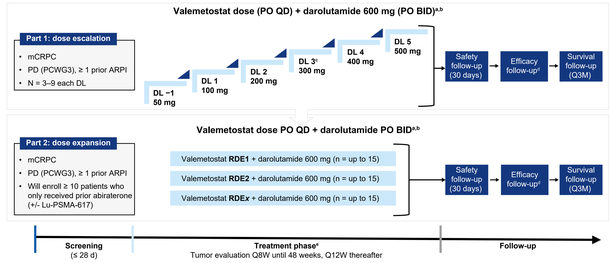
- Darolutamide is an AR antagonist with demonstrated efficacy and favorable tolerability in CRPC and hormone-sensitive PC[4,5]
- By targeting EZH1, EZH2, and AR, valemetostat plus darolutamide is proposed to disrupt both PRC2-mediated repression and EZH2-driven AR reprogramming, addressing multiple layers of ARPI resistance[6]
  - Darolutamide minimally induces cytochrome P450 (CYP) enzymes, which, combined with weak CYP3A inhibition by valemetostat, creates a favorable PK relationship, potentially removing the need for dose escalation[14,15]
- Here, we describe the study design of an ongoing phase 1 trial of valemetostat + darolutamide in patients with ARPI-resistant mCRPC

METHODS

Study design

- DS3201-343 (NCT07244341) is a multicenter, open-label, phase 1 trial evaluating the safety, tolerability, and preliminary efficacy of valemetostat in combination with darolutamide in patients with mCRPC who progressed after prior ARPI and who have castrate testosterone levels on ongoing ADT
- The trial is composed of a dose-escalation phase (part 1) to establish the recommended doses for expansion (RDE) of valemetostat, followed by a dose-expansion phase (part 2) to evaluate the safety, tolerability, and preliminary efficacy of valemetostat plus darolutamide (**Figure 2**)
  - Part 1: patients receive oral valemetostat at escalating doses of 100–500 mg once daily (QD) and oral darolutamide at a fixed 600-mg dose twice daily (BID), following a Bayesian optimal interval (BOIN) dose-escalation design
  - Part 2: up to 15 patients will be enrolled per valemetostat dose level across ≥ 2 cohorts
- Target enrollment is ~ 30 patients in part 1 and ~ 15 patients per dose level in part 2
  - The key eligibility criteria are shown in **Table 1**
- Treatment will continue until death, unacceptable toxicity, radiographic progressive disease (PD) (Prostate Cancer Working Group 3 [PCWG3]-modified Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria[16]) or clinical progression, withdrawal of consent, or significant protocol deviation
- The study began in December 2025 and is expected to last ~ 5 years
  - Enrollment is currently ongoing in Australia, China, Ireland, Japan, and the United States

Figure 2. Study design



[a]Darolutamide will be given in combination with continued ADT (as per SOC). [b]Ten cycles of docetaxel with prednisone at 75 mg Q3W (as per SOC). [c]Dose level 3 can be adjusted based on emerging clinical data from earlier dose levels. [d]During the efficacy follow-up, patients who discontinued trial interventions without radiographic PD will continue to undergo tumor assessments at the same protocol-specified frequency until the investigator determines radiographic PD or until participant discontinues the efficacy follow-up. [e]Treatment administered until PD.
DL, dose level; Lu, lutetium; PD, progressive disease; PO, orally; PSMA, prostate-specific membrane antigen; Q3M, every 3 months; Q3/8/12W, every 3/8/12 weeks; QD, once daily; SOC, standard of care.

Table 1. Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Male and ≥ 18 years of age[a] • Histologically confirmed adenocarcinoma of the prostate[b] • Documented CRPC, defined as disease progression despite ADT, and serum testosterone < 50 ng/dL • Prior ARPI therapy – A minimum of 10 patients who have only received prior abiraterone and no other ARPI in the mHSPC, nmHSPC, or CRPC setting will be enrolled – These patients may also have received prior docetaxel chemotherapy in the HSPC setting and/or prior Lu-PSMA-617 for the treatment of CRPC • Evidence of metastatic disease as confirmed by radiographic imaging (CT, MRI, or bone scan) • Evidence of disease progression per PCWG3-modified RECIST v1.1 criteria • Ongoing androgen deprivation at time of enrollment • ECOG PS of 0 or 1 • Baseline PSA expression level of ≥ 2 ng/mL • Adequate organ and bone marrow function as assessed by local laboratory within 28 days prior to enrollment	• Prior treatment with epigenetic agents including EZH or PRC2 inhibitors • Has a superscan as seen in the baseline bone scan • Active brain metastases, spinal cord compressions, or leptomeningeal carcinomatosis • Uncontrolled or significant cardiovascular disease • Ongoing use of moderate or strong CYP3A and/or P-gp inducers or strong/moderate CYP3A or P-gp inhibitors • History of another primary malignancy within the 3 years prior to enrollment/ randomization[c] • Unresolved toxicities from previous anticancer therapy • Has received a live attenuated vaccine within 30 days prior to the first dose of trial intervention

[a]Or the minimum legal adult age, whichever is greater. [b]Cases exhibiting neuroendocrine differentiation are eligible for enrollment, except those with a diagnosis of pure small cell carcinoma, which is excluded. [c]Except for locally curable cancer that is currently considered cured, such as cutaneous basal or squamous cell carcinoma, superficial bladder cancer, or gastric cancer or carcinoma in situ of the prostate or breast.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HSPC, hormone-sensitive prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; P-gp, P-glycoprotein; PSA, prostate-specific antigen.

Objectives and endpoints (Table 2)

- Part 1 will assess the safety and tolerability of escalating doses of valemetostat combined with darolutamide and determine the RDEs for valemetostat
  - RDEs will be determined based on the incidence of dose-limiting toxicities (DLTs); adverse events of special interest (AESIs); treatment-emergent adverse events (TEAEs) associated with trial intervention discontinuation, interruption, and dose reduction; and clinically significant changes from baseline in vital signs, clinical laboratory results, and electrocardiograms (ECGs)
  - Sentinel dosing will be used for each new dose cohort with a period of 24 hours between the first patient to receive a dose and others, and an evaluation will be conducted by the safety review committee after each cohort of ≥ 3 patients
- Part 2 will further evaluate the safety and tolerability of valemetostat at the RDEs established in part 1 in combination with darolutamide
  - Safety and tolerability will be assessed based on the incidence of TEAEs, AESIs, deaths, serious TEAEs, and clinically significant changes from baseline in vital signs, clinical laboratory results, and ECGs
  - Preliminary clinical activity will also be assessed

Exploratory endpoints

- Exploratory endpoints include (**Table 2**):
  - Changes in H3K27me3 in tumor tissue and plasma to validate direct PRC2 suppression by valemetostat and its correlation with PSA response
  - Transcriptional profiling by RNA sequencing to evaluate whether valemetostat disrupts both canonical PRC2 repression and noncanonical EZH2–AR cooperation in ARPI resistance
  - AR alterations and circulating tumor DNA (ctDNA) dynamics to identify potential resistance mechanisms, evaluate tumor burden and clonal evolution, and discover potential biomarkers associated with clinical benefit
- Emerging evidence suggests that EZH2/EZH1 inhibition may trigger compensatory DNA methylation changes[17]; future analyses of cell-free DNA methylation patterns could provide mechanistic insights into the crosstalk between DNA methyltransferases and PRC2

Table 2. DS3201-343 trial endpoints

Primary endpoints	
• DLTs (part 1 only) • TEAEs • TEAEs requiring dose modification or discontinuation	• SAEs • AESIs • ECG parameters, physical examination (including ECOG PS), vital signs, and laboratory tests
Secondary endpoints	
• PSA50[a] • PSA90[a] • PSA nadir[a] • ORR (CR or PR per PCWG3-modified RECIST v1.1) • Time to rPFS[b]	• Time to PSA progression • Time to first SSRE • OS • Valemetostat plasma concentrations, PK of valemetostat plus darolutamide
Exploratory endpoints	
• Changes in H3K27me3 • Biomarkers, including androgen receptor mutations, and relationship to efficacy	• Transcriptional changes in tumors/blood and relationship to efficacy • Exposure–response analyses of valemetostat and darolutamide

[a]Percentage of patients who achieved PSA declines of ≥ 50% (PSA50), ≥ 90% (PSA90), or to PSA ≤ 0.2 ng/mL (PSA nadir) at any time during the treatment period. [b]As assessed by the investigator based on the PCWG3-modified RECIST v1.1 criteria or death due to any cause.
AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PR, partial response; PSA50/90, ≥ 50/90% decrease in PSA; rPFS; radiographic progression-free survival; SAE, serious AE; SSRE, symptomatic skeletal-related event.

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ACKNOWLEDGMENTS

- This study is sponsored by Daiichi Sankyo Co., Ltd
- All authors contributed to and approved the presentation
- Editorial support was provided by Linda Tirou, PhD, of Omnicom Health Medical Communications, funded by Daiichi Sankyo Co., Ltd, and in accordance with Good Publication Practice (GPP) guidelines.

DISCLOSURES

R.R.M.: AstraZeneca, Aveo, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera, Caris, Denderon, Exelixis, Janssen, Merck, Myovant, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Tempus – consultancy/advisory board; Artera, AstraZeneca, Bayer, Bristol Myers Squibb, Exelixis, Oncternal, Tempus – institutional research funding.

Presented at the European Society for Medical Oncology (ESMO) Congress; October 23–27, 2026; Madrid, Spain.

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