

Rinzimetostat, an Allosteric PRC2 Inhibitor Combined with Darolutamide: A Global Phase 3 Study in Patients with mCRPC Previously Treated with Abiraterone Acetate (Himalayas-1)

Joaquin Mateo,¹ Karim Fizazi,² Johann de Bono,³ Arun A. Azad,⁴ Elisabeth I. Heath,⁵ Rahul Aggarwal,⁶ Wassim Abida,⁷ Rupal Patel,⁸ Jian Wang,⁸ Vanessa Tassell,⁸ Edna Chow Maneval,⁸ Pratik S. Multani,⁸ Matthew R. Smith⁹

¹Vall d’Hebron Institute of Oncology (VHIO), Vall d’Hebron University Barcelona Hospital Campus, Barcelona, Spain; ²Department of Cancer Medicine, Centre Oscar Lambret, University of Paris Saclay, Lille, France; ³Division of Clinical Studies Royal Marsden Hospital Institute of Cancer Research, Sutton, London, UK; ⁴Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; ⁵Mayo Clinic Rochester, Rochester, MN, USA; ⁶University of California San Francisco, San Francisco, CA, USA; ⁷Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁸ORIC Pharmaceuticals, Inc., South San Francisco, CA, USA; ⁹Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA

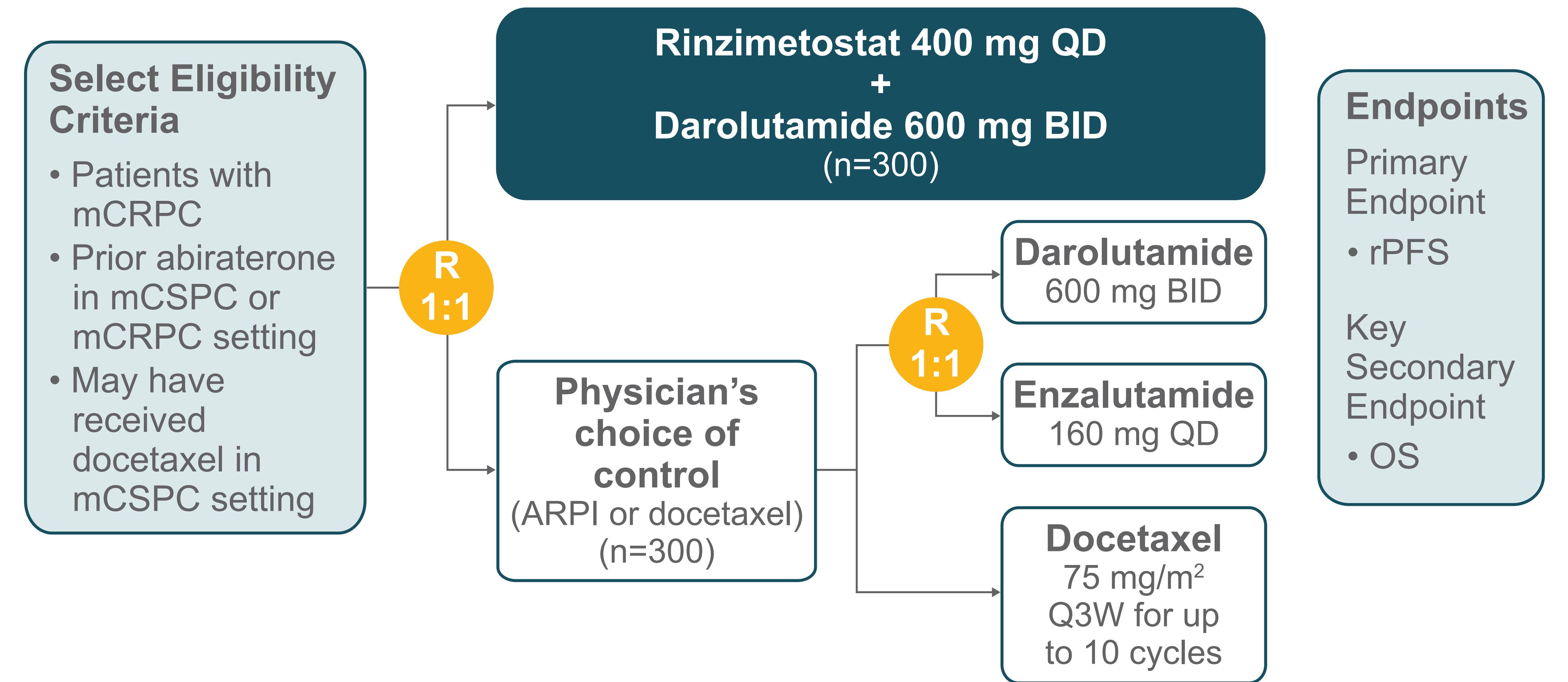
BACKGROUND AND RATIONALE

- In metastatic castration-resistant prostate cancer (mCRPC), androgen receptor pathway inhibitors (ARPIs) such as abiraterone play a critical role in disease management.¹ However, resistance eventually develops and remains a significant treatment challenge²
 - Such resistance may be driven by mechanisms that promote epigenetic reprogramming and lineage plasticity.^{2,3} Polycomb repressive complex 2 (PRC2) has been implicated in these adaptive processes³⁻⁵
- Rinzimetostat is an oral, potent, selective allosteric inhibitor of PRC2 that targets the embryonic ectoderm development (EED) subunit.⁶ Combining rinzimetostat with darolutamide may limit tumor cell adaptation and prolong clinical benefit from continued androgen receptor pathway inhibition^{7,8}
- Phase 1b dose-optimization data supported selection of rinzimetostat 400 mg once daily (QD) in combination with darolutamide 600 mg twice daily (BID) for evaluation in Himalayas-1
- Himalayas-1 is evaluating whether rinzimetostat plus darolutamide improves outcomes compared with physician's choice of an ARPI or docetaxel in patients with mCRPC previously treated with abiraterone

METHODS

- Himalayas-1 (NCT07723248) is a global, randomized, open-label Phase 3 study evaluating rinzimetostat plus darolutamide versus a prespecified physician's choice of ARPI or docetaxel control in approximately 600 patients with mCRPC previously treated with abiraterone
- Key eligibility criteria are shown in **Table 1**
- Patients will be randomized 1:1 to receive rinzimetostat 400 mg QD plus darolutamide 600 mg BID, or prespecified physician's choice of control (ARPI or docetaxel) (**Figure 1**)
 - Patients randomized to docetaxel will receive 75 mg/m² intravenously every 21 days for up to 10 cycles
 - If the prespecified control is ARPI, patients will undergo a second 1:1 randomization to darolutamide 600 mg BID or enzalutamide 160 mg QD
 - Randomization will be stratified by prior docetaxel use in the metastatic castration-sensitive prostate cancer (mCSPC) setting, prespecified control category (ARPI versus docetaxel), and presence of hepatic metastases
- The primary endpoint is radiographic progression-free survival (rPFS), with overall survival (OS) as the key secondary endpoint; additional endpoints and assessments are summarized in **Table 2**

Figure 1. Himalayas-1 Study Design



ARPI, androgen receptor pathway inhibitor; BID, twice daily; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; n, number of patients in subgroup; OS, overall survival; Q3W, every 3 weeks; QD, once daily; R, randomization; rPFS, radiographic progression-free survival.

Table 1. Key Eligibility Criteria

Inclusion	Exclusion
- Male patients aged ≥18 years - Histologically or cytologically confirmed prostate adenocarcinoma without small cell features - Progressive disease in the setting of surgical or medical castration, with evidence of disease progression as per PCWG3 on treatment with abiraterone ≥12 weeks in the mCSPC setting or first-line mCRPC setting - Metastatic disease in bone documented on bone scan, or in soft tissue documented on CT/MRI scan - ECOG PS of 0 or 1 - Adequate organ function	- Prior systemic anticancer therapy, beyond protocol-permitted abiraterone-based treatment and docetaxel in the mCSPC setting - Radiotherapy within 2 weeks before randomization - Known or suspected brain metastases or active leptomeningeal disease - Clinically significant cardiovascular disease - Active inflammatory gastrointestinal disease, chronic diarrhea, or previous gastric resection or lap-band surgery

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Working Group 3.

Table 2. Study Endpoints and Assessments

Endpoints	Assessments
Primary Radiographic progression-free survival	BICR per RECIST v1.1 for soft-tissue disease or per PCWG3 criteria for bone disease, or death from any cause, whichever occurs first
Key secondary Overall survival	Death due to any cause
Selected secondary - Objective response rate - Duration of response - PSA response rate - Time to PSA progression - Safety and tolerability - Patient-reported outcomes	- Confirmed complete or partial response in patients with measurable soft-tissue disease - Time from first response to radiographic progression or death - Confirmed ≥50% and ≥90% PSA declines from baseline per PCWG3; maximum PSA decline - Time from treatment start to PSA progression per PCWG3 criteria - Incidence and severity of adverse events per NCI-CTCAE v6.0 and protocol-specified clinical safety assessments - BPI-SF, FACT-P, EQ-5D-5L, PRO-CTCAE, FACT-GP5

BICR, blinded independent central review; BPI-SF, Brief Pain Inventory - Short Form; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FACT-GP5, Functional Assessment of Cancer Therapy-General Physical Well-Being item 5; FACT-P, Functional Assessment of Cancer Therapy-Prostate; NCI-CTCAE v6.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 6.0; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

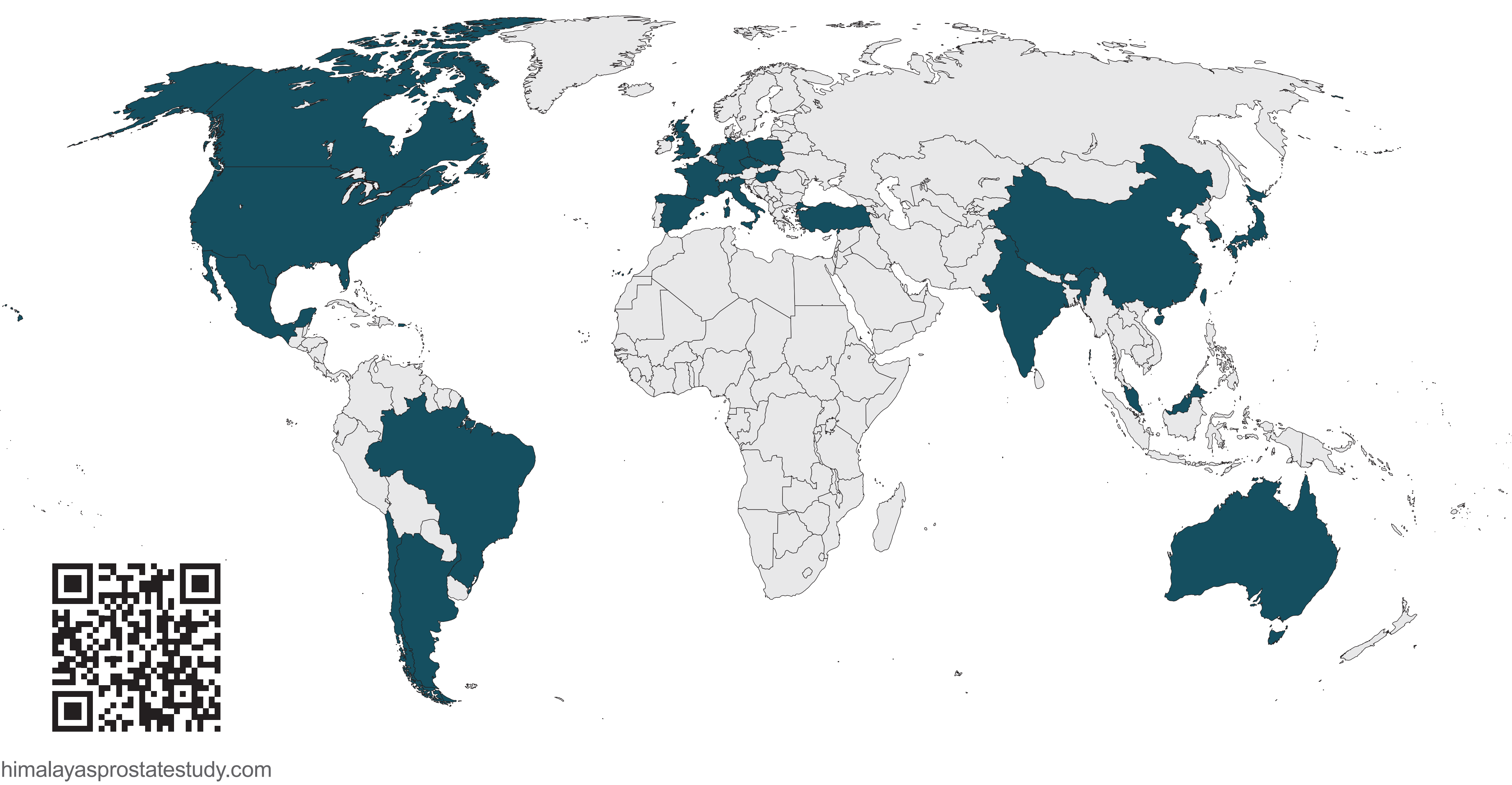
STATISTICAL ANALYSIS

- Approximately 600 patients will be randomized 1:1 to rinzimetostat plus darolutamide versus physician's choice of ARPI (1:1 to darolutamide or enzalutamide) or docetaxel
- rPFS will be compared between treatment groups using a stratified log-rank test based on the three randomization stratification factors. The hazard ratio and corresponding 95% confidence interval will be estimated using a stratified Cox regression model, and Kaplan-Meier methods will be used to summarize rPFS
- OS will be formally tested only if the primary rPFS analysis is statistically significant and will be analyzed using corresponding stratified log-rank, Cox regression, and Kaplan-Meier methods

STUDY GEOGRAPHY

- Himalayas-1 is a global study planned across approximately 250 study sites in 25 countries (**Figure 2**)
- Study initiated in July 2026

Figure 2. Global Himalayas-1 Study Footprint



himalayasprotestudy.com

For current enrolling study locations and additional trial information, scan the QR code.

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DISCLOSURES

JM has received research funding from Amgen, AstraZeneca, and Pfizer; has participated in advisory boards with Amgen, Amunix, AstraZeneca, Janssen, Nuage Therapeutics, Roche, and Pfizer; and has been an invited speaker for AstraZeneca, Guardant Health, and MSD.

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