

Title: Translating MetAP2 inhibition in aggressive variant prostate cancer: preclinical rationale for the EVADE-1 trial of SDX-7320 (evexomostat)

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Background:

Prolonged, widespread use of androgen signaling-targeted therapies has driven the emergence of aggressive variant prostate cancer (AVPC), a lethal, androgen-independent phenotype. AVPC frequently presents as PSMA-low or PSMA/FDG-discordant metastatic disease, rendering these patients ineligible for PSMA-targeted radioligand therapy and in need of AR-independent options. Methionine aminopeptidase-2 (MetAP2), a metalloprotease linked to prostate cancer grade and stage, is inhibited by the novel agent SDX-7320 (evexomostat), which we previously showed suppresses tumour growth in androgen-sensitive, castration-resistant (CRPC), and enzalutamide-resistant models. Here we extend these findings to AVPC models and describe their translation into EVADE-1, a planned Phase IIa trial of evexomostat in this population.

Methods: LTL545, LuCaP 49, LTL331R and LTL370 AVPC patient-derived xenografts (PDX) were grown to 100mm³ in mice, randomized to vehicle or SDX-7320 (8 mg/kg, s.c., every 4 days), with tumours measured three times weekly and collected at endpoint for RNA sequencing, proteomics and histology. Building on this rationale, EVADE-1 (ACTRN12626000736347) is a single-arm, open-label Phase IIa pilot study (Princess Alexandra Hospital/QUT, Brisbane), expected to open to recruitment in Q4 2026, enrolling men with metastatic castration-resistant prostate cancer harbouring PSMA-low (SUVmax<15) and/or FDG-avid AVPC lesions unsuitable for PSMA-radioligand therapy. Evexomostat (49 mg/m²) will be administered subcutaneously every 14 days alongside continued ADT. The primary endpoint is ⁶⁸Ga-PSMA PET/CT-defined progression-free survival (PSMA-PFS); secondary endpoints include FDG-PFS, concordance between PSMA and FDG responses, and correlative changes in ctDNA, PSA, and metabolic, hormonal, angiogenic and inflammatory biomarkers.

Results: SDX-7320 significantly reduced endpoint tumour mass, prolonged median survival, and reduced angiogenic marker CD34 across all AVPC PDX models. Tumour suppression reflected heterogeneous responses, with some models showing predominantly reduced proliferation (Ki-67) and others increased apoptosis (cleaved caspase-3, cleaved-PARP), potentially linked to ER stress (ATF4). Molecular analyses revealed altered oxidative phosphorylation, RNA processing and cytoskeletal signatures, alongside reduced plasticity regulators EZH2, c-Myc, SOX2 and PROX1 across CRPC and

AVPC models. Reduced CD34 and downregulation of EZH2, c-Myc, SOX2 and PROX1 suggest anti-angiogenic and de-differentiation effects, to be tested clinically via the paired PSMA/FDG PET-CT and ctDNA correlates in EVADE-1.

Conclusions: These preclinical data establish MetAP2 inhibition as a rational, AR-independent strategy for AVPC and directly informed the design of EVADE-1, planned to open to recruitment in Q4 2026, which will determine whether evexomostat confers imaging-defined disease control and identify biomarkers of response in a population with no PSMA-radioligand or standard targeted option.

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