

The methionine aminopeptidase-2 inhibitor, evexomostat, potently suppresses tumour growth in aggressive variant prostate cancer models

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Background and Preliminary Data

- The emergence of treatment-resistant aggressive variant prostate cancer (AVPC) following the prolonged clinical use of androgen receptor (AR)-targeted therapies has created an urgent need for effective, AR-independent therapies.
- Methionine aminopeptidase-2 (MetAP2), a regulator of protein synthesis, metabolism, plasticity and angiogenesis, is highly expressed in AVPC and correlates with disease aggressiveness¹.
- We have previously demonstrated that the MetAP2 inhibitor, SDX-7320/evexomostat² potently suppressed tumour growth CRPC models (Fig 1).
- Here, we extend these findings to AVPC model and describe their translation into EVADE-1, a planned Phase IIa trial of evexomostat in this population.

We aimed to assess the efficacy of evexomostat in aggressive variant prostate cancer models and identify key mechanisms which may underpin its anti-tumour activity.

1) Xie J. et al. Cancer Res. 2021;81(9):2510-22

2) Cornelius P. et al Mol Cancer Ther. 2024;23(5):595-605

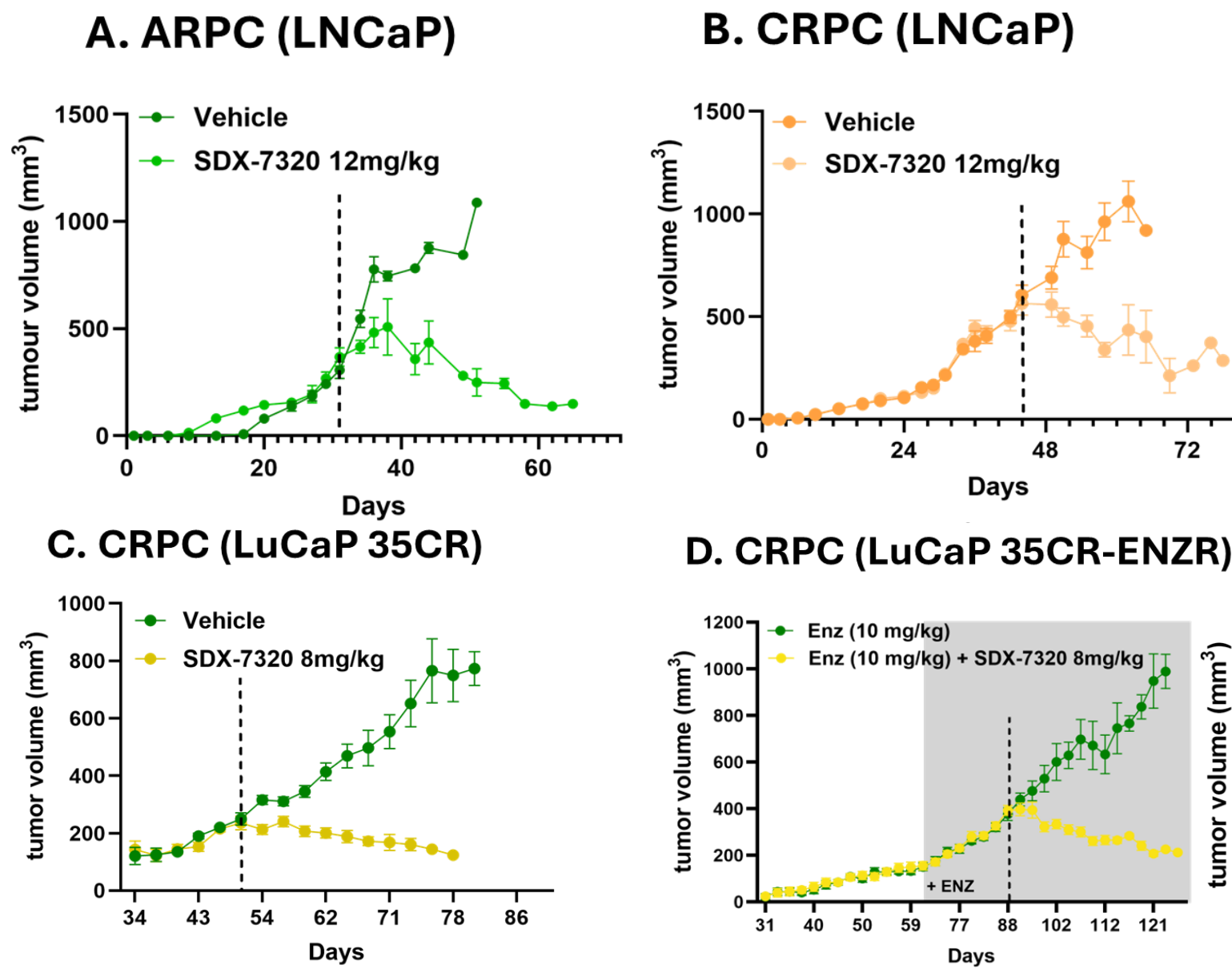
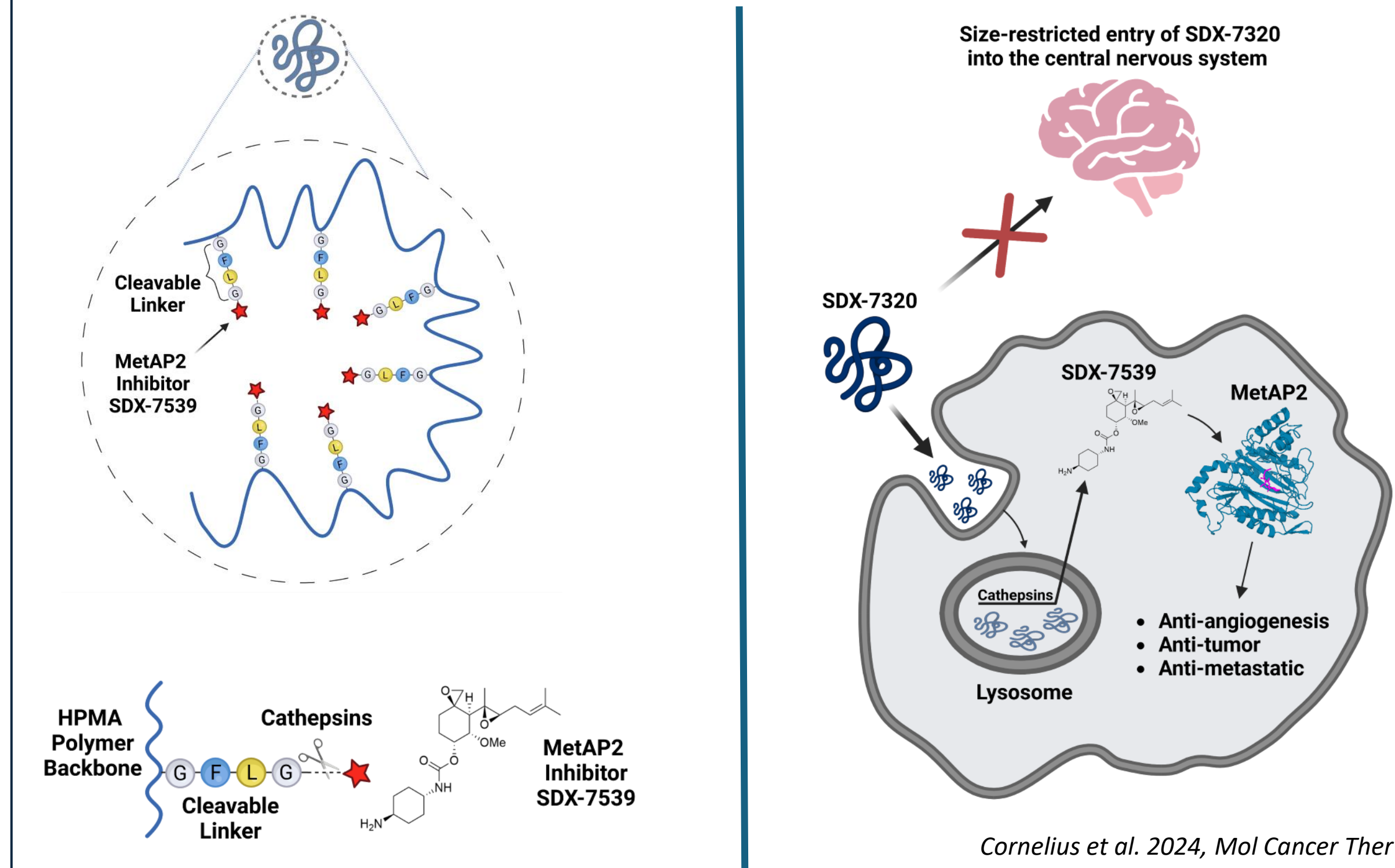


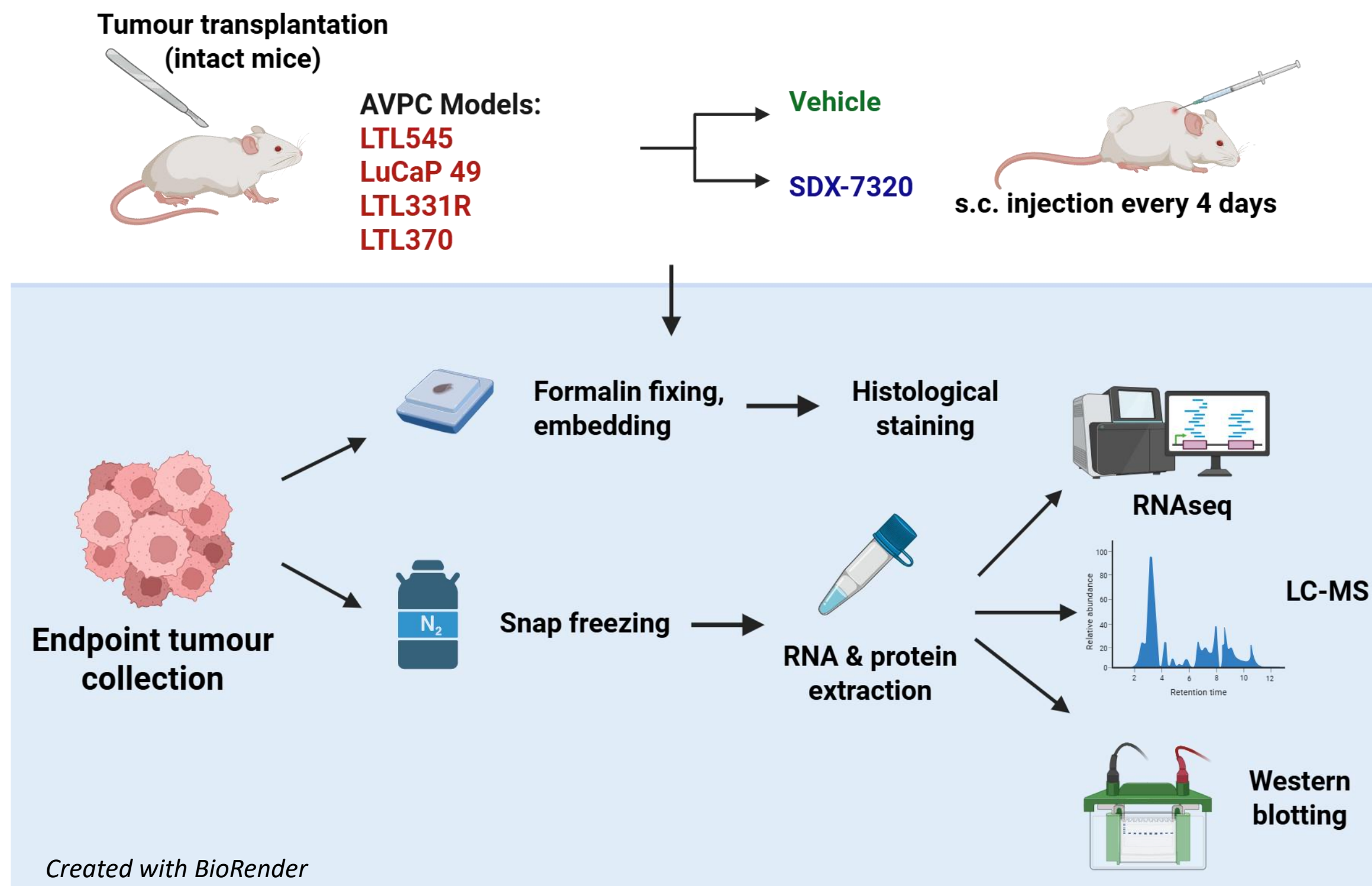
Figure 1. SDX-7320 potently reduced tumour growth in models of androgen-sensitive and castrate-resistant prostate cancer (A-D). Dotted line indicates time of randomisation.

Evexomostat / SDX-7320



Cornelius et al. 2024, Mol Cancer Ther

Methods



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SDX-7320 potently suppressed tumour growth and angiogenesis in multiple models of aggressive variant prostate cancer

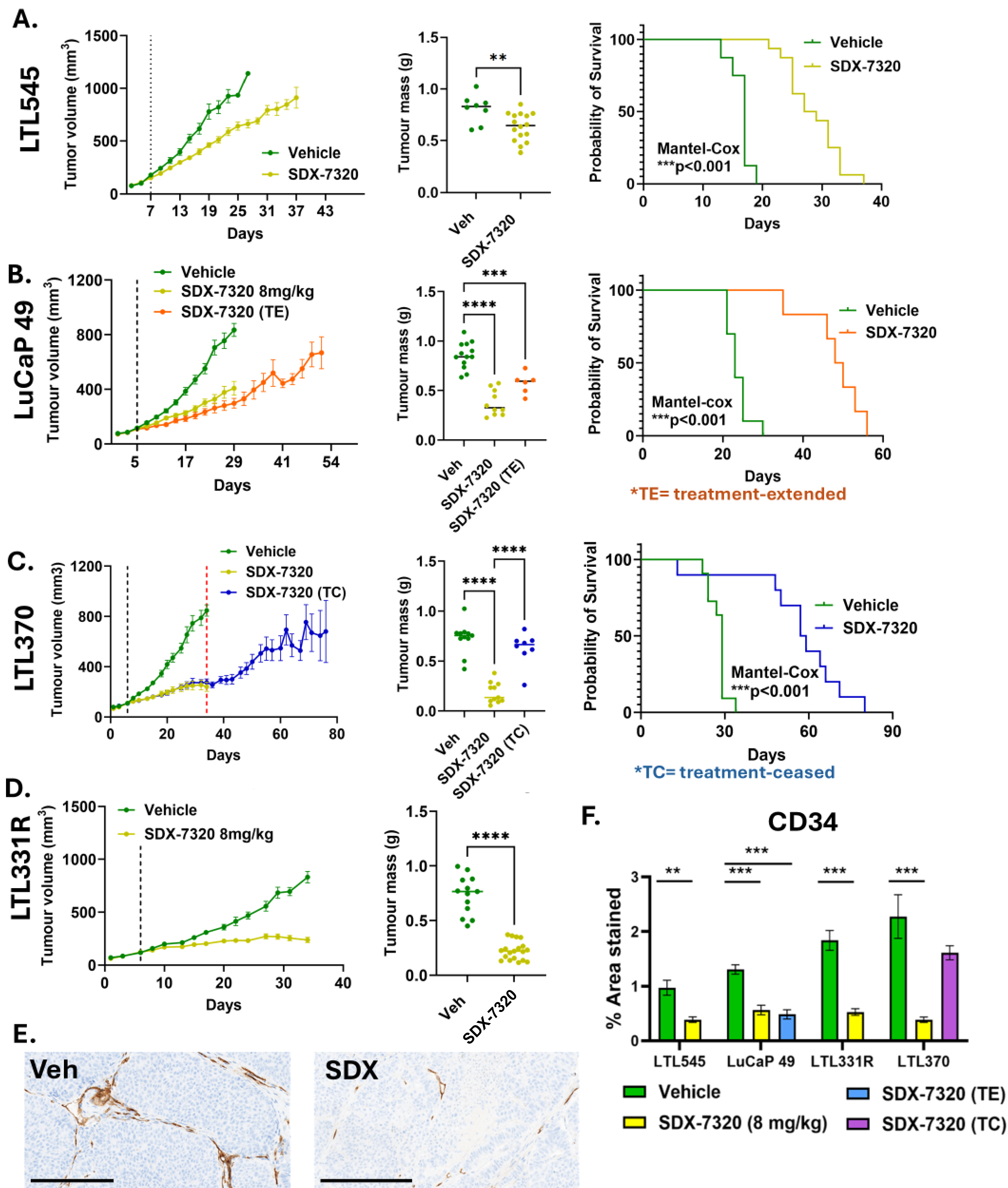


Figure 2. SDX-7320 treatment significantly reduced tumour growth, endpoint tumour mass and extended survival of mice bearing LTL545 (A), LuCaP.49 (B), LTL370 (C) and LTL331R (D) models of AVPC. The angiogenic marker CD34 was significantly reduced in SDX-7320-treated tumours (E&F). Scale bar 200 uM.

*treatment extended arm (TE) and treatment ceased arm (TC) in LuCaP49 and LTL370 models include mice who continued receiving SDX-7320 until tumours reached 1000 mm³ (TE), and mice whose SDX-7320 treatment was stopped after 8 cycles and allowed to live until tumours reached 1000mm³ (TC).

Anti-tumour mechanisms of SDX-7320 include suppression of proliferation and increased apoptosis

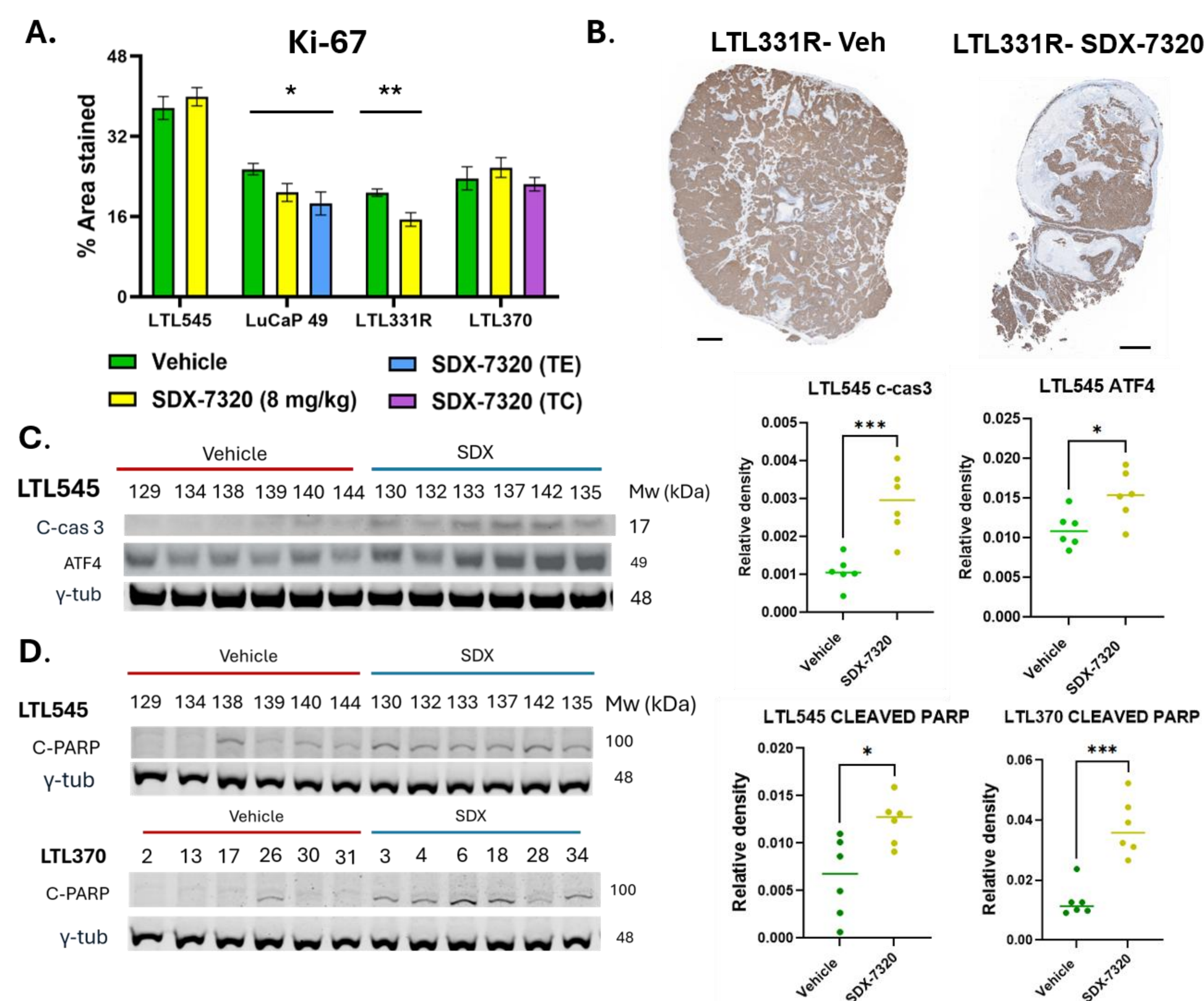


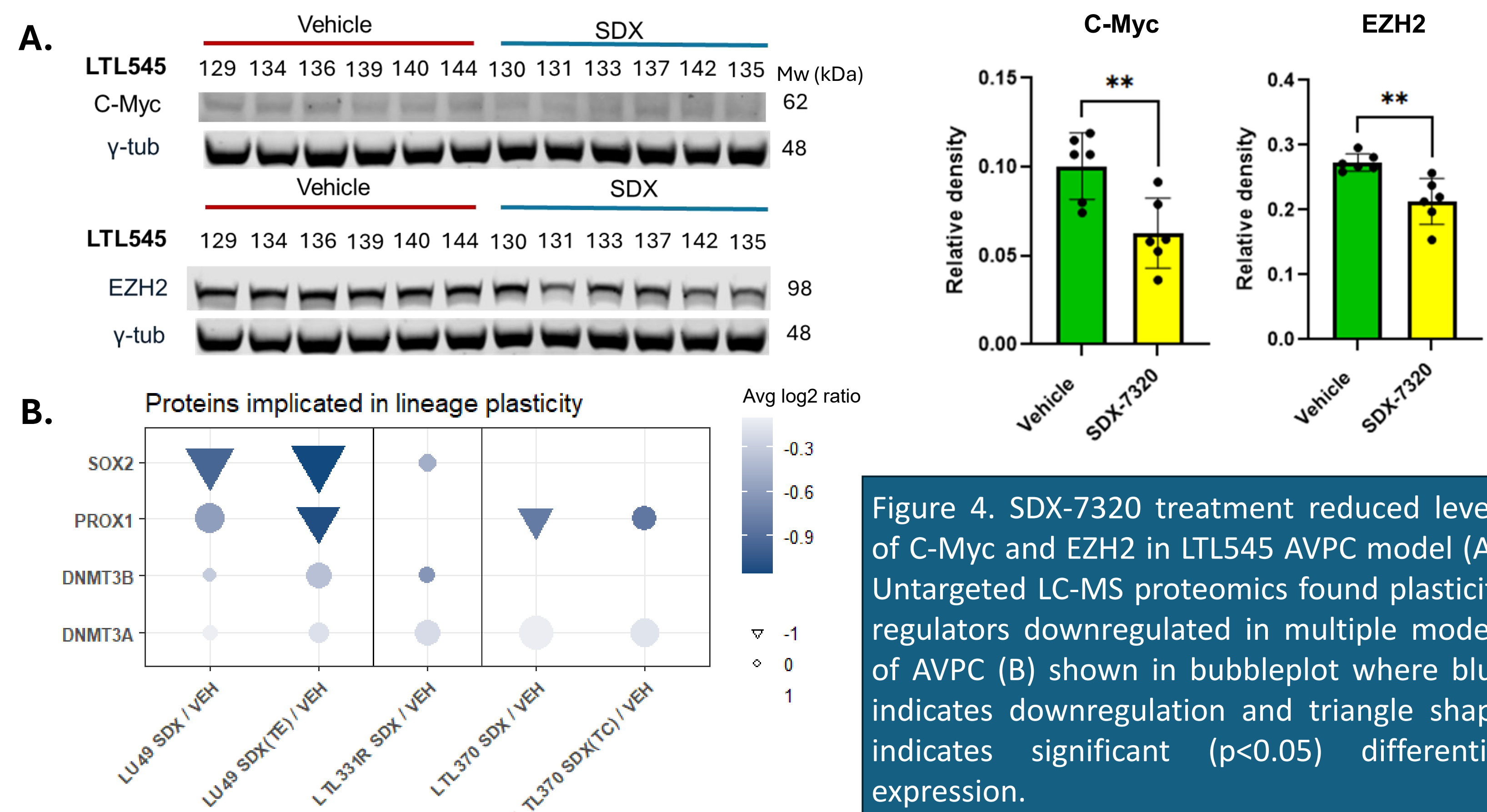
Figure 3. SDX-7320 treatment induced heterogenous responses. LuCaP.49 and LTL331R showed reduced proportion of staining with proliferation marker Ki-67 (A,B) (Scale bar= 1mm), while LTL545 and LTL370 showed a predominant increase in apoptosis, potentially linked to ER stress with increased cleaved Caspase-3 (c-cas3), cleaved-PARP, and increased ATF4 (C,D).

Conclusion

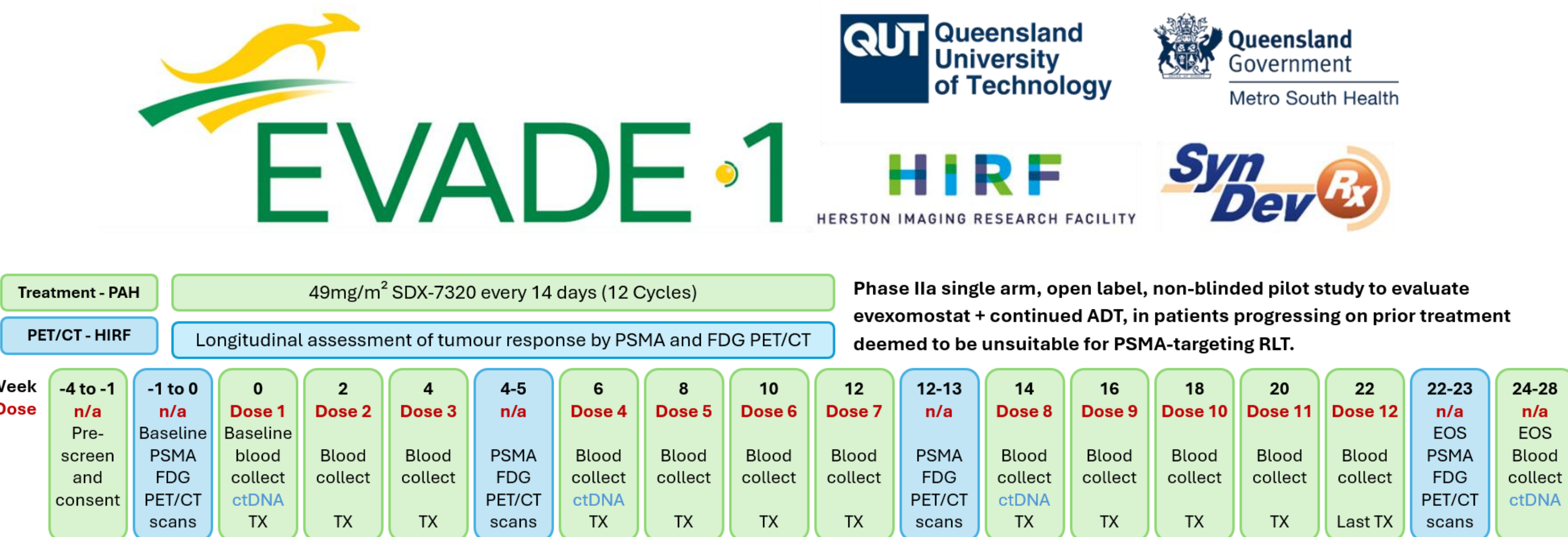
- Evexomostat significantly suppressed tumour growth in AR- aggressive variant prostate cancer models via multiple mechanisms, including suppression of angiogenesis, proliferation, and increased apoptosis.
- Evexomostat reduced multiple plasticity regulators, including C-Myc, EZH2 and SOX2, suggesting de-differentiation effects.

Our findings support the advancement of SDX-7320 (evexomostat) to clinical trials for patients with advanced prostate cancer, where there is a high clinical need for novel effective therapeutics.

SDX-7320 downregulates multiple regulators of lineage plasticity



EVADE-1: a Phase IIa study of evexomostat in patients with metastatic castrate-resistant AVPC



- Phase IIa, single-arm, open-label pilot study of evexomostat + continued ADT in mCRPC progressing on prior therapy (n≤15), with aggressive-variant phenotype metastases (PSMA-PET/CT SUVmax <15, or ≥1 lesion ≥10 mm on FDG PET/CT) unsuitable for PSMA-targeted radionuclide therapy.
- Evexomostat 49 mg/m² SC q14d, up to 12 doses (~24 weeks). (ACTRN 12626000736347, HREC/2026/QMS/124843), with primary endpoint (PSMA-PFS by ⁶⁸Ga-PSMA PET/CT, RECIP v1.0).
- Opening in Brisbane, Australia, Q4, 2026 (PI Prof Aaron Hansen).

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