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From Biology to Therapy for Advanced Prostate Cancer

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Disclosures

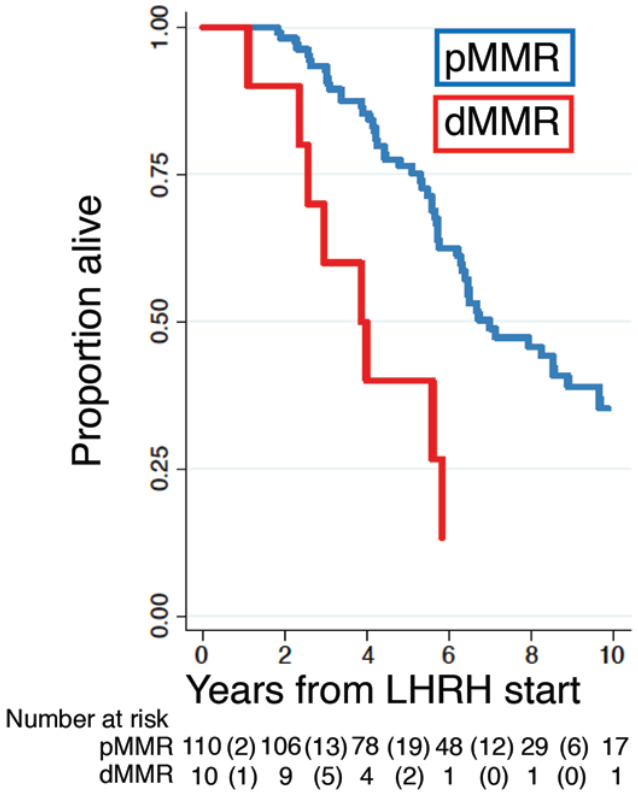
- ***All biases in my interpretations are mine.***
- My institution has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income)
- I have served on advisory boards for many companies including Astra Zeneca, Astellas, Bayer, Boehringer Ingelheim, Genentech/Roche, Genmab, GSK, Janssen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Sanofi Aventis, Taiho.
- My institution has received funding or other support for my research work from AZ, Astellas, Bayer, Genentech, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Taiho.
- I have been the CI/PI of many industry sponsored clinical trials

Talk Outline

- **Introduction**
- B7-H3
- HER3
- CXCR2
- Conclusion

Introduction

- Advanced PCa is a molecularly heterogenous disease
- AR blockade still a mainstay of therapy
  - Resistance to endocrine therapy
    - AR alterations, RTK/AKT signaling, senescence/SASP
- DNA repair defects common in advanced Pca
  - BRCA2, ATM, mismatch repair defective disease
    - MMRd disease has poor prognosis without ICI
  - This has impacted care with PARP inhibitors and ICI

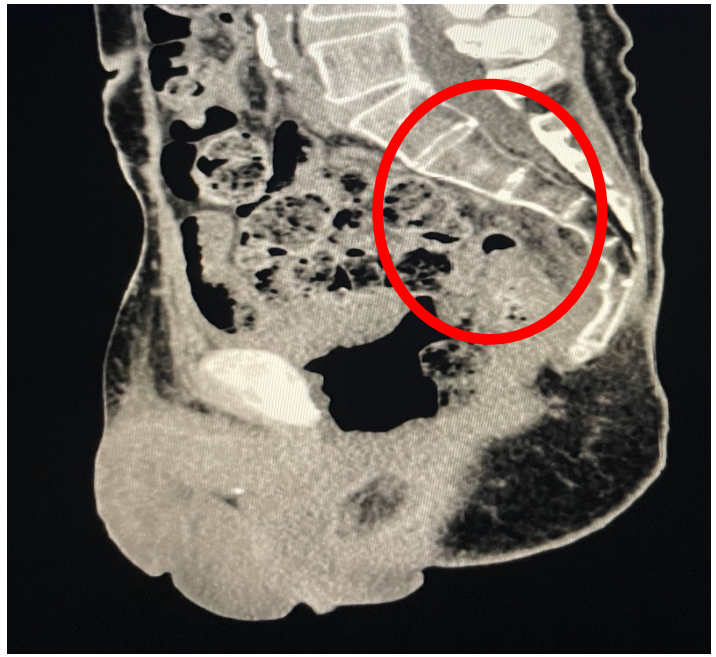


Nava Rodrigues et al, JCI 2018

MMRd advanced PCa treated with pembrolizumab: Still in complete response after >6-years! Cured?

- Gleason 10, post Docetaxel, Abiraterone, enzalutamide. PSA 0.43
- Genomics: MSH6 p.Y214*, MSH6 IHC loss. CDK12 p.R979*, ERCC3 p.Q677*

Baseline 7.11.2016



Best response 14.03.2017, CR >5years!

Rescigno P et al, Eur Urol 2020

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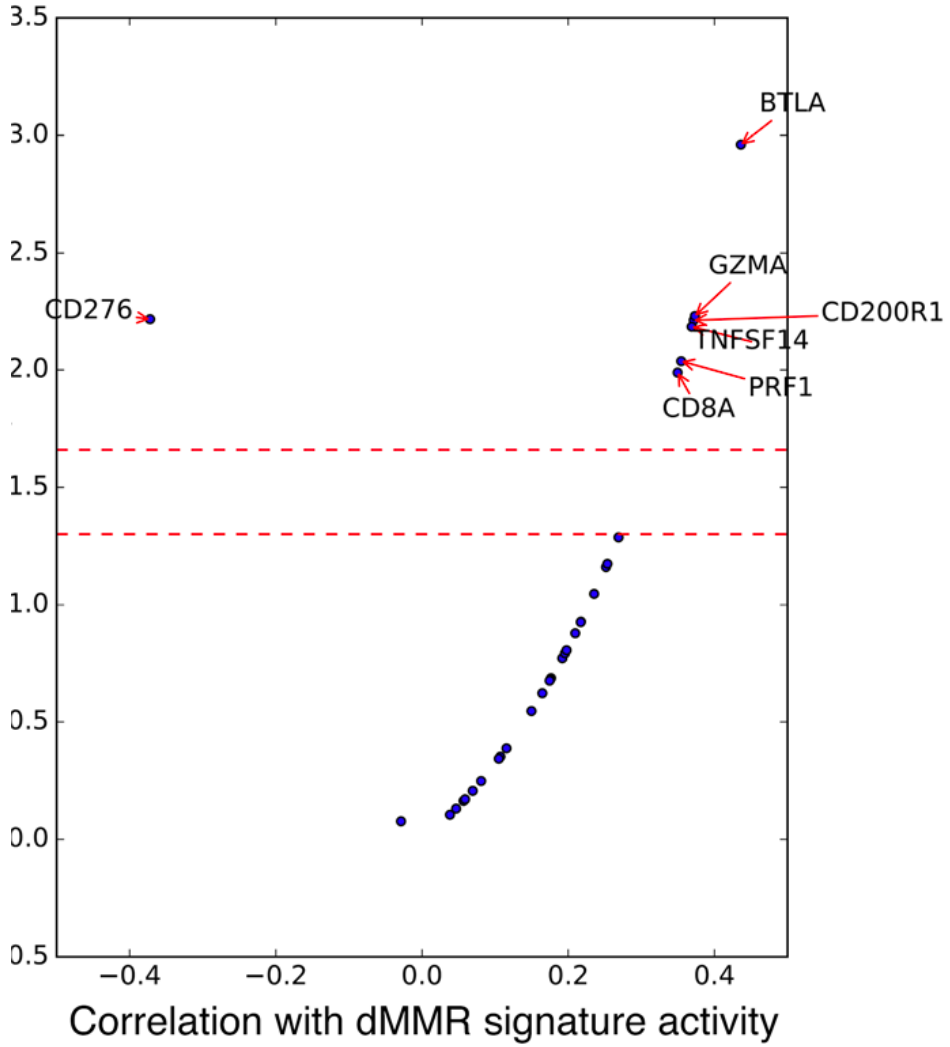
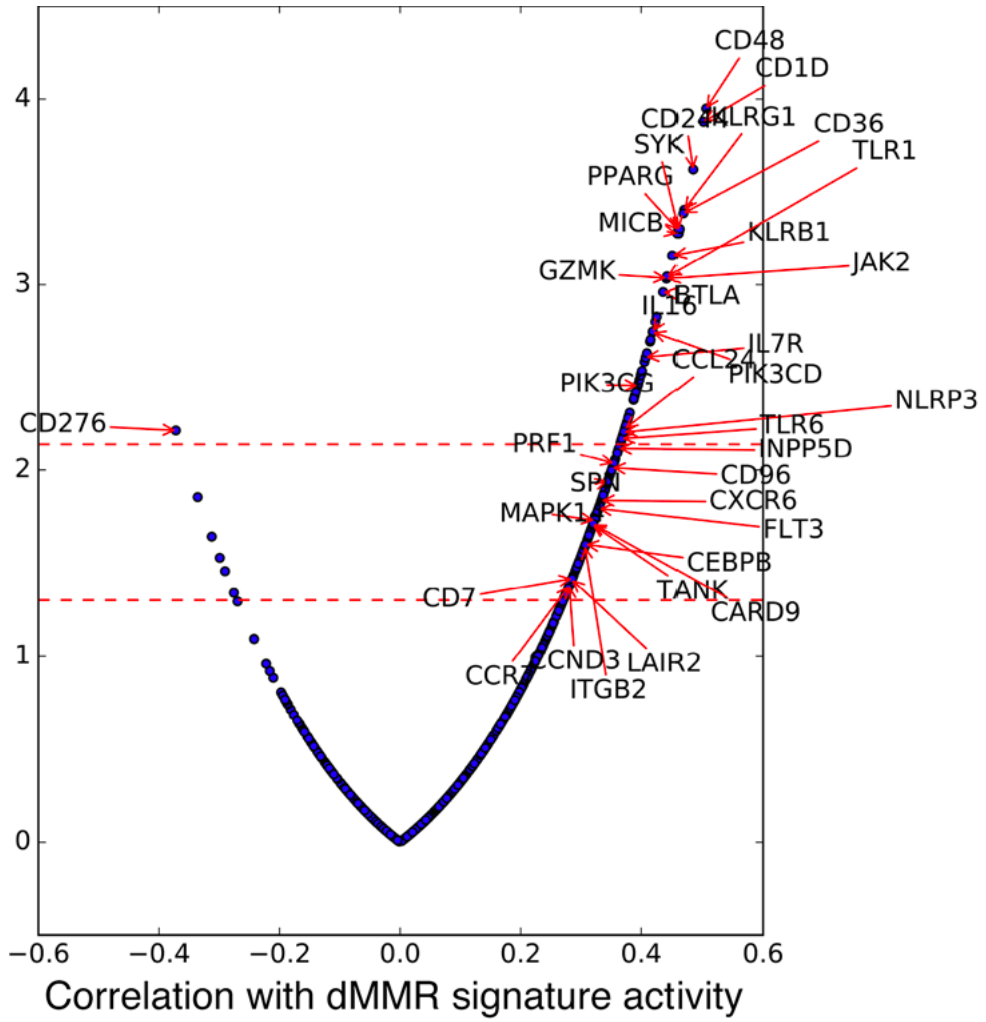
When analysing RNAseq data for MMRd mCRPC CD276 or B7-H3 stood out as negatively associated with MMRd

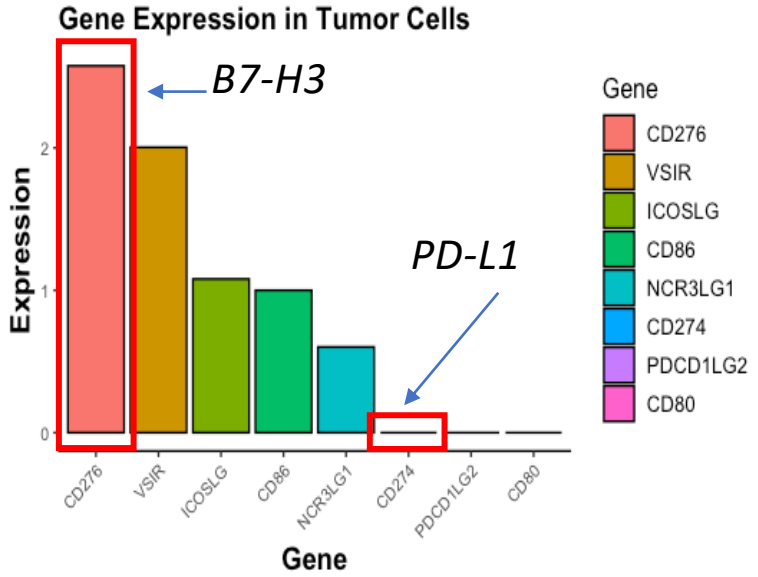




Rodrigues et al, JCI 2018

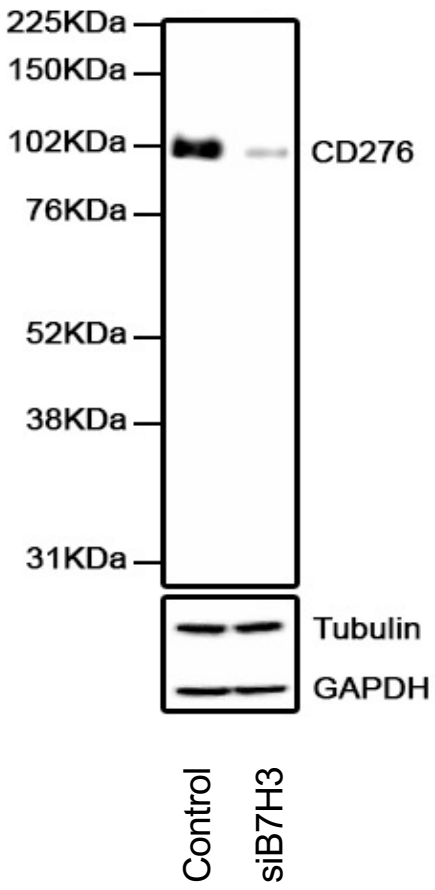
B7-H3/CD276

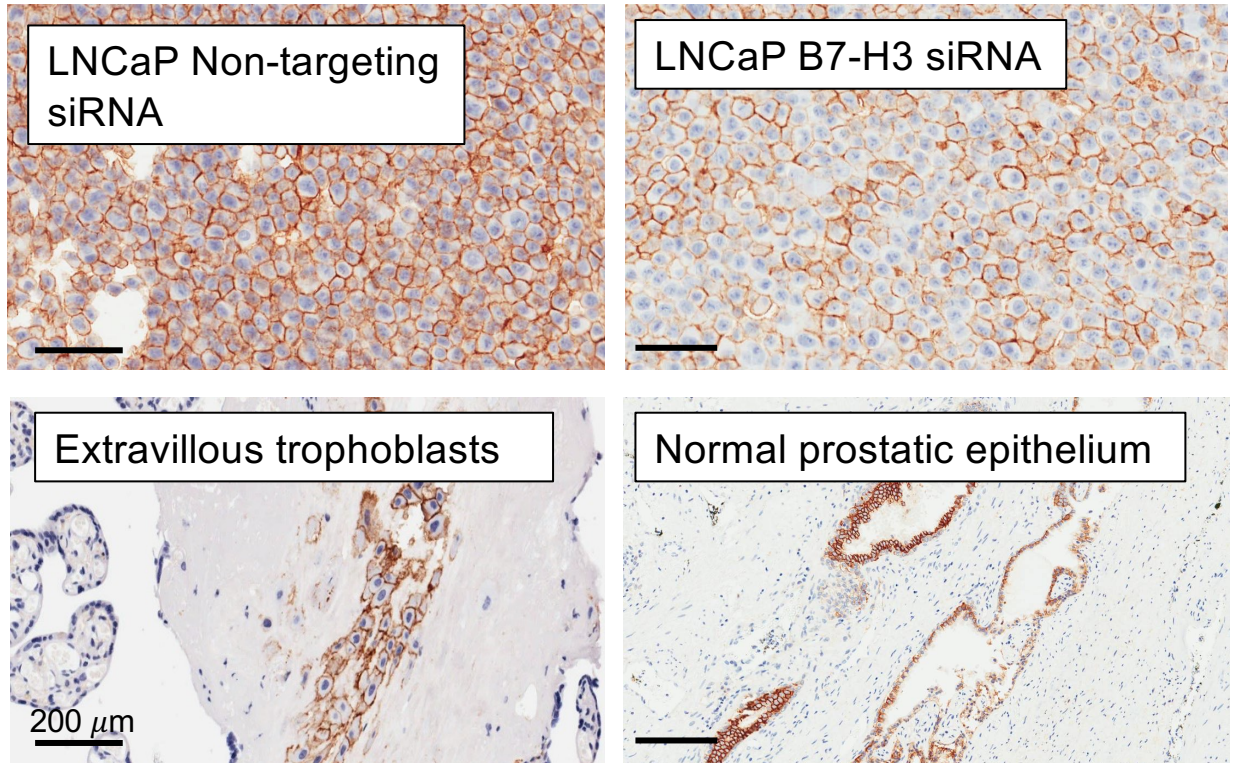
- B7-H3 is a member of the B7 family of proteins like PD-L1/B7-H1
  - PD-L1 not highly expressed in most advanced PCa although prognostic and expression associated with MMRd
- B7-H3 is the most highly expressed immune checkpoint in Pca and among top 10% of most highly expressed immune genes in two RNAseq cohorts
- B7-H3 expressed in human placenta but in few normal tissues



Sartor, de Bono, NEJM, 2017; Kwon et al., Lancet Oncol, 2014; Benzon et al. Prostate Cancer Prostatic Dis, 2017; Haffner et al., Am J Pathol, 2018; Antonarakis, JCO, 2020; Rodrigues, JCI, 2018

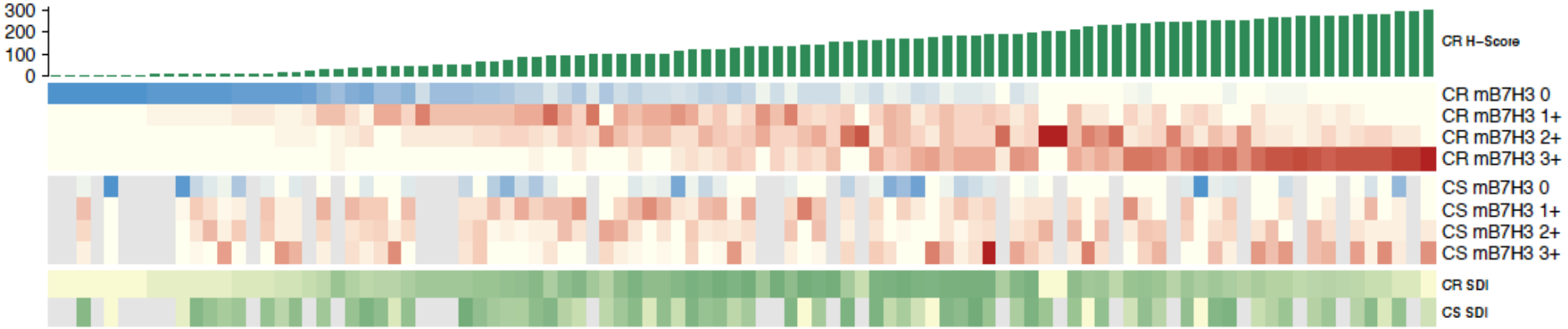
Validation of B7-H3 antibody

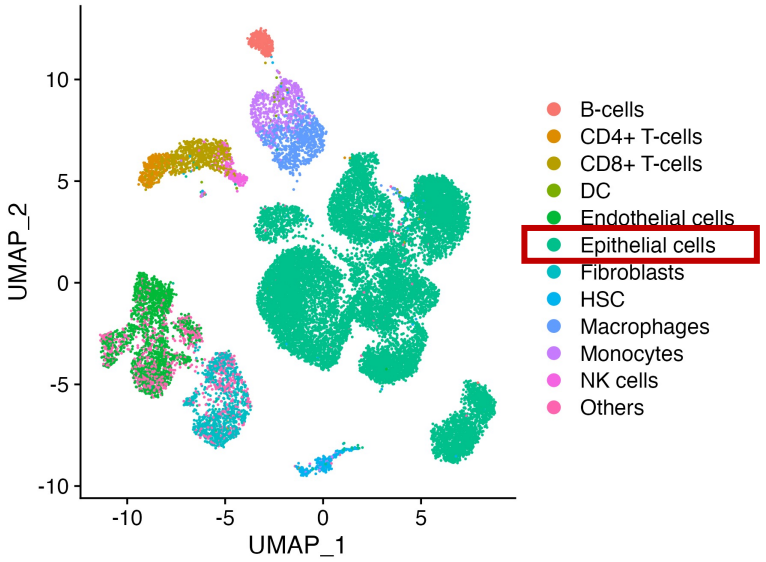


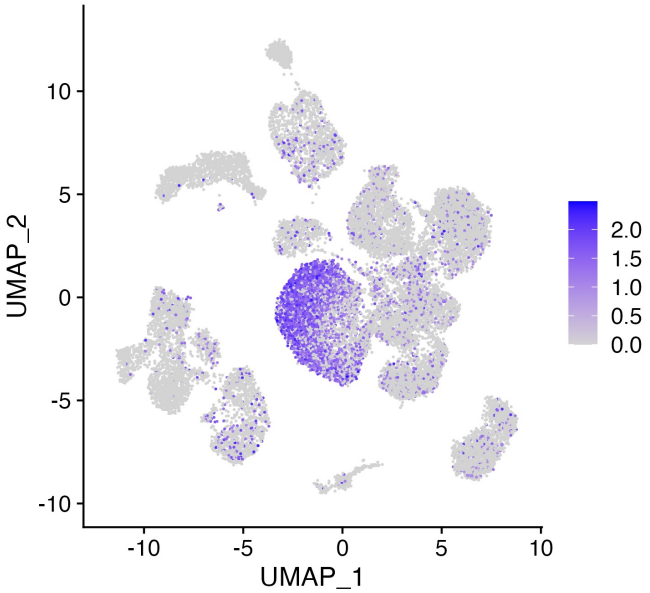


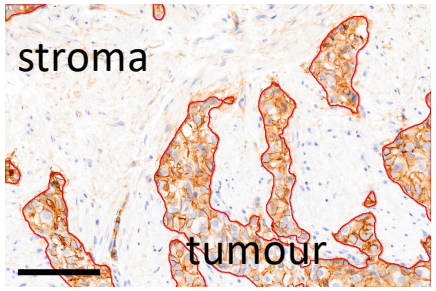
Guo C et al, European Urology 2022

B7-H3 is highly expressed in advanced PCa



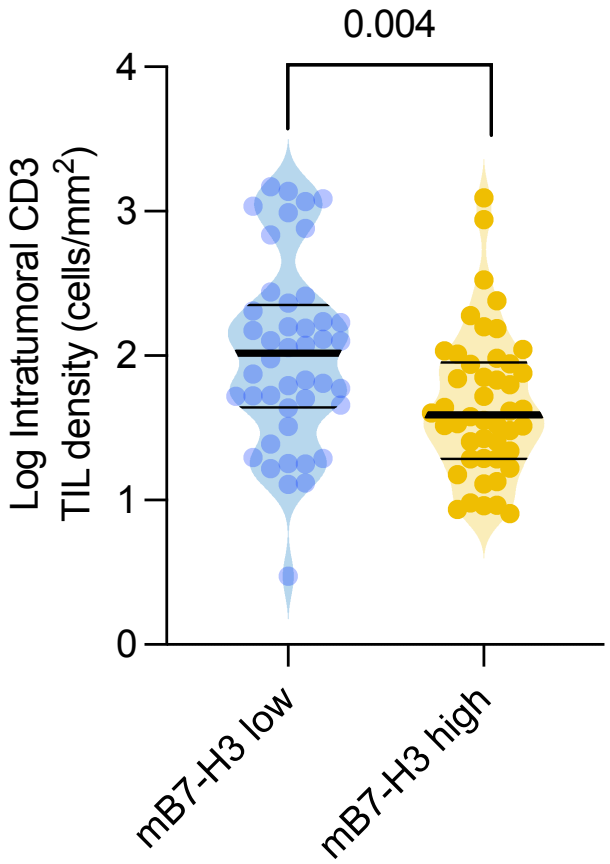


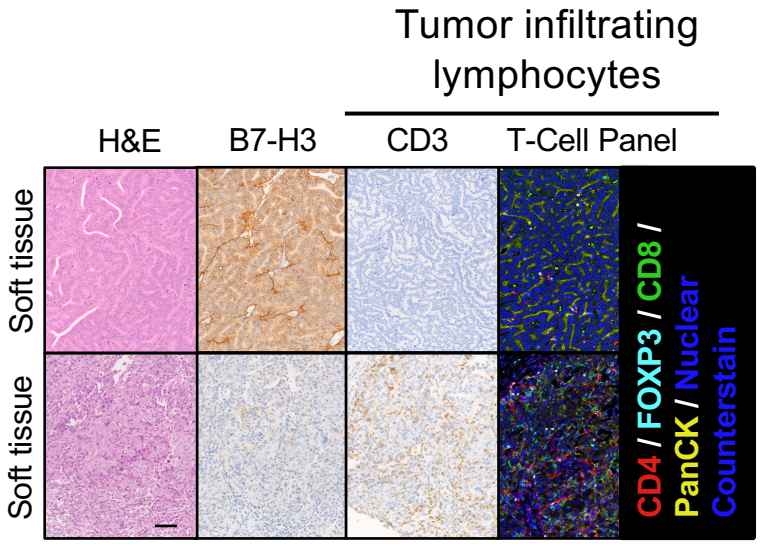




Guo C et al, European Urology 2022

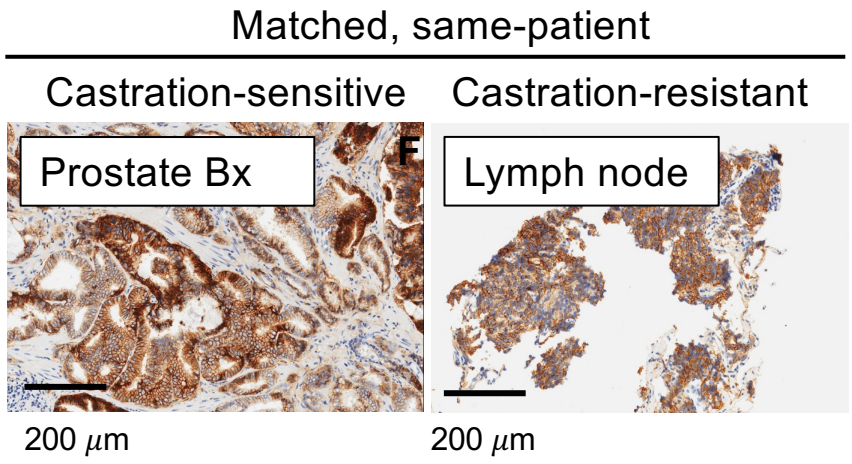
High B7-H3 associated with lower tumour-infiltrating CD3^{+} T cells

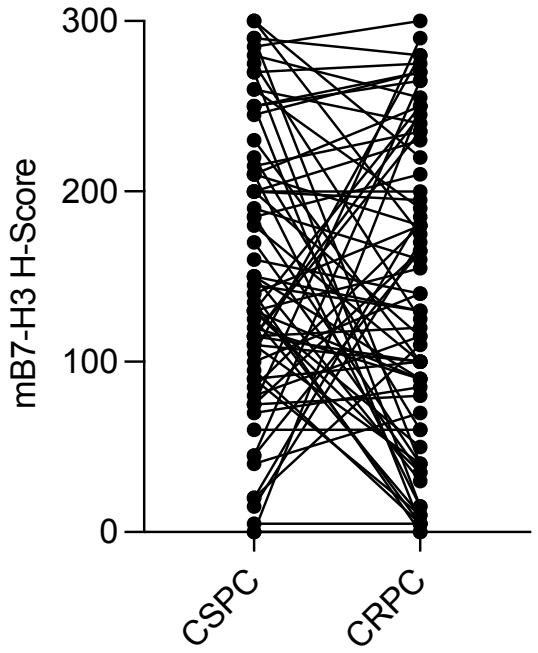




Guo C et al, European Urology 2022

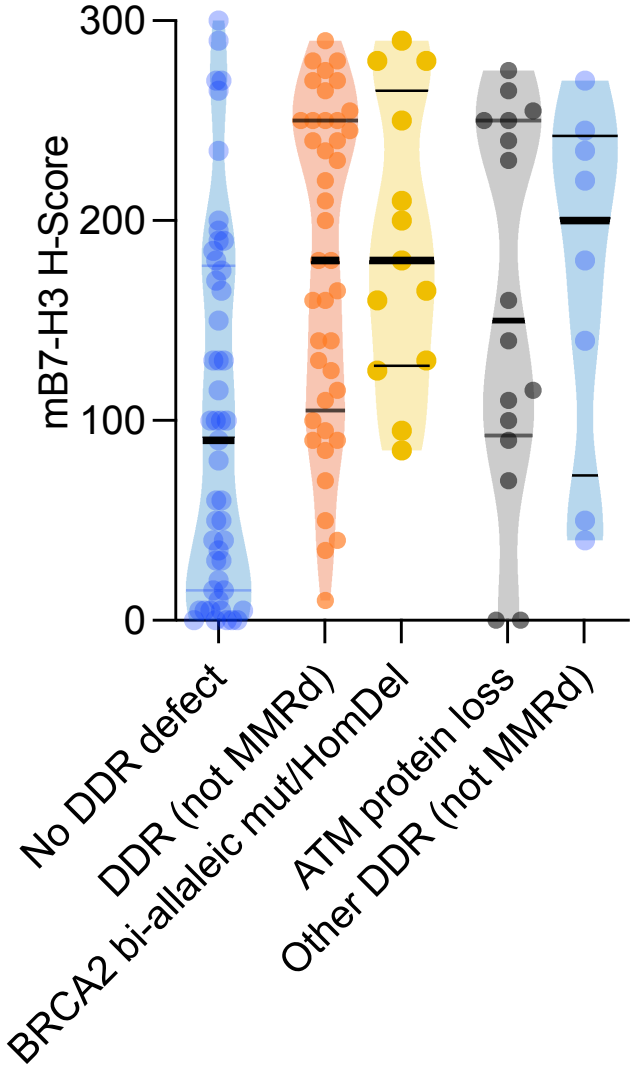
B7-H3 in matched, same patient, HSPC and mCRPC biopsies





Guo C et al, European Urology 2022

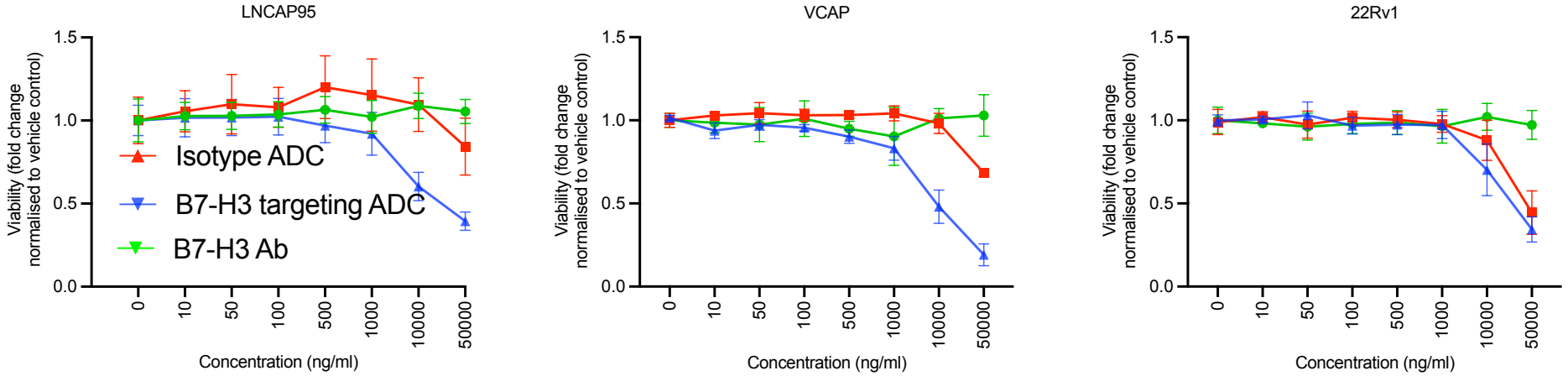
B7-H3 is higher in tumours with HRD



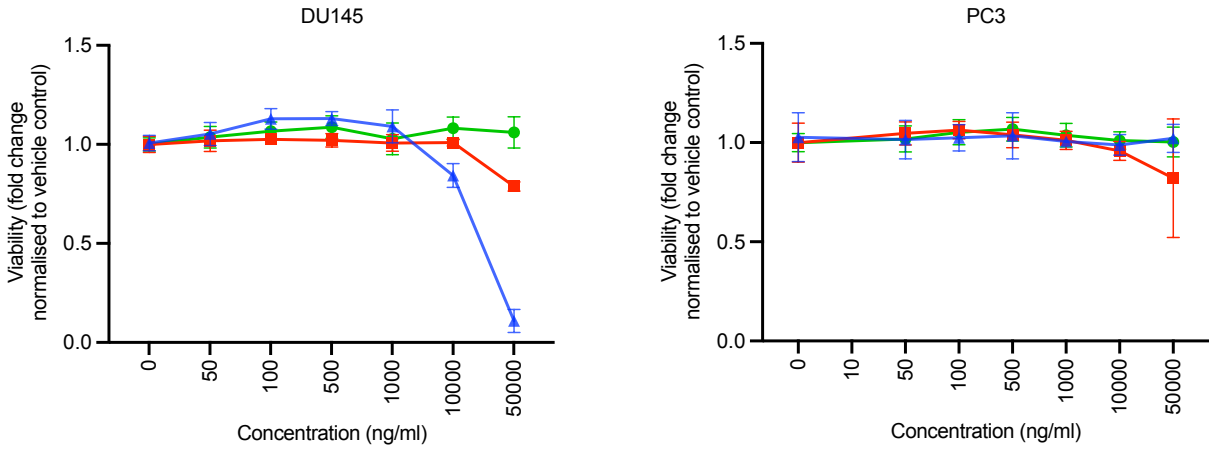
Guo C et al, European Urology 2022

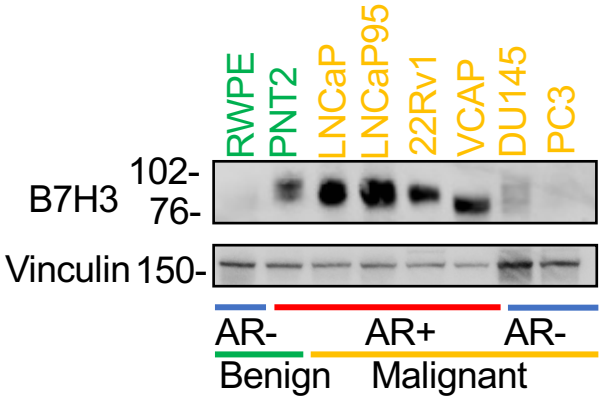
B7-H3 targeting ADC has B7-H3 expression-dependent antitumour activity in human PC cell lines

B7-H3 high PC cell lines



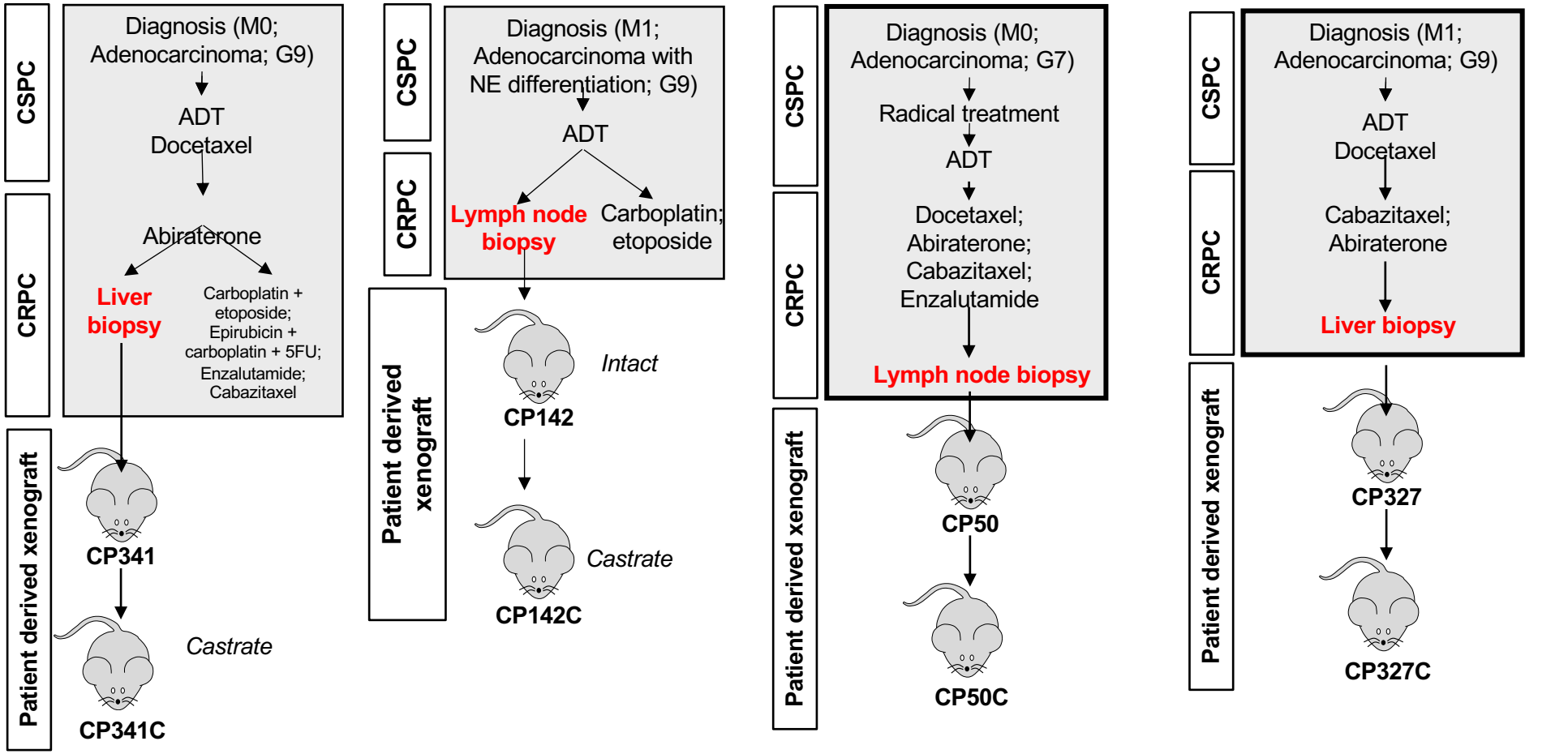
B7-H3 low PC cell lines





Guo C et al, European Urology 2022

PDXs and PDX-Os: Evaluation of B7-H3 targeting ADC in treatment refractory human PC models

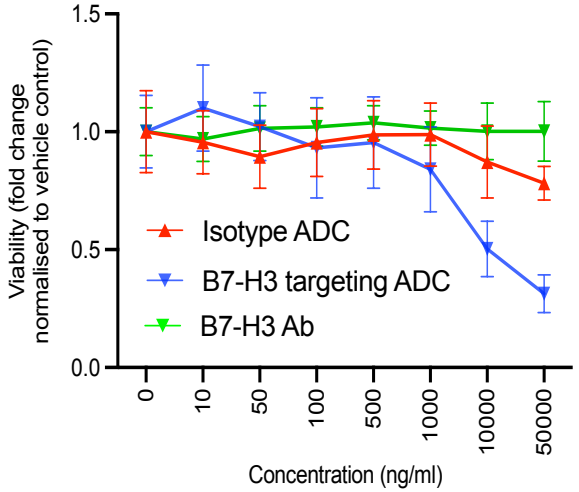


Guo C et al, European Urology 2022

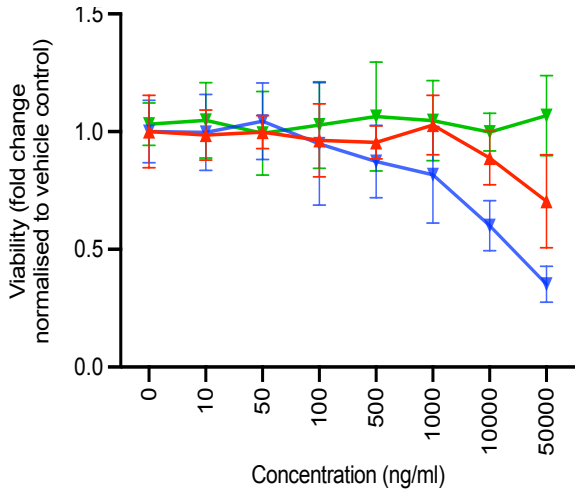
PDXs and PDX-Os: Evaluation of B7-H3 targeting ADC in treatment refractory human PC models in vitro

B7-H3 high PC

Adenocarcinoma

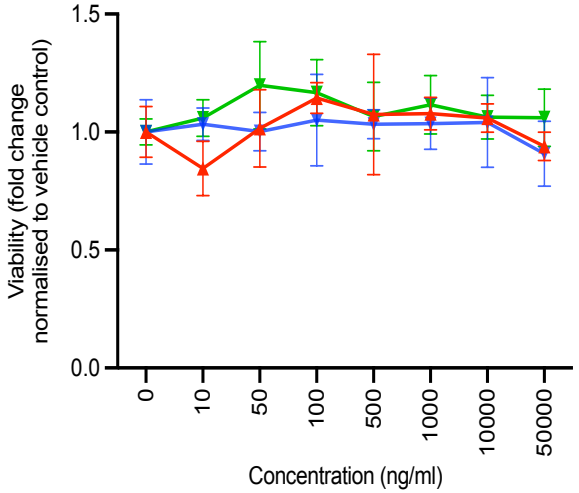


Neuroendocrine

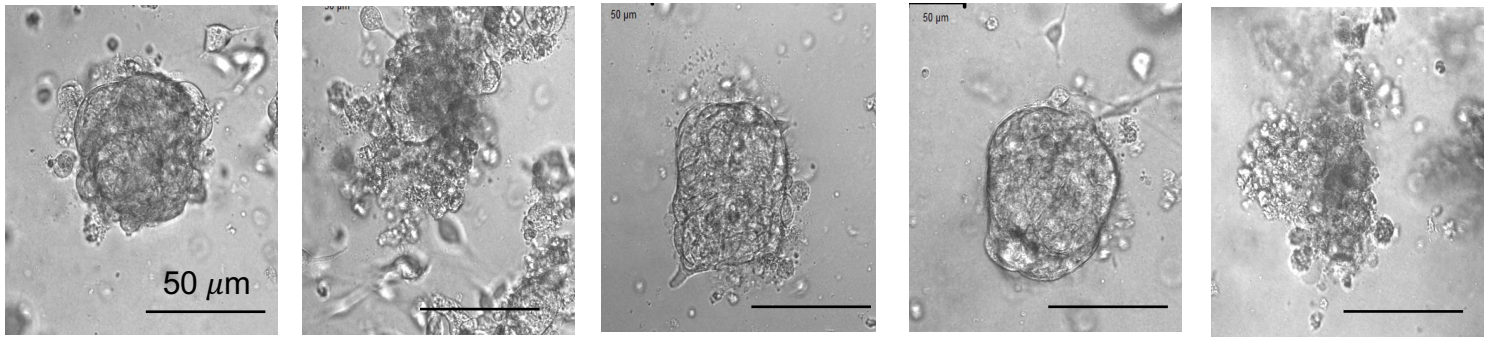


B7-H3 negative PC

Adenocarcinoma



Vehicle **Anti-B7-H3 ADC** **Anti-B7-H3 Ab** **Isotype ADC** **Topo-I inhibitor**



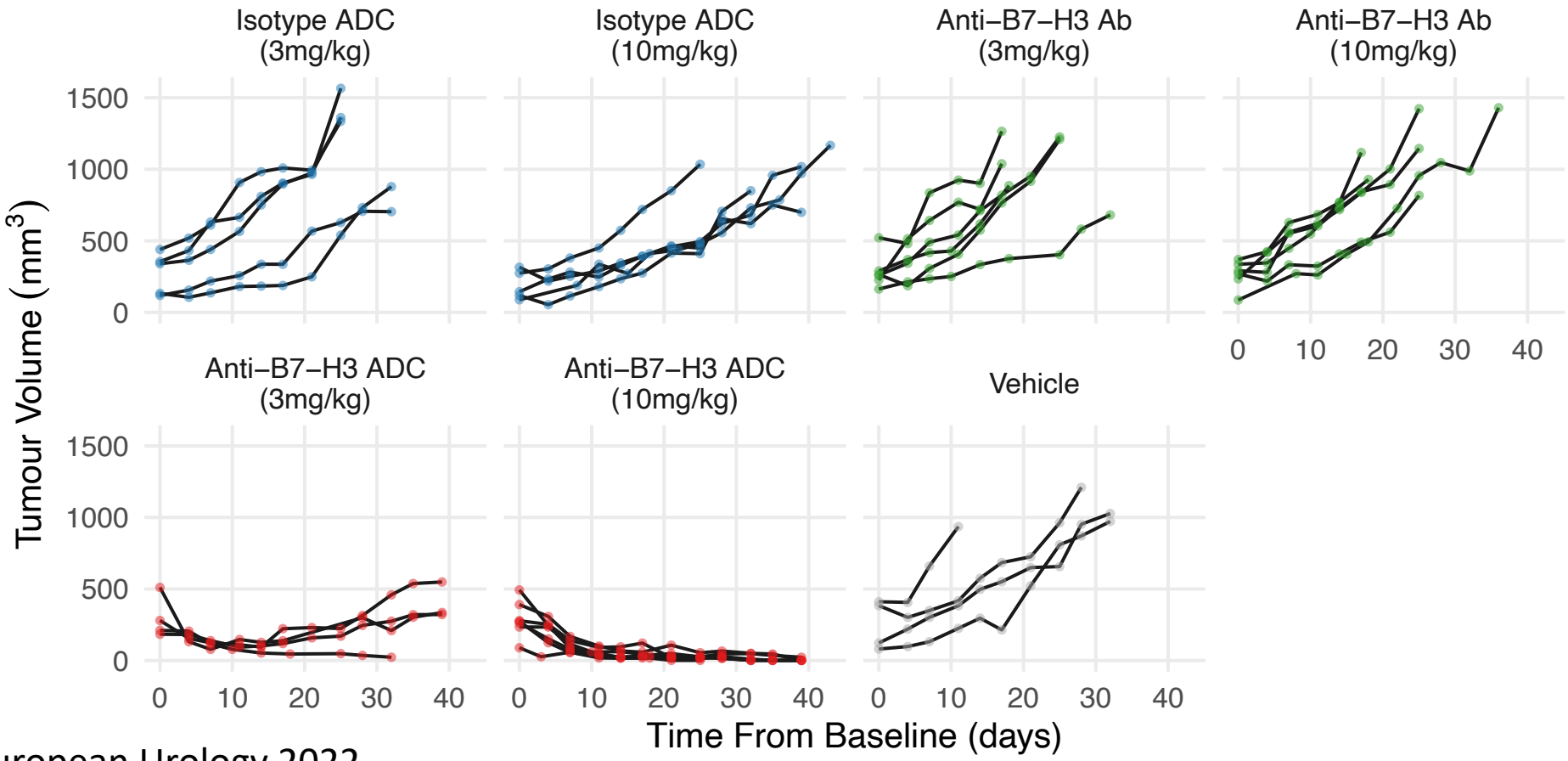
Guo C et al,
European Urology 2022

A B7-H3 ADC has antitumour activity in **B7-H3 positive** PC patient-derived xenografts models in vivo

Gleason 9 and metastatic disease at diagnosis

CRPC - progressed on ADT, abiraterone, docetaxel, cabazitaxel

Bone, liver, lymph node metastases; TP53 mutation, ATM mutation; B7-H3 HS: ~200



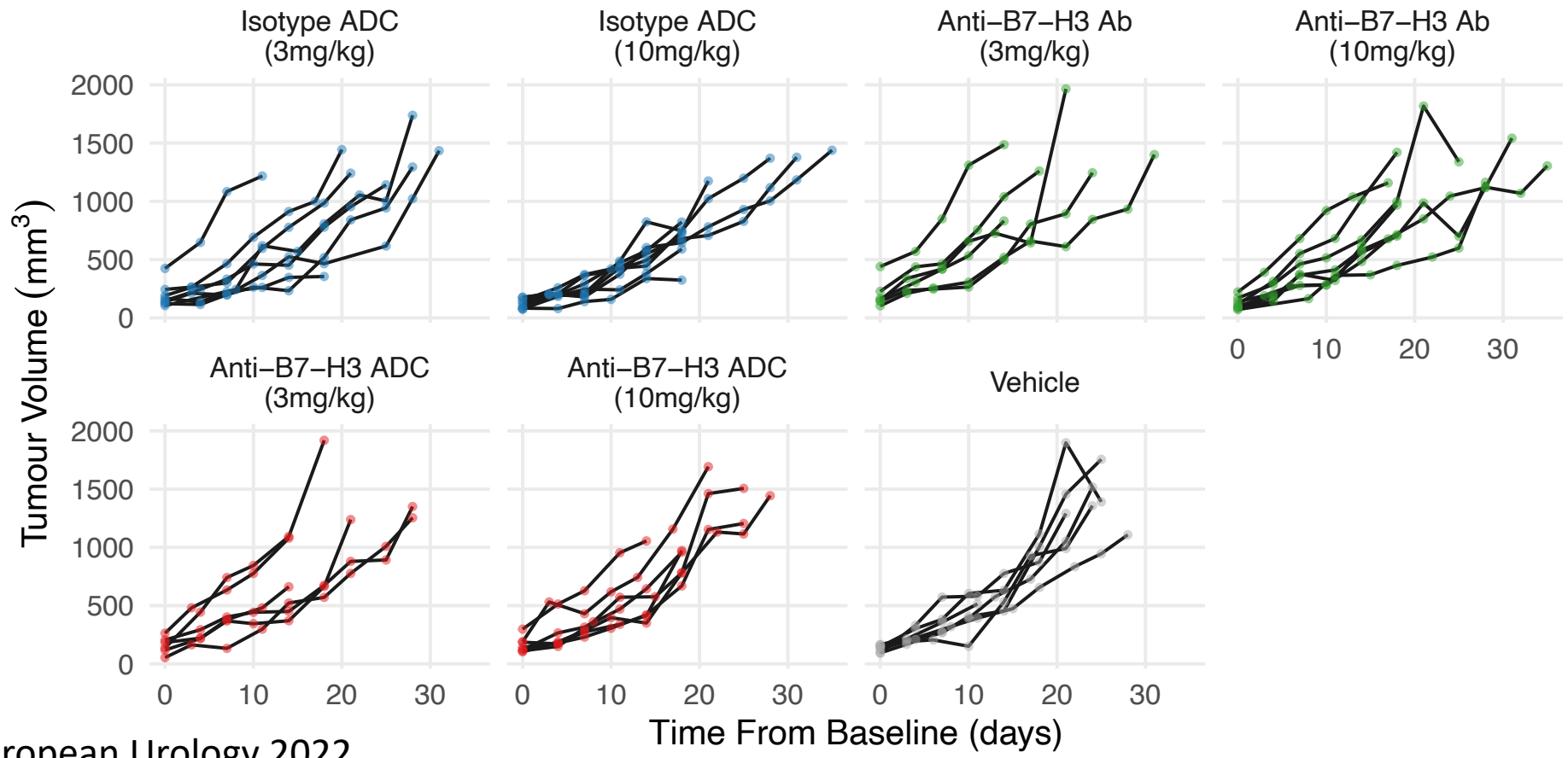
Guo C et al, European Urology 2022

A B7-H3 ADC has no antitumour activity in **B7-H3 negative** PC patient-derived xenografts models in vivo

Gleason 9 and metastatic disease at diagnosis

CRPC - progressed on ADT, abiraterone, docetaxel, cabazitaxel

Bone, liver, lymph node metastases; TP53 mutation, MMRd; B7-H3 HS: 0-5



Guo C et al, European Urology 2022

B7-H3 ADC in Phase I/II clinical trial

- B7-H3 targeting ADCs are being evaluated in clinical trials
  - Phase I has shown antitumour activity with tolerability at active doses

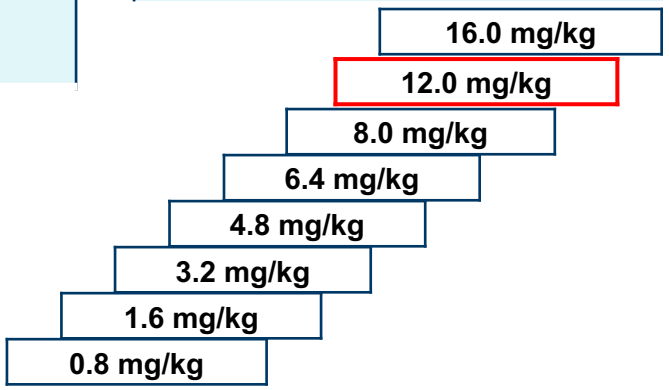
Doi et al ESMO 2022

Trial Design (NCT04145622)

- Part 1 of the study demonstrated that DS-7300 was generally well tolerated with early signs of antitumor activity[1,2]
  - 12.0 mg/kg was selected for the dose for Part 2
- We present extended follow-up data for a larger cohort of patients with selected tumor types, focusing on the 4.8-mg/kg (minimum effective dose) to 16.0-mg/kg doses

Patients with advanced/unresectable or metastatic solid tumors (unselected for B7-H3 expression) N≈205

Part 1: dose escalation
- DS-7300 IV Q3W monotherapy for advanced solid tumors[a]



RDE

Part 2: dose expansion (12.0 mg/kg)
- DS-7300 IV Q3W monotherapy for selected advanced solid tumors

Cohort 1: ESCC (n=25)

Cohort 2: mCRPC (n=40)

Cohort 3: sqNSCLC (n=20)

Key primary endpoints
- *Dose escalation*: DLTs, SAEs, TEAEs, AESI
- *Dose expansion*: ORR, DOR, DCR, PFS, OS

Key secondary endpoints
- PK
- Immunogenicity

AESI, adverse event of special interest; ESCC, esophageal squamous cell carcinoma; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; HNSCC, head and neck squamous cell carcinoma; IV, intravenous, mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event; SCLC, small cell lung cancer; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event.
[a] Tumor types included advanced/unresectable or metastatic HNSCC, ESCC, mCRPC, sqNSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, and breast cancer.

1. Patel MR, et al. *ASCO-GU*. 2022. Poster 87. 2. Johnson ML, et al. *Ann Oncol*. 2021;32:S583-S585.

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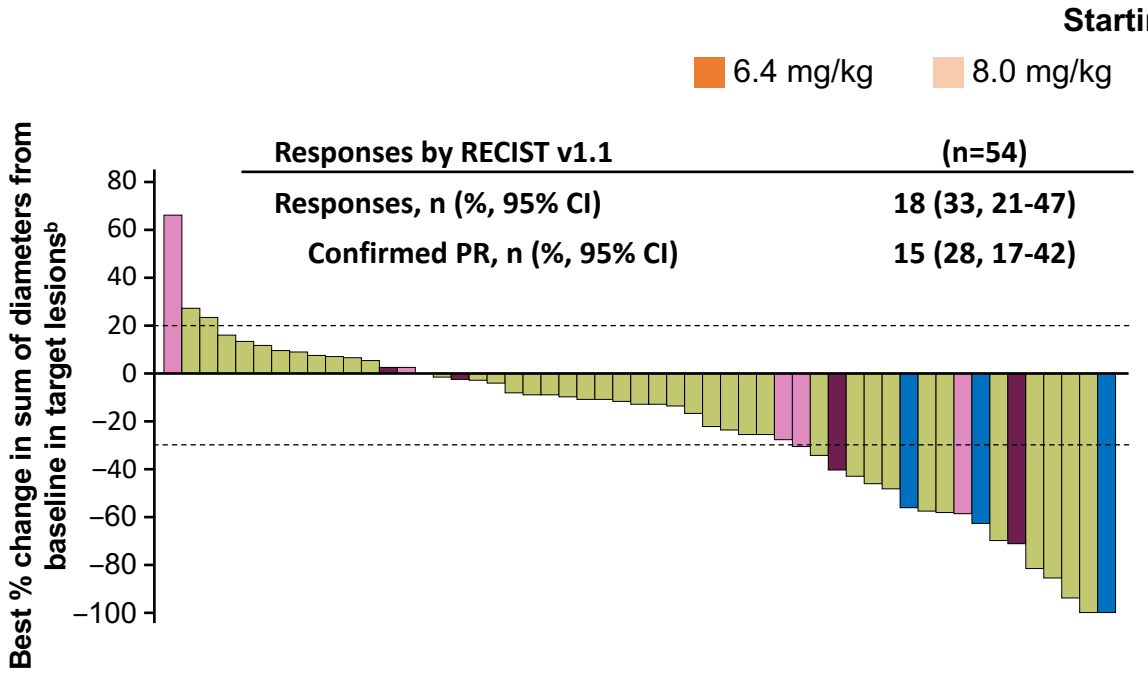
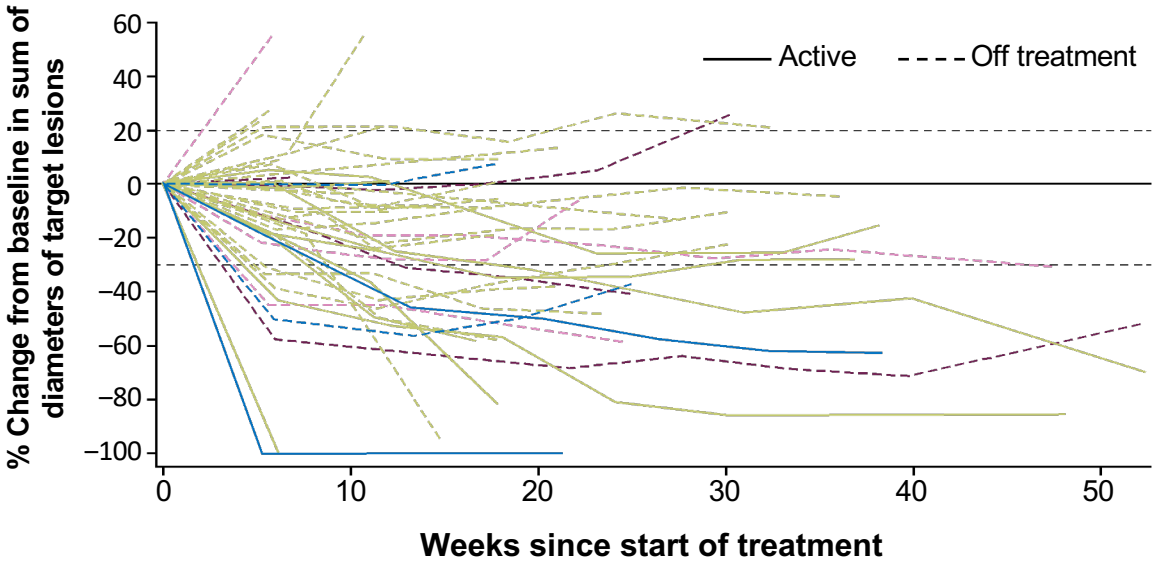
Antitumor Activity: mCRPC Subset[a]





- 18/54 (33%) patients achieved a PR
- 25/54 (46%) patients had liver metastases at baseline of which 10 (40%) patients had a response

- Median duration of response was 4.4 months (95% CI, 2.7-NR); 7 responders remain on treatment
- Median follow-up (months [95% CI]): 9.3 (7.5-10.6)

DCO, data cutoff; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
[a] Patients from dose escalation and expansion parts measurable disease at baseline and a least 2 post-baseline tumor scans and/or discontinued the treatment at DCO are included in best overall response calculations. 1 patient did not have post-baseline tumor scans and was not included in the waterfall or spider plots. [b] This version differs from the version originally presented at ESMO 2022; the dose for 2 patients was corrected from 12 mg/kg to 6.4 mg/kg and for one patient from 8.0 mg/kg to 12.0 mg/kg.

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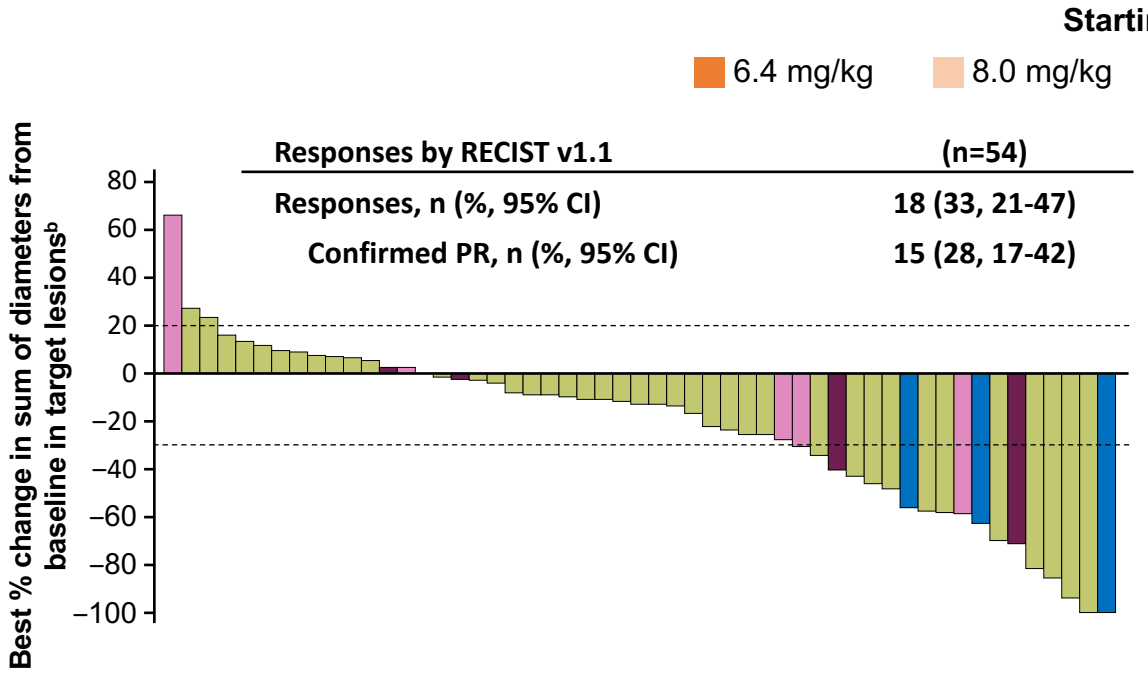

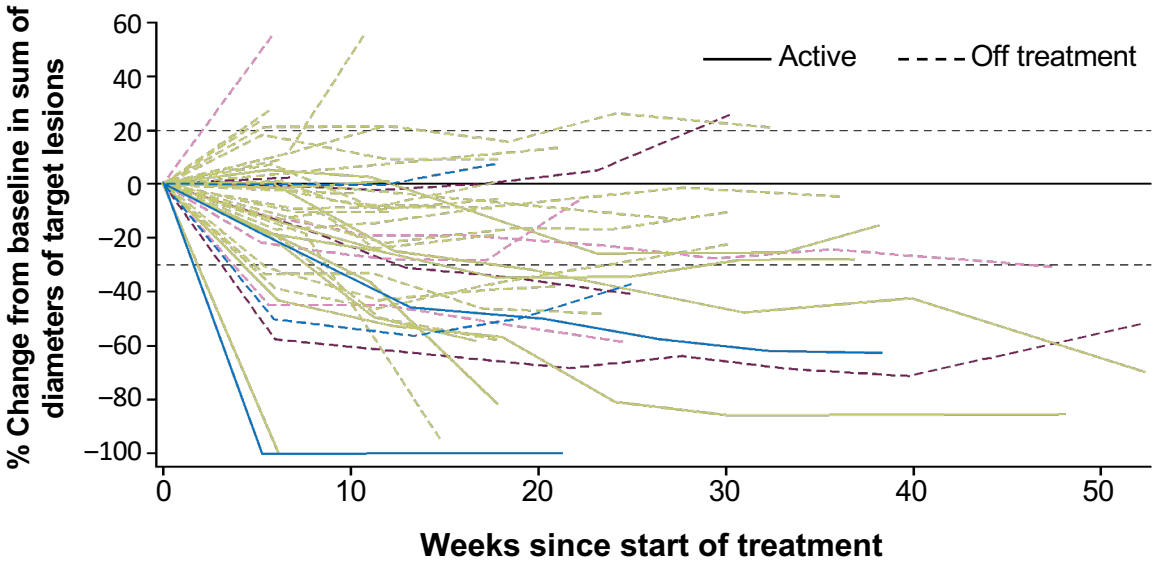

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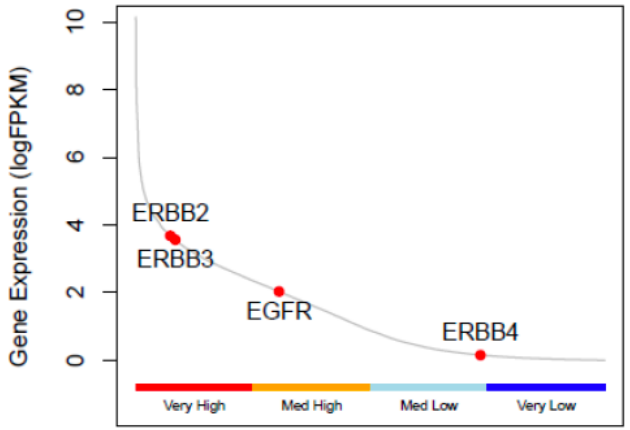
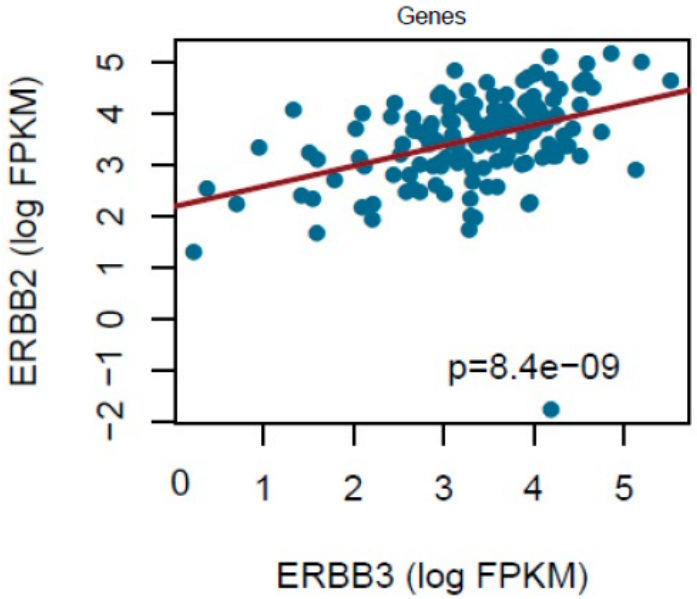
ErbB receptors implicated in endocrine therapy resistance

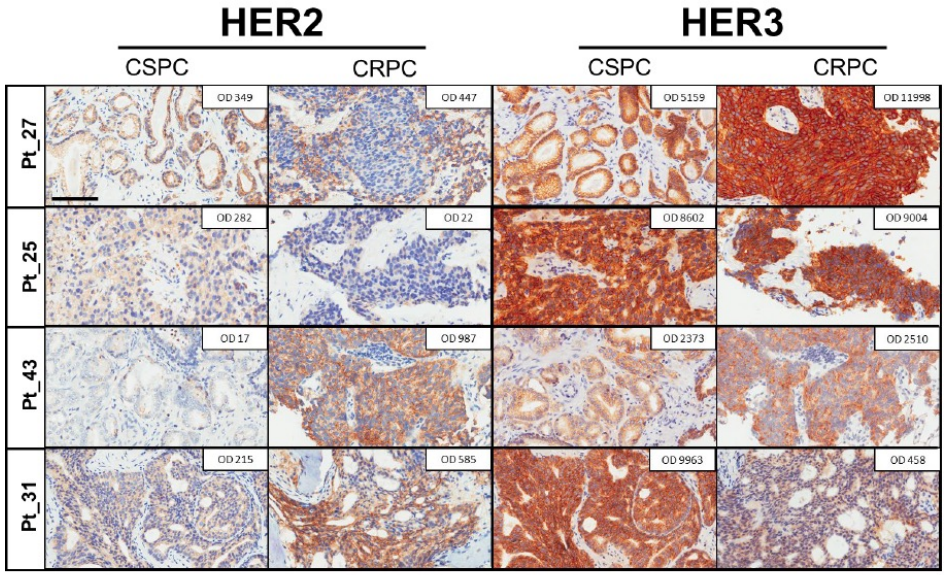
- ErbB receptor targeting has had utility for treating many tumours
- HER2/HER3 blockade suggested to block tumour growth
- HER2 signaling implicated in castration resistance/AR signaling
- We ran several (negative) trials targeting erbB many years ago
  - Pertuzumab single agent (pre abi/enza approvals; n=68)
  - Afatinib (with and without multikinase inhibitor nintedanib; n=85)

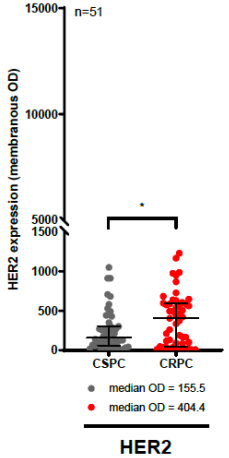
Agus D et al 2002; Melinghoff I et al, 2004; de Bono et al, JCO 2007; Molfe et al, 2014; Zhang et al, Cancer Cell 2020

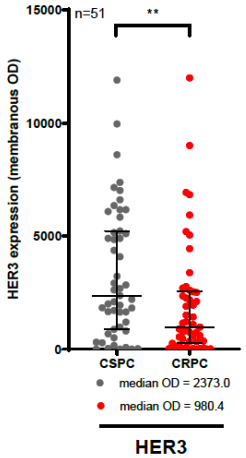
ErbB receptors in mCRPC

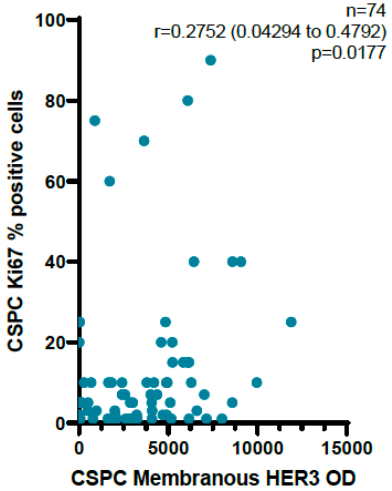


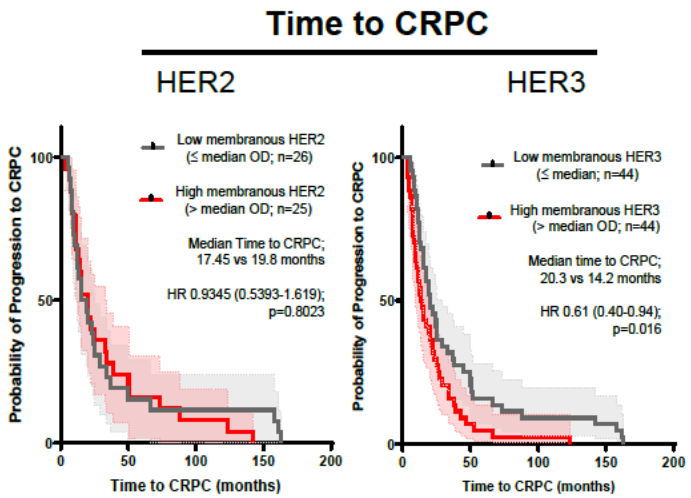


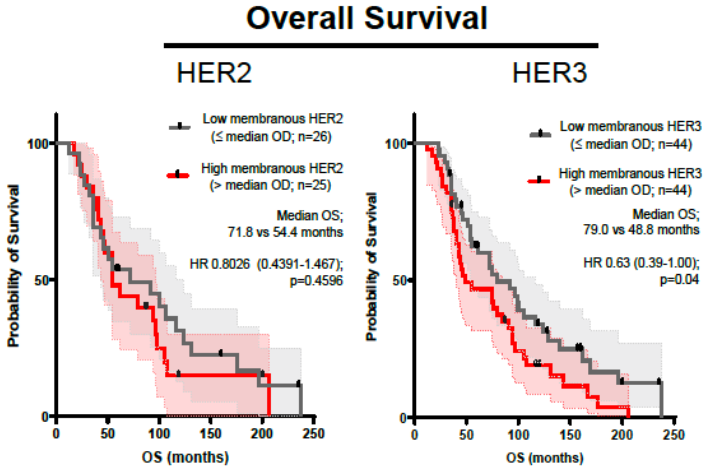












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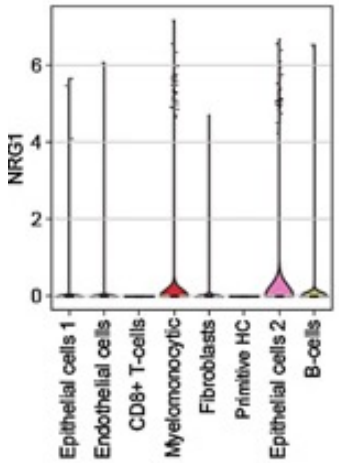
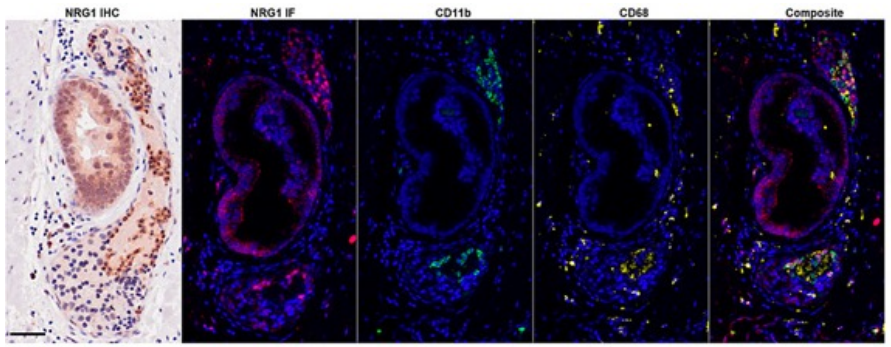
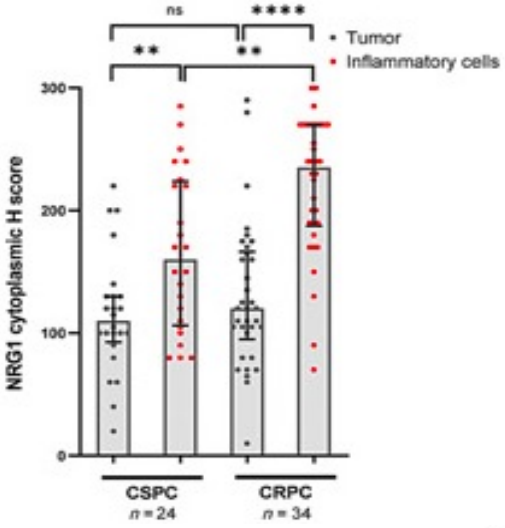
HER3 ligand: NRG1

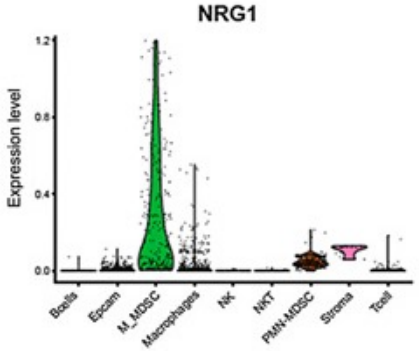
Human data

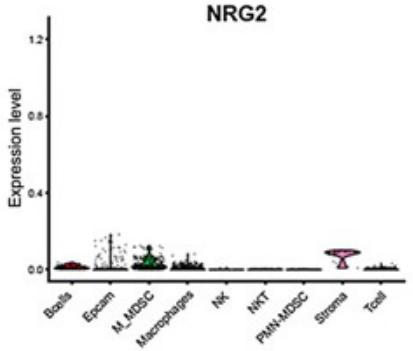


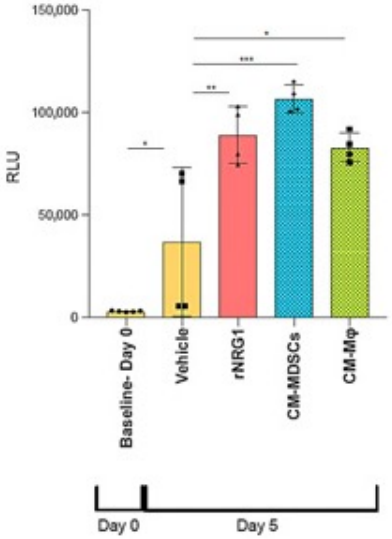


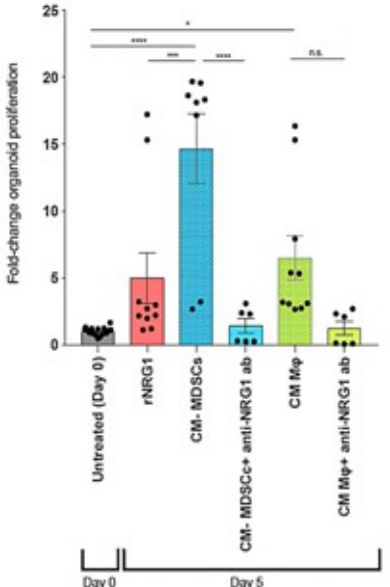


Transgenic mouse data (Alimonti lab)









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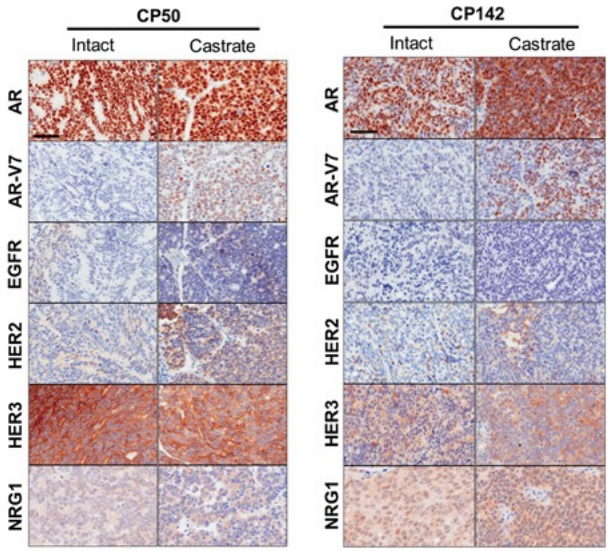
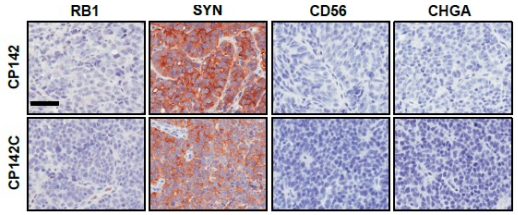
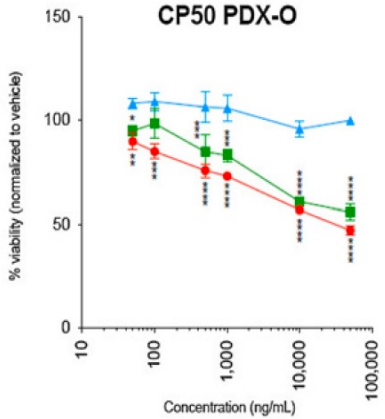
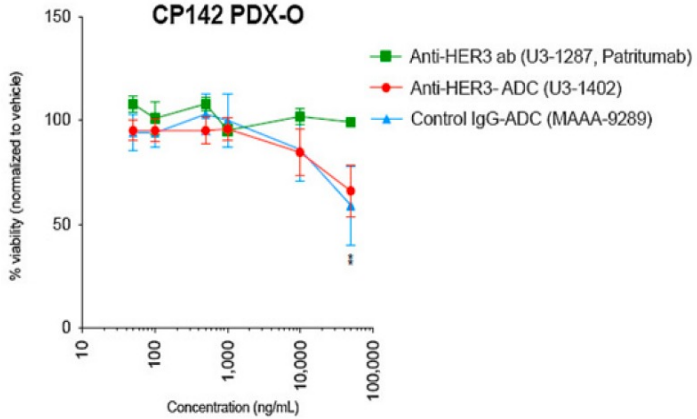
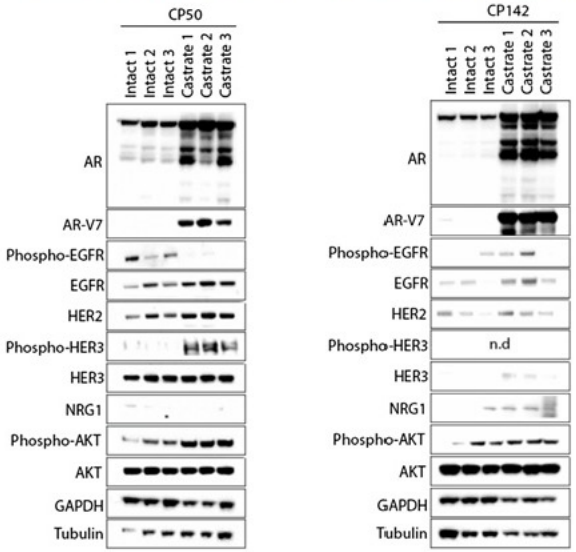
ErbB receptors in patient-derived models

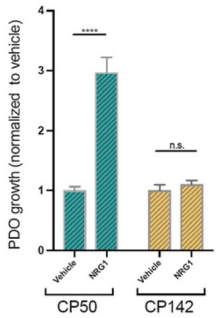


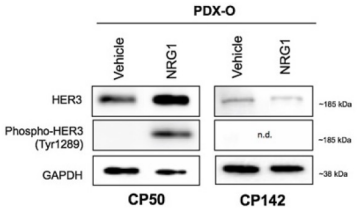


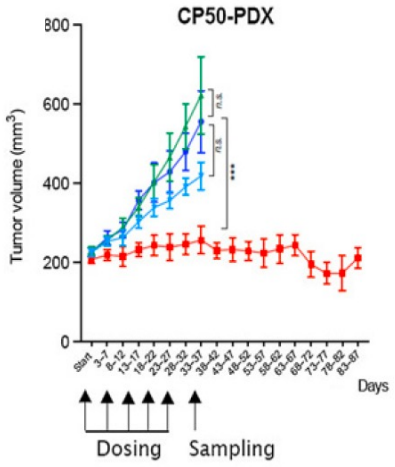


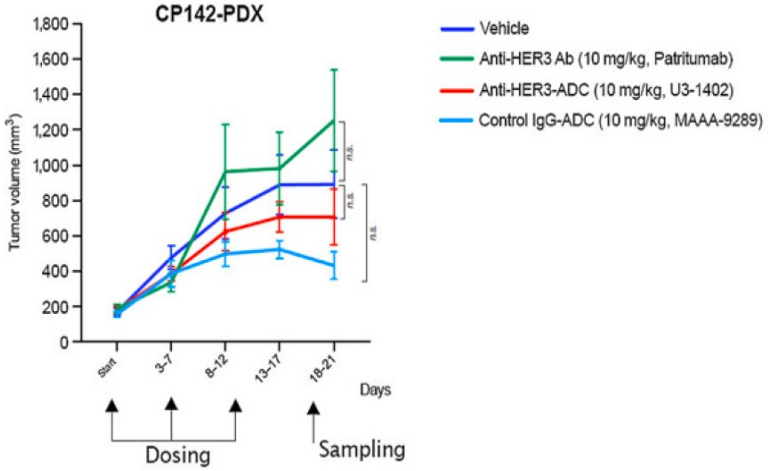












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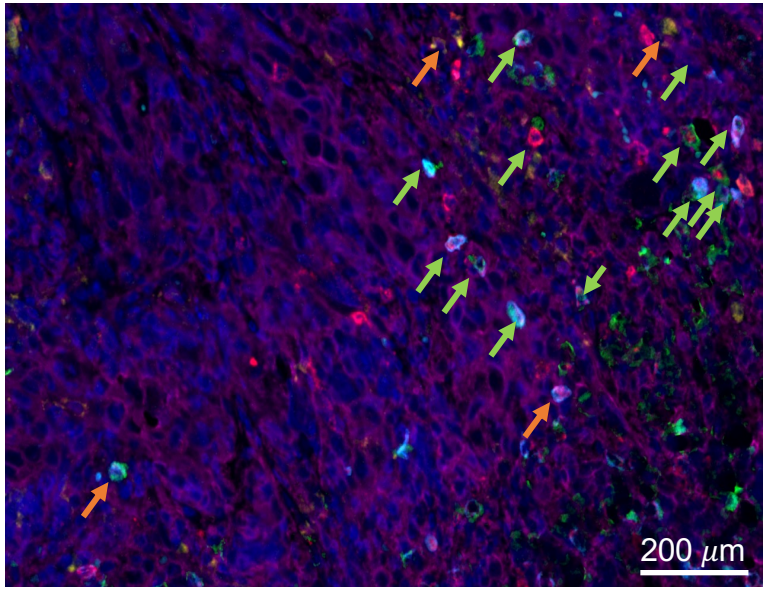
Clinical trials targeting HER3

- Trials targeting HER3
  - Naked antibody combinations
  - Immunoconjugates
  - Radioimmunoconjugates

Myeloid inflammation and prostate cancer therapy resistance

- Myeloid inflammation is implicated in advanced prostate cancer (PC) progression and therapy resistance
- PC clinical outcomes not improved by advances in cancer immunotherapy
- Peripheral blood and intratumoral myeloid inflammation associate with:
  - Shorter survival
  - Rx resistance (taxanes, anti-androgens)

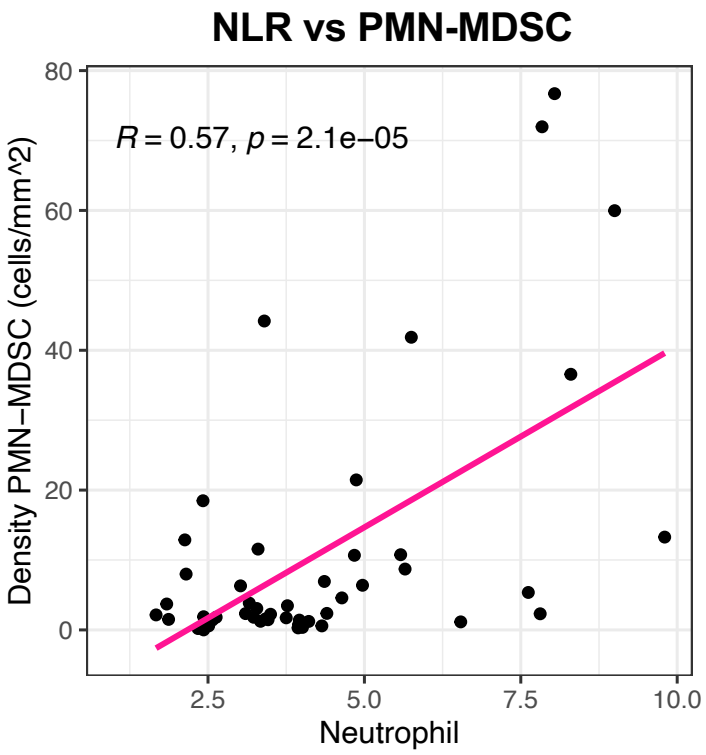


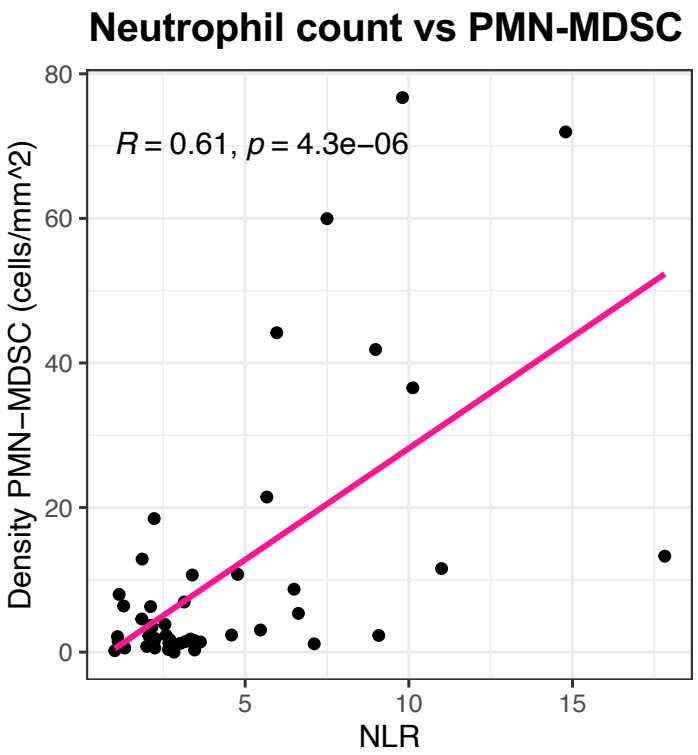
Polymorphonuclear (PMN)-myeloid derived suppressor cells (MDSC) = CD11b^{+}HLA-DR^{lo}CD15^{+} CD14^{-}

Monocytic (M)-MDSC = CD11b^{+}HLA-DR^{lo}CD15^{-}CD14^{+}CXCR2 DAPI

De Marzo et al., Nat Rev Ca, 2007, Di Mitri et. al. Nat, 2014; de Bono, Guo et al., Nat Rev Ca, 2020; Calcinotto et al., Nat, 2018; Gil, Miranda et al, Ca Res, 2021; Lopez-Bujanda et al., Nat Ca, 2021, Leibowitz-Amit et al, Ann Oncol, 2014; Olmos et al. Lanc Oncol, 2012., Seaton et al., Carcinogenesis, 2008, Acosta et al., Cell, 2008.

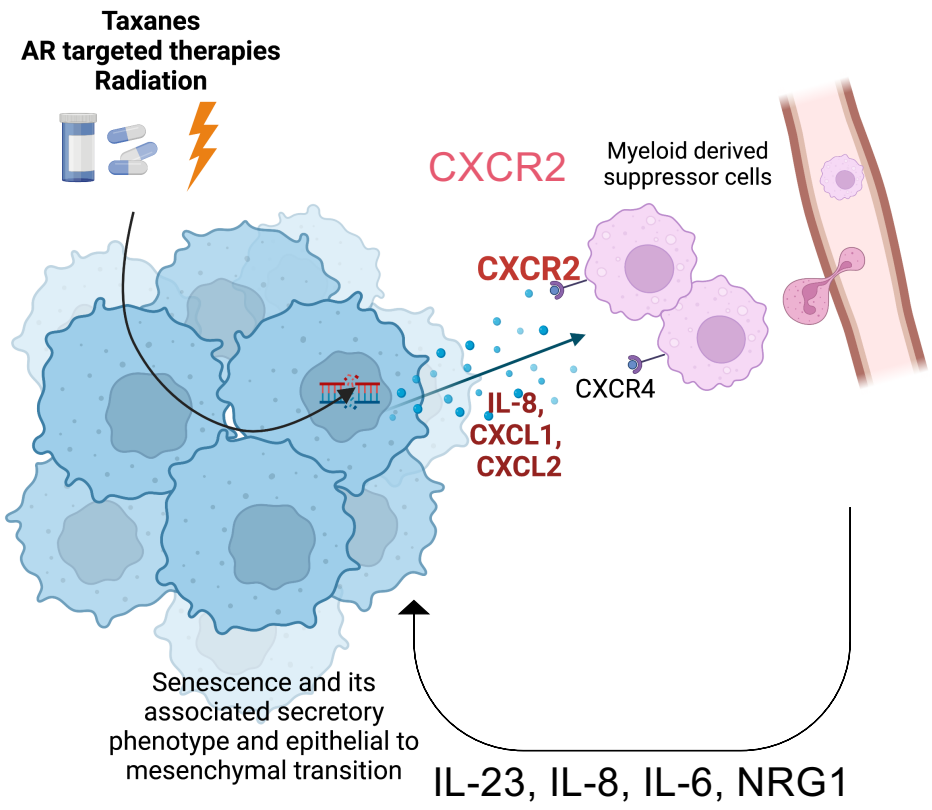
Peripheral blood neutrophilia & neutrophil-to-lymphocyte ratio associate with intratumor myeloid infiltration





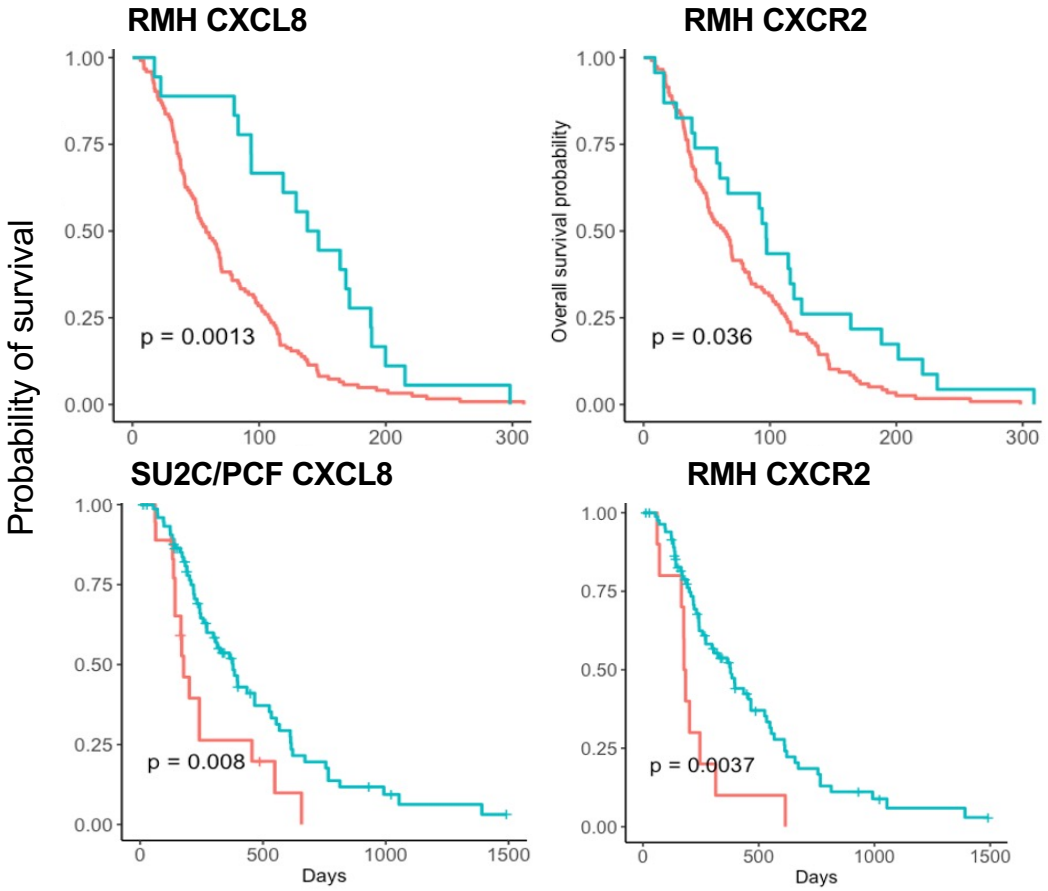
Myeloid inflammatory cells are recruited to the prostate tumour bed down chemokine gradients via CXCR2

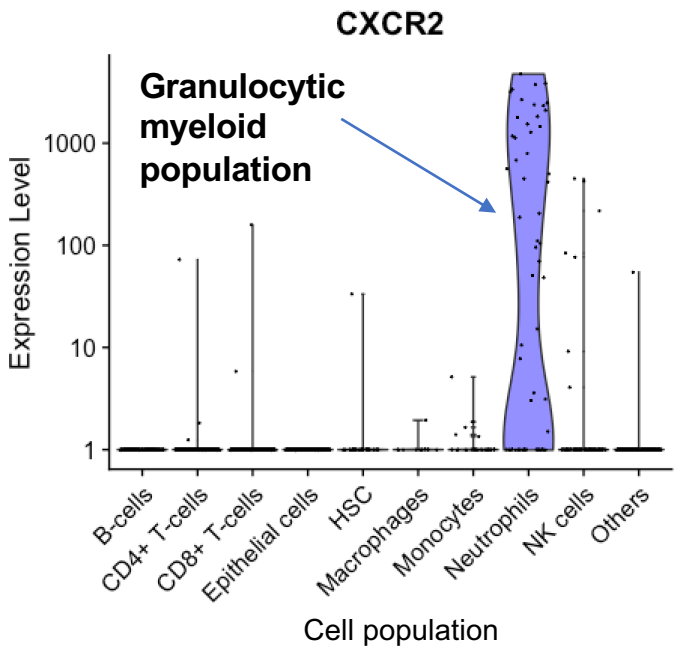
- PCa Rx induce tumour cell senescence associated secretory phenotype (SASP)
- Senescent epithelial cells release inflammatory cytokines and chemokines (e.g. IL-8/CXCL8, CXCL1, CXCL2) - high affinity ligands for G-protein coupled receptor CXCR2
- CXCR2 is expressed by myeloid inflammatory cells ➔ facilitate myeloid cell recruitment into tumour microenvironment
- Secrete paracrine factors ➔ PCa growth + Rx resistance



De Marzo et al., Nat Rev Ca, 2007, Di Mitri et. al. Nat, 2014; de Bono, Guo et al., Nat Rev Ca, 2020; Calcinotto et al., Nat, 2018; Gil, Miranda et al, Ca Res, 2021; Lopez-Bujanda et al., Nat Ca, 2021, Leibowitz-Amit et al, Ann Oncol, 2014; Olmos et al. Lanc Oncol, 2012., Seaton et al., Carcinogenesis, 2008, Acosta et al., Cell, 2008.

CXCR2 and its ligand expression are prognostic



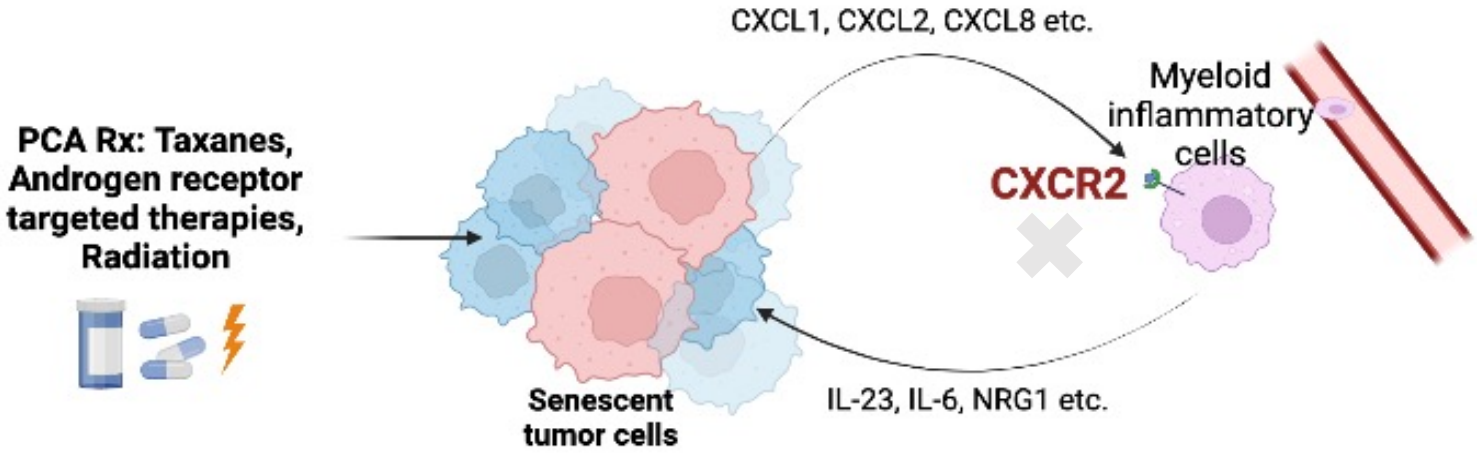


Single cell RNASeq (Chen et al., 2021)

Minimal tumour cell expression

Hypothesis

Targeting **myeloid chemotaxis** via the **CXCR2 receptor** axis can inhibit myeloid inflammatory cell recruitment into the prostate tumour bed and block the **paracrine effects** of myeloid inflammation in driving prostate tumour growth and therapeutic resistance

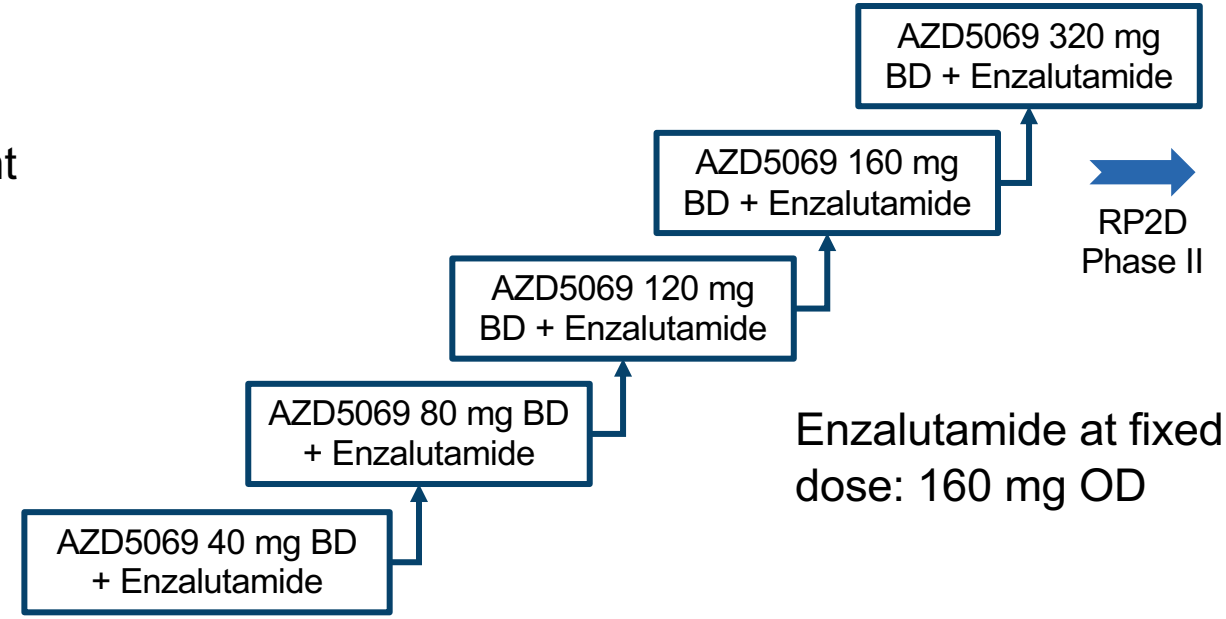


Clinical trial design

Multicentre, open-label, proof-of-mechanism / proof-of-concept Ph1

Key eligibility:

- Metastatic castration-resistant prostate adenocarcinoma
- ECOG PS 0-2
- Confirmed progression on androgen receptor targeted therapy



Enzalutamide at fixed dose: 160 mg OD

Key phase I endpoints:

- Primary endpoint: toxicity, recommended phase 2 dose
- Secondary endpoints: pharmacokinetic, pharmacodynamics, antitumor activity

Safety profile

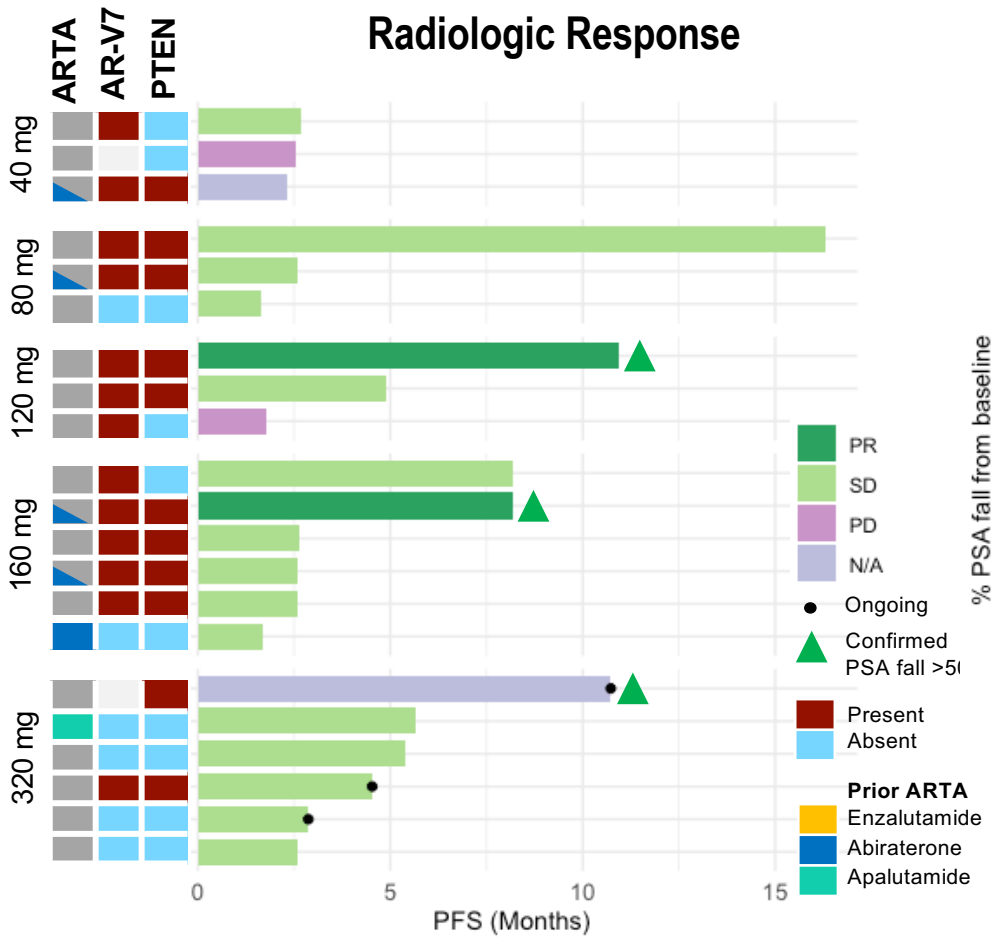
Treatment-related adverse event (>10%)	AZD5069 40mg BD (n=3)		AZD5069 80 mg BD (n=3)		AZD5069 120 mg BD (n=3)		AZD5069 160 mg BD (n=6)		AZD5069 320 mg BD (n=6)		Total (n=21)
	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	All grade
Neutropenia	2		2	1	1	2	1	4	2	4	19 (90%)
Fatigue			1		1		2		2		8 (38%)
Nausea	1				1		2		1		6 (28%)
Anaemia	1				1		1	1			4 (19%)
Thrombocytopenia					1		1				2 (10%)

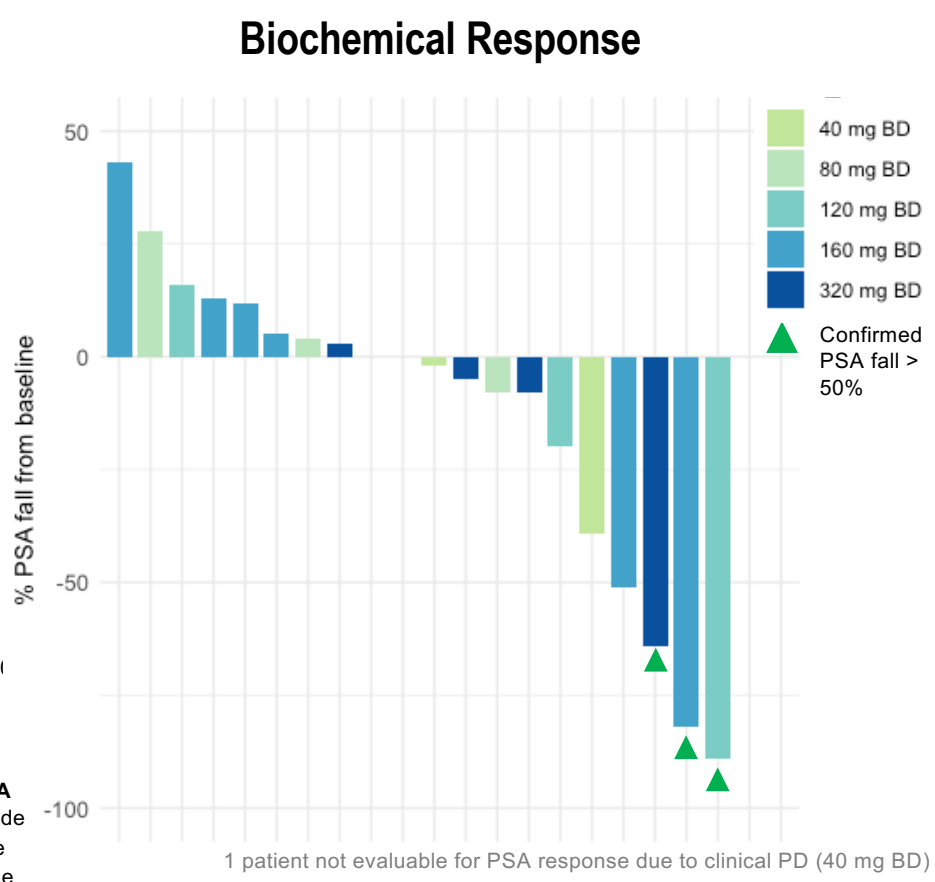
Uncomplicated, reversible, neutropenia is the most common side effect

No dose-limiting toxicity

No treatment discontinuation or dose-reduction due to drug-related adverse event

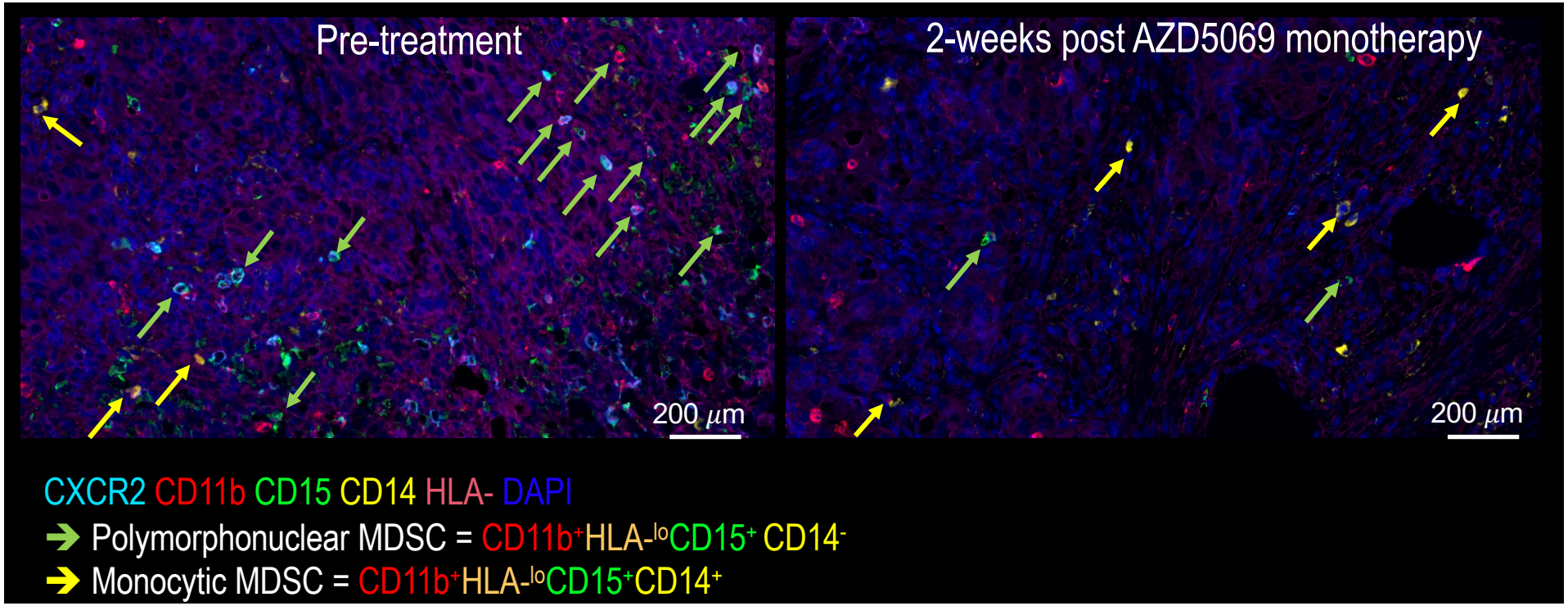
Antitumor activity: Responders post-enzalutamide and AR-V7+



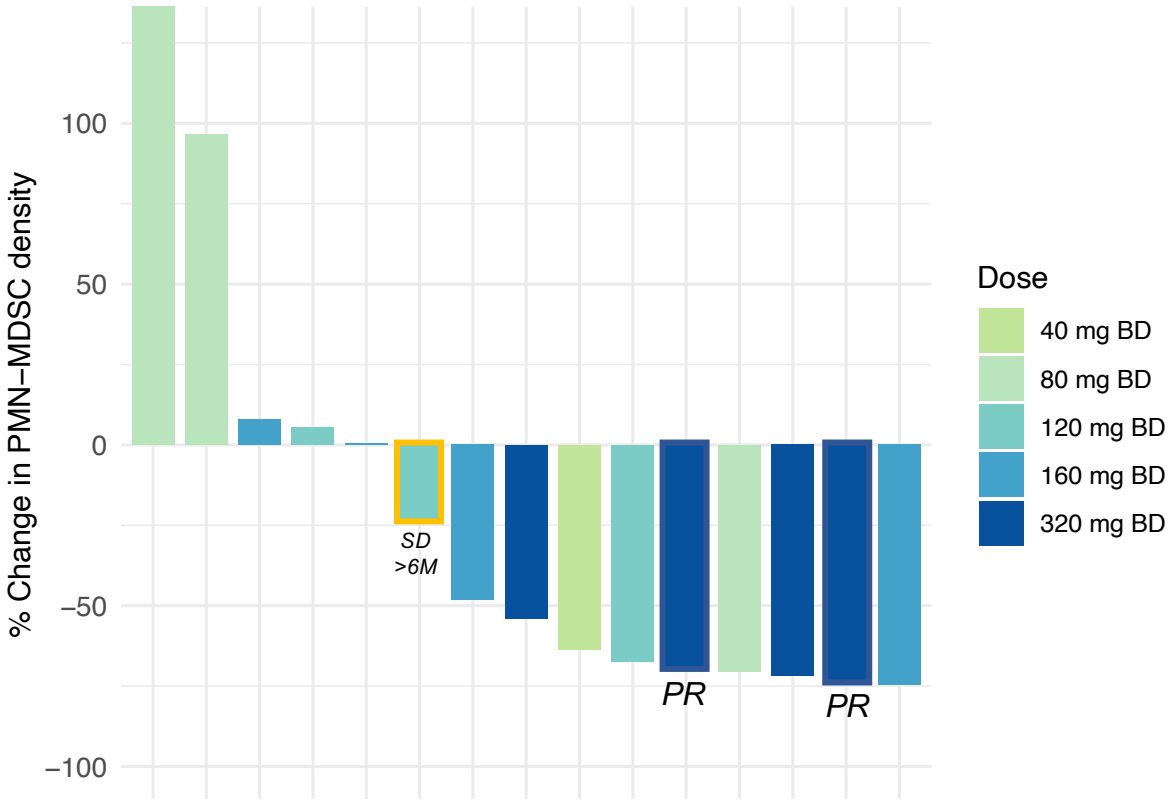


CXCR2 inhibition markedly reduced intratumoral myeloid inflammatory cell infiltration

- 15/21 patients with pre- and post-treatment tumor biopsies
- CXCR2 inhibition → ↓ intratumoral PMN-MDSCs (p=0.02)



CXCR2 inhibition reduced intratumor myeloid inflammatory cells



Targeting CXCR2

- Combined AR and CXCR2 blockade is well tolerated
- **Proof-of-mechanism:** Inhibiting myeloid cell chemotaxis via CXCR2 blockade reduced PMN-MDSC infiltration in mCRPC
- **Proof-of-concept:** Blockade of myeloid cell chemotaxis in CRPC can reverse resistance to AR-targeted therapy and confer **clinical benefit in some patients with mCRPC**

Conclusions

- Molecular testing is now a key part of care
  - MMRd; BRCA

- Multiple novel therapeutic strategies under evaluation
  - B7-H3 targeting
  - ErbB pathway targeting
  - Myeloid derived suppressor cell paracrine interactions with tumour

- Further advances in prostate cancer care envisioned in the near future