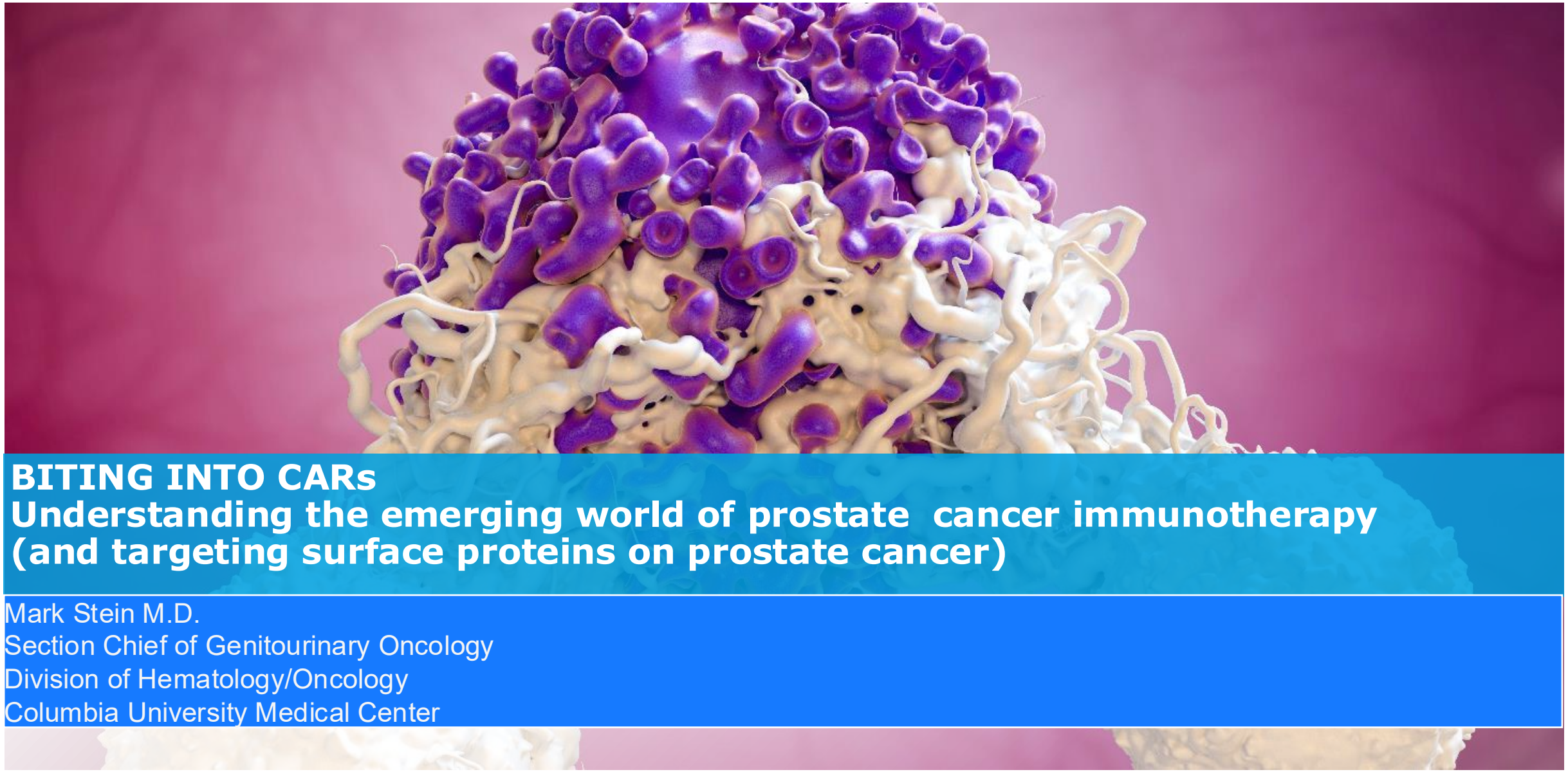
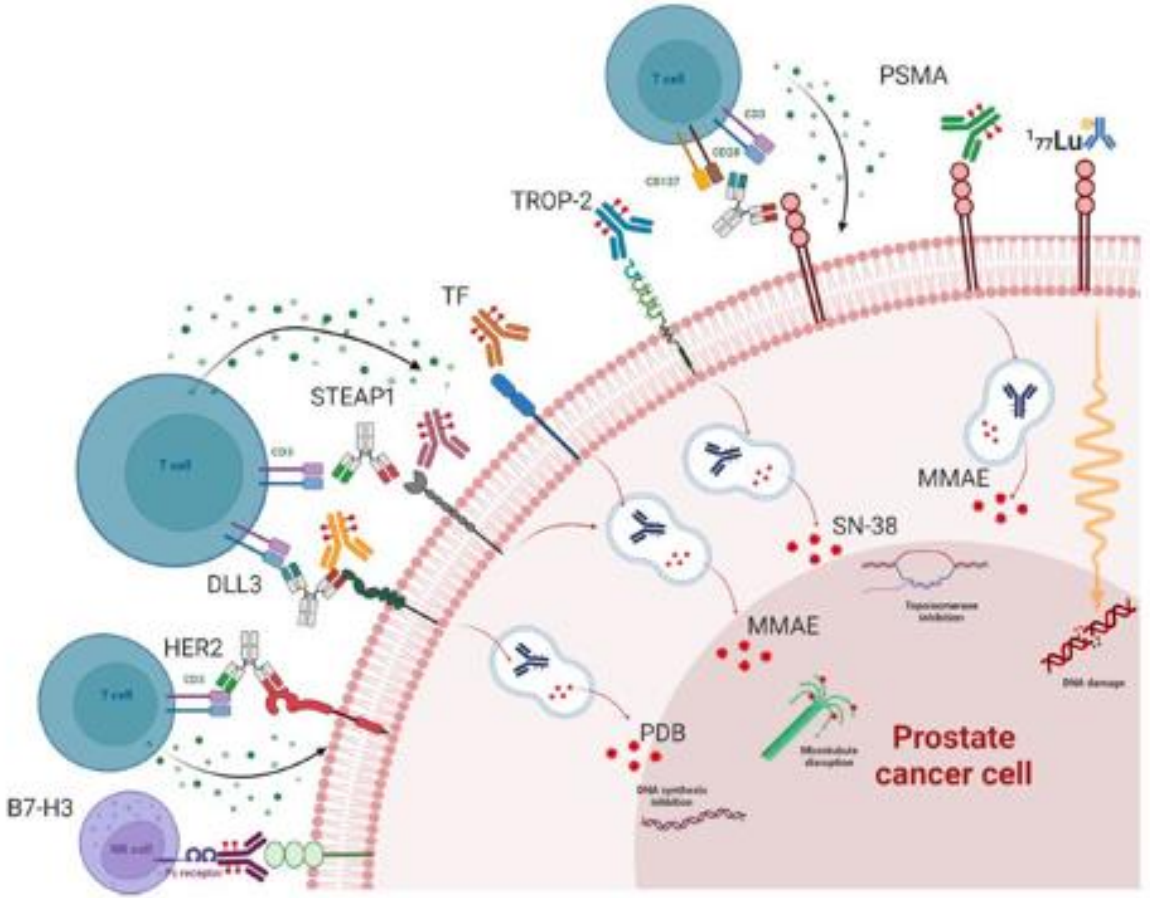


BITING INTO CARs
Understanding the emerging world of prostate cancer immunotherapy (and targeting surface proteins on prostate cancer)

Mark Stein M.D.
Section Chief of Genitourinary Oncology
Division of Hematology/Oncology
Columbia University Medical Center

Cell surface protein targeting

- T-cell engagers
- Radiopharmaceuticals
- Antibody drug conjugates
- CAR- T cells



nature reviews urology

Review article

Check for updates

Targeting the tumour cell surface in advanced prostate cancer

Cristina Boixareu, Tarek Tahu, Varadha Balaji Venkadakrishnan, Johann de Bono & Himisha Beltran

EUROPEAN UROLOGY 88 (2025) 437–448

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

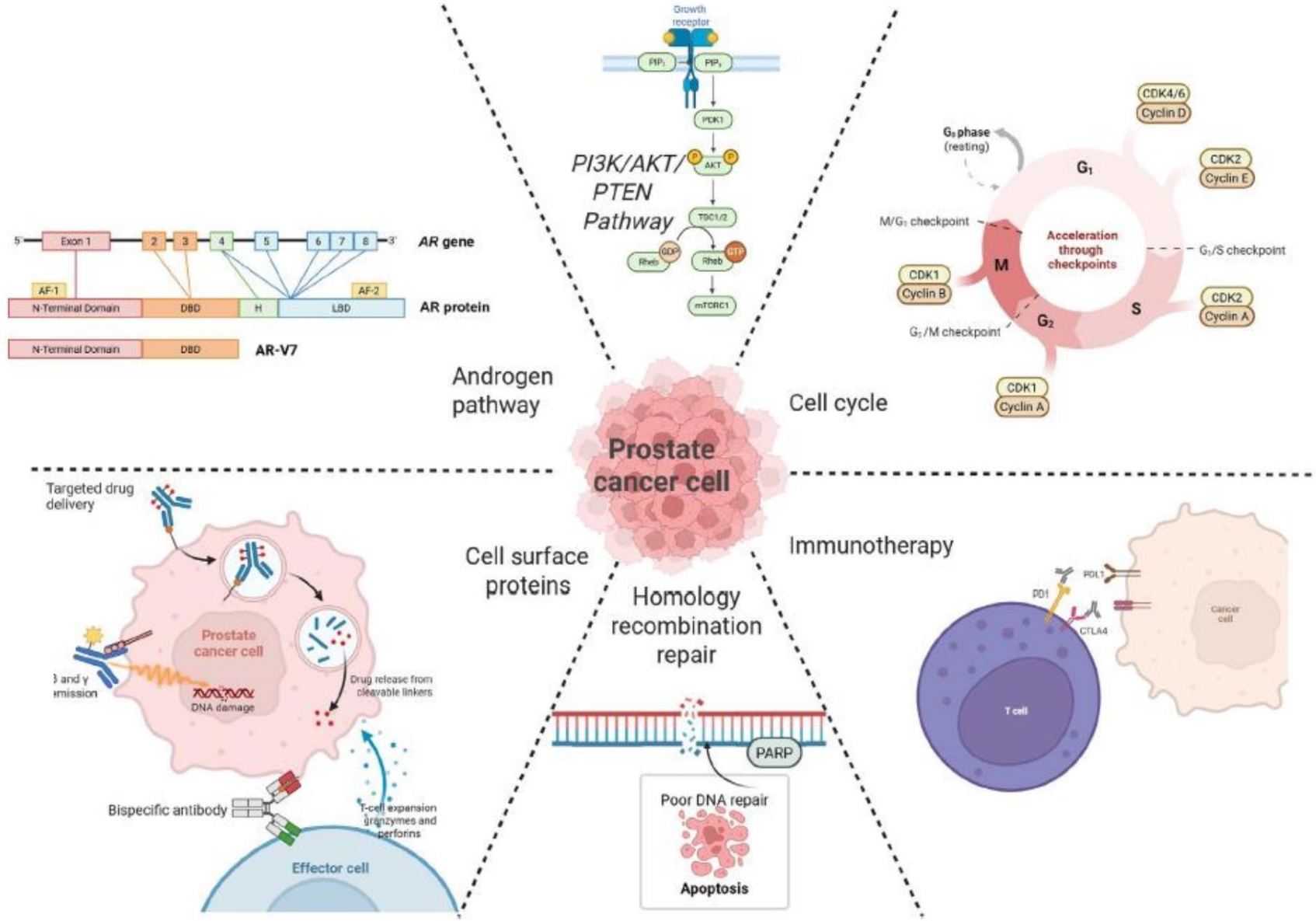
European Association of Urology

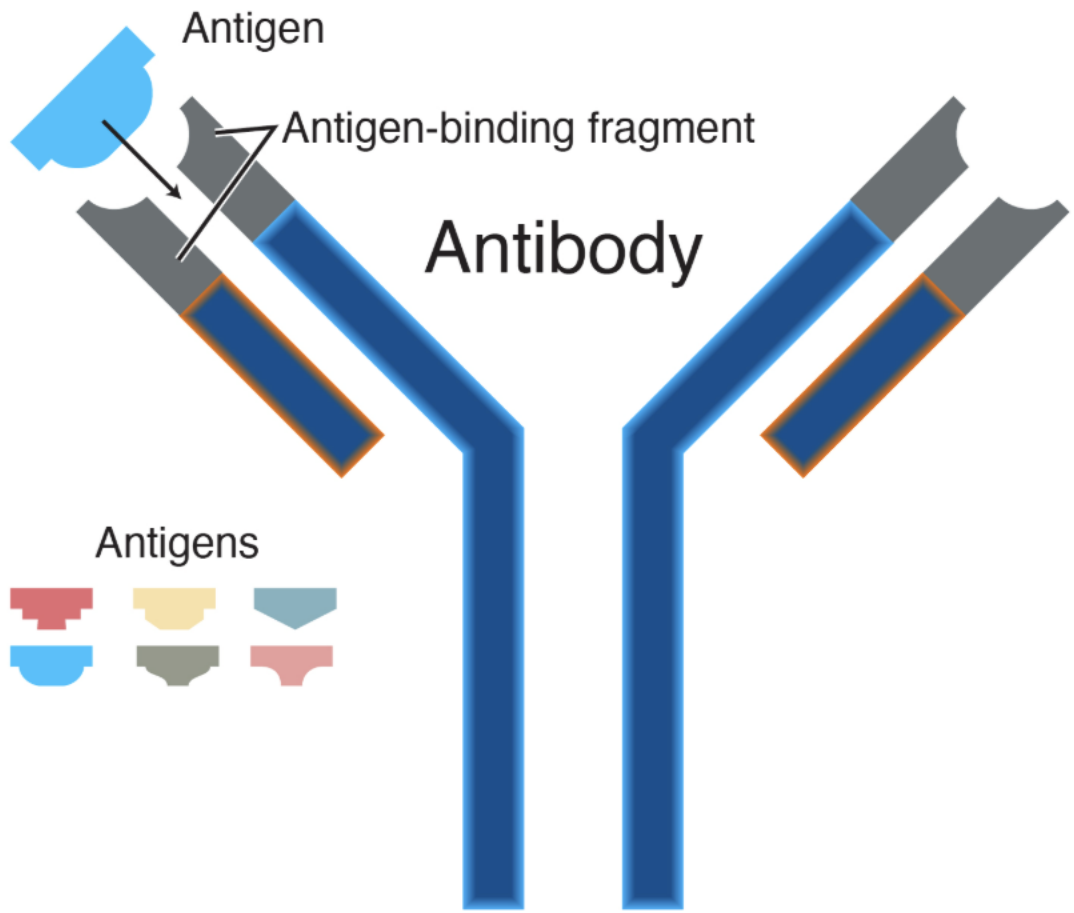
Review – Prostate Cancer

Novel Therapeutic Strategies for Metastatic Prostate Cancer Care

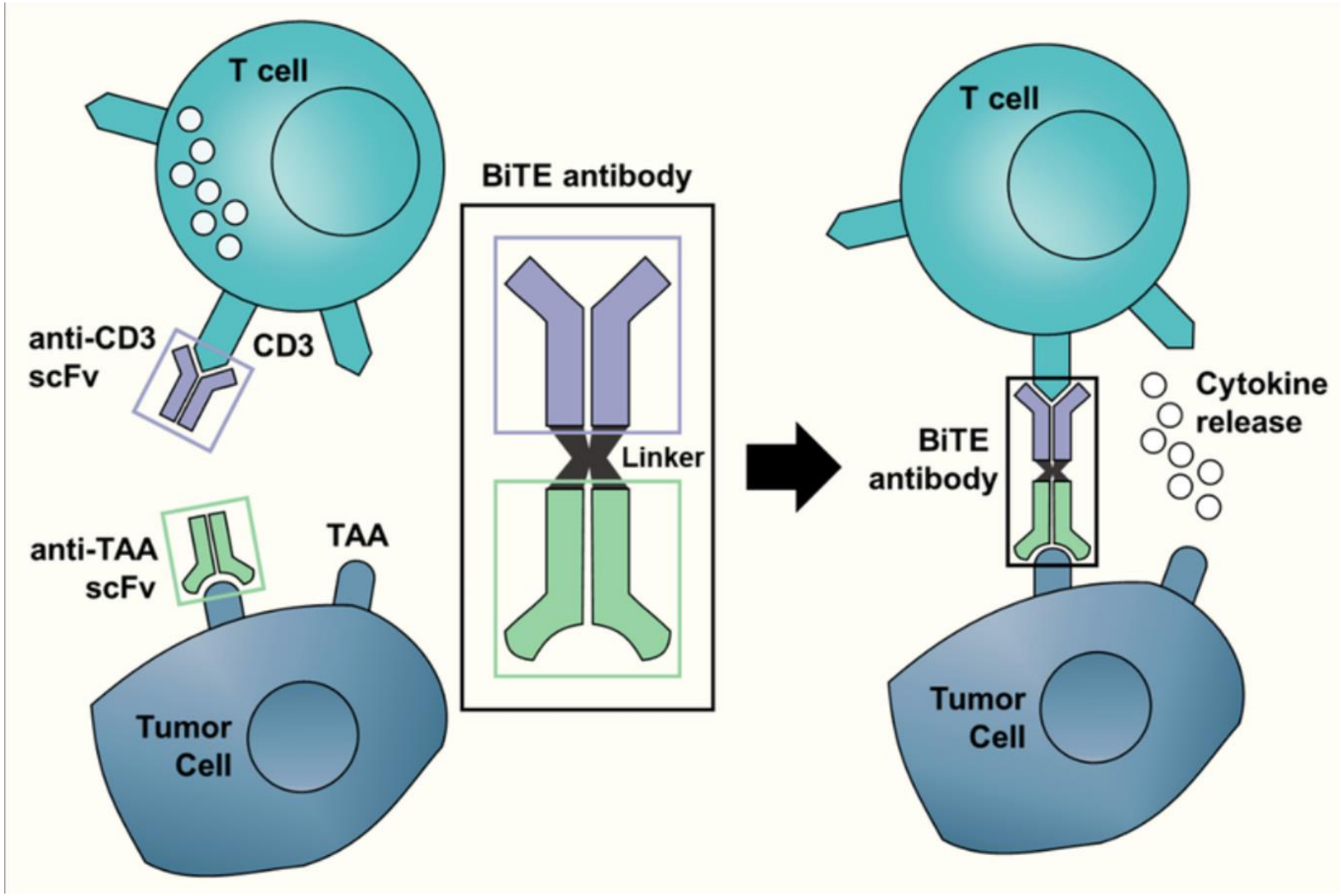
Alessia Cimadamore [a,†], *Cristina Boixareu* [b,c,†], *Adam Sharp* [b,c], *Himisha Beltran* [d], *Johann S. de Bono* [b,c,*]

[a] Institute of Pathological Anatomy, Department of Medicine, University of Udine, Udine, Italy; [b] The Royal Marsden Hospital, London, UK; [c] The Institute of Cancer Research, London, UK; [d] Dana-Farber Cancer Institute, Boston, MA, USA

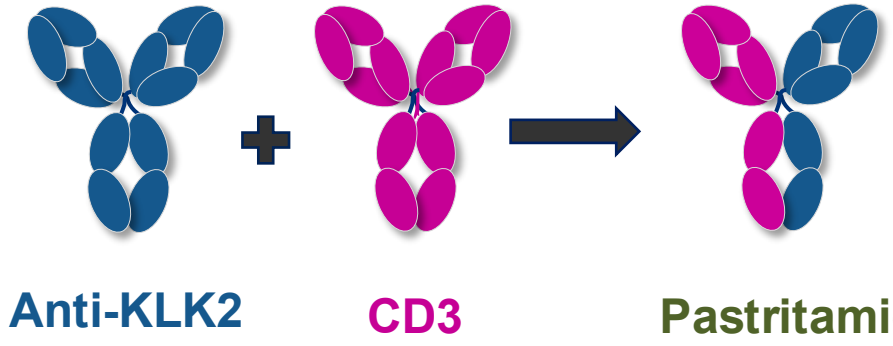


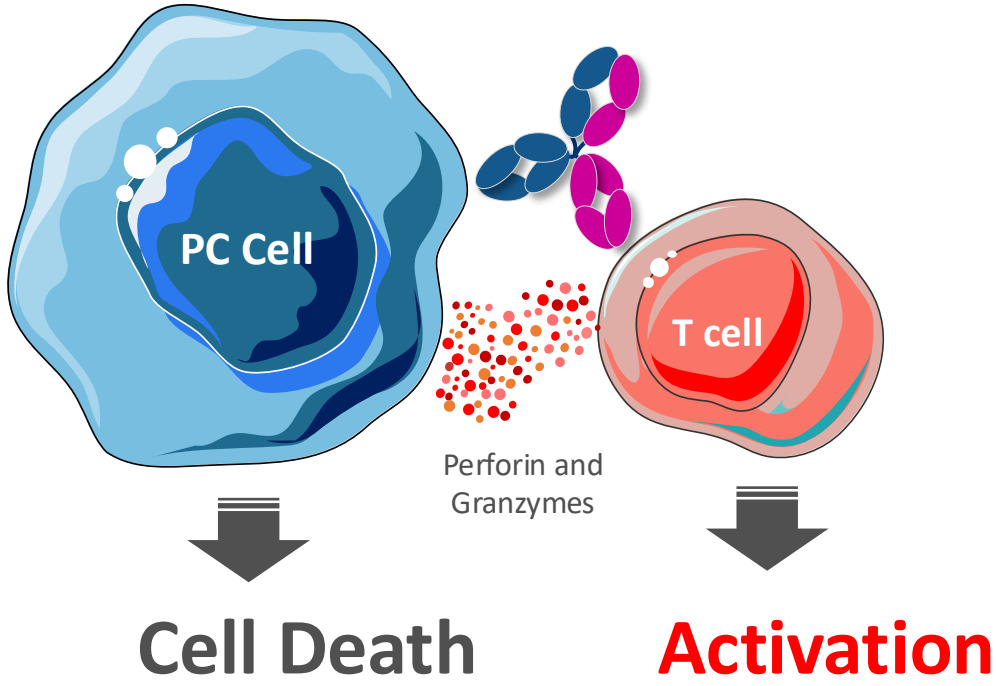

Antigen
Antigen-binding fragment
Antibody
Antigens

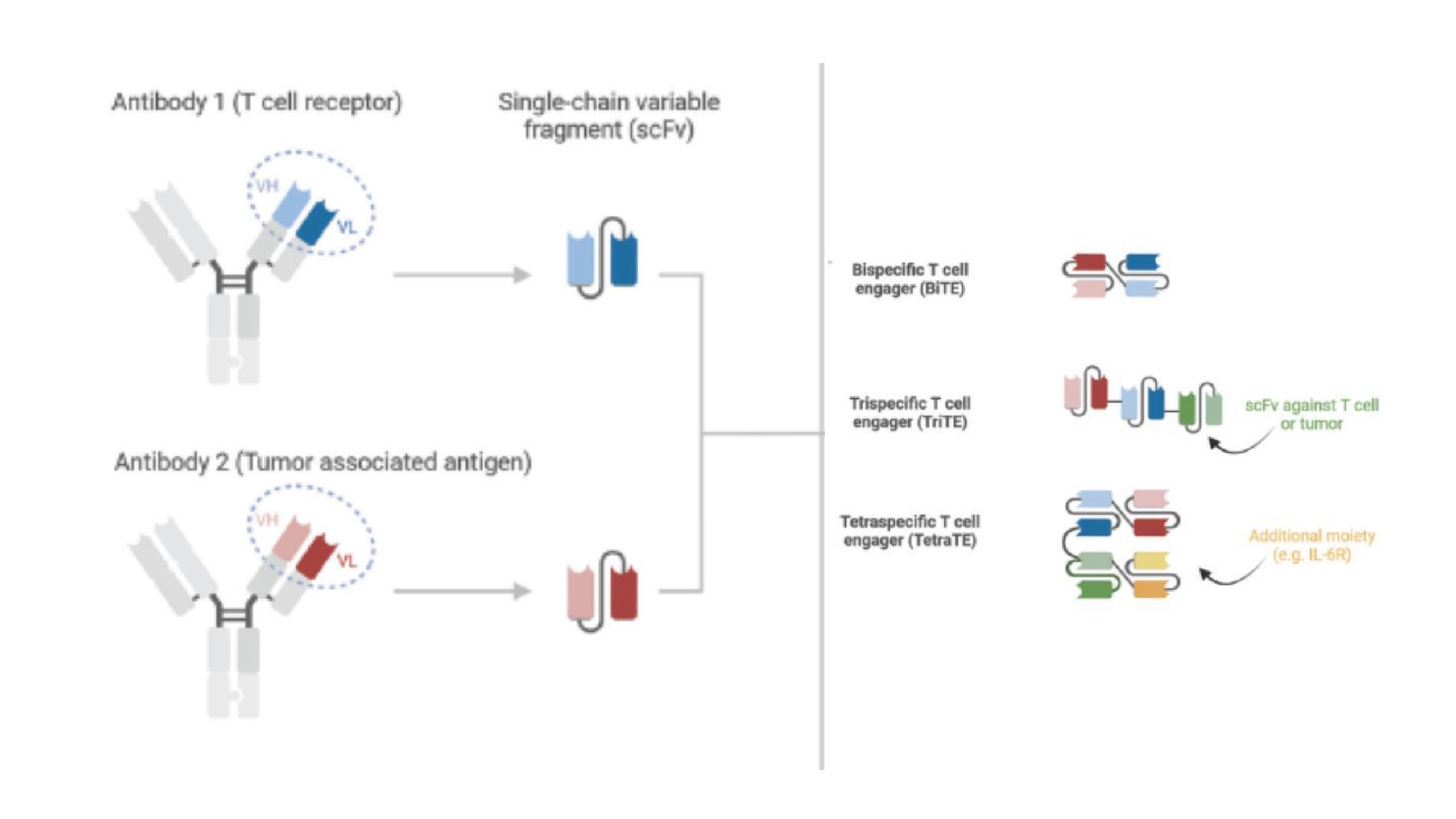
HOW DOES A BITE WORK??



CD3 T Cell Engagers (TCE)
Proximity AND Activation






Antibody 1 (T cell receptor)
Single-chain variable fragment (scFv)
VH
VL
Antibody 2 (Tumor associated antigen)
VH
VL
Bispecific T cell engager (BiTE)
Trispecific T cell engager (TriTE)
scFv against T cell or tumor
Tetraspecific T cell engager (TetraTE)
Additional moiety (e.g. IL-6R)

T-Cell engagers against prostate cancer

- Tumour associated targets include
  - **PSMA** (folate hydrolase; increased by DNA damage)
  - **STEAP-1** (AR driven)
  - **KLK2** (kallikrein enzyme; AR driven; PSA is KLK3)
  - B7-H3 (PD-L1 family of proteins; AR driven)
  - DLL3 (NE change)
  - Many others

Reviewed by Lampe et al, Frontiers in Pharmacology 2024

STEAP1xCD3 targeting by xaluritamig

Primary objectives: Safety and tolerability, MTD
Secondary objectives: PK, preliminary anti-tumor activity
Exploratory objectives: PD, immunogenicity

Key inclusion criteria:
- mCRPC refractory to prior novel hormonal therapy and 1–2 taxane regimens*
- ECOG PS 0–1
- Adequate organ function

Key exclusion criteria:
- Histology other than adenocarcinoma
- Active autoimmune disease

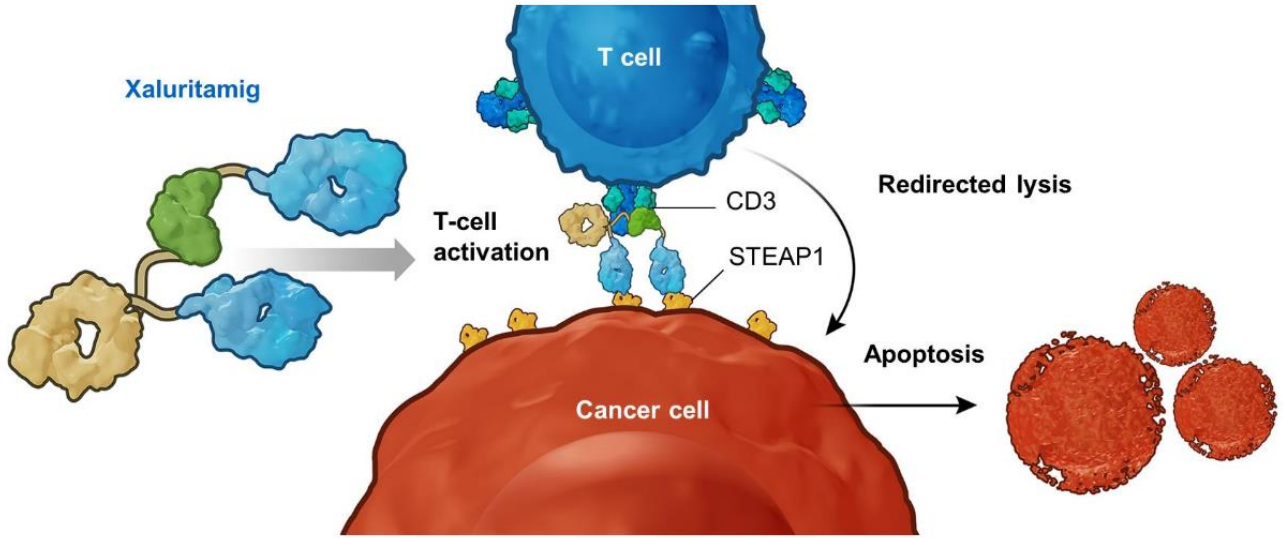
Part 1: FIH Monotherapy

Dose exploration

MTD

Dose expansion

- **A global, first-in-human, open-label study in patients with advanced prostate cancer (NCT04221542)**

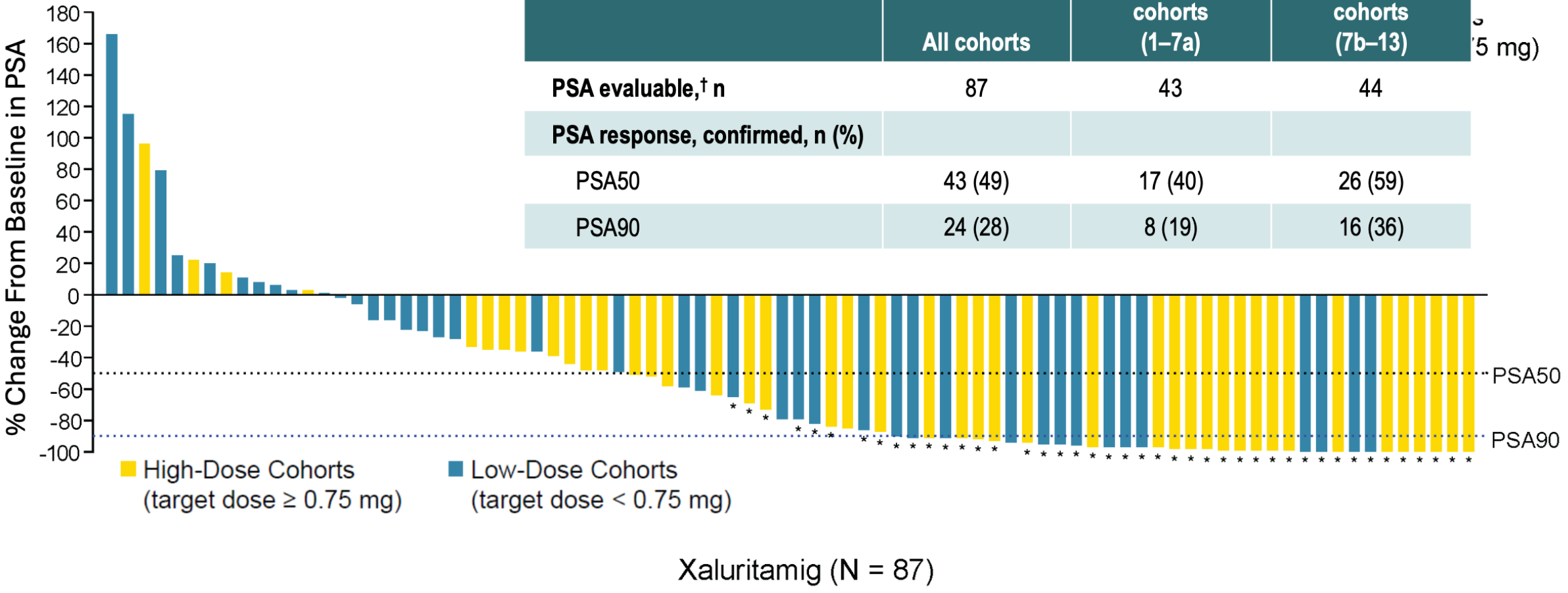


Xaluritamig is an XmAb® 2+1 T-cell engager designed to facilitate T cell–mediated lysis of STEAP1-expressing cells[3,4]

Kelly K ESMO 2024; Kelly K et al, Cancer Discovery 2024

STEAP1xCD3 targeting by xaluritamig: PSA responses

	All cohorts	Low-dose cohorts (1–7a)	High-dose cohorts (7b–13)
PSA evaluable,† n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)

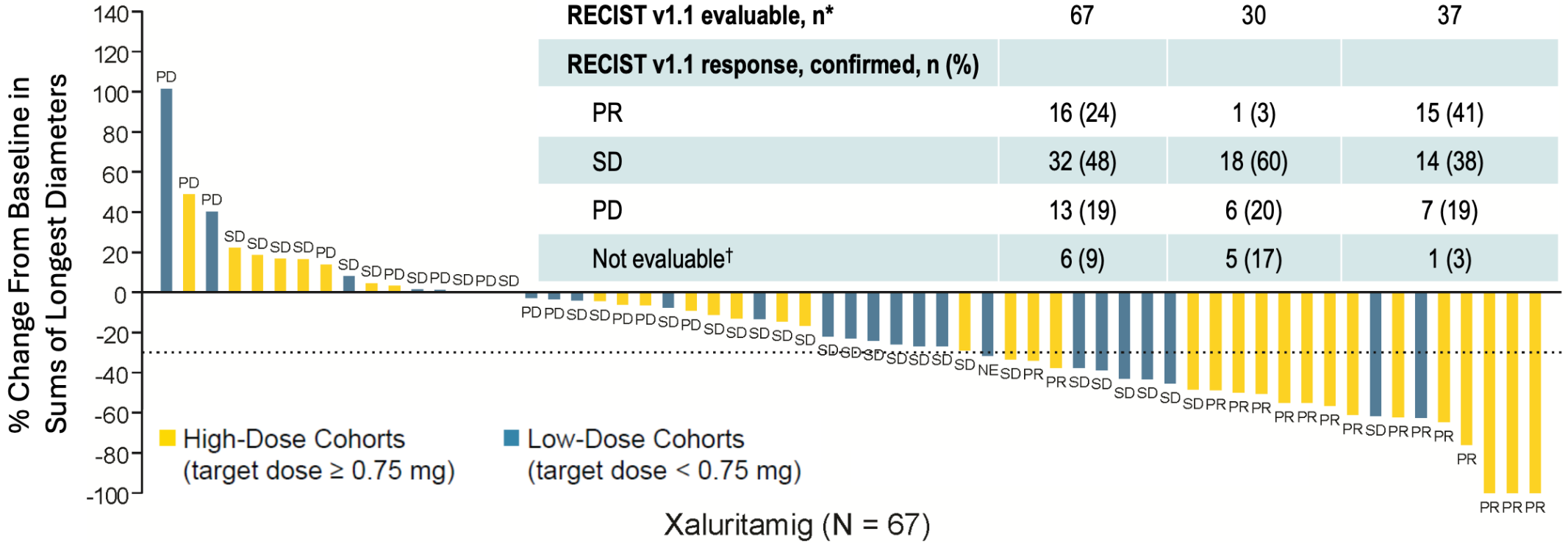


MADRID 2023 ESMO congress

*Confirmed PSA responders of PSA50 or better.
†10 patients were not PSA evaluable: 6 patients were missing baseline PSA values, and 4 patients did not have sufficient follow-up duration.
PSA, prostate-specific antigen.

STEAP1xCD3 targeting by xaluritamig: RECIST responses more common at higher dose cohorts

	All cohorts	Low-dose cohorts (1–7a)	High-dose cohorts (7b–13)
RECIST v1.1 evaluable, n*	67	30	37
RECIST v1.1 response, confirmed, n (%)			
PR	16 (24)	1 (3)	15 (41)
SD	32 (48)	18 (60)	14 (38)
PD	13 (19)	6 (20)	7 (19)
Not evaluable†	6 (9)	5 (17)	1 (3)



Dashed line indicates 30% reduction in tumor sum of longest diameters from baseline. *Historically, ~40% of mCRPC patients have RECIST-measurable disease.[1,2] †BOR of NE includes 5 patients without post-baseline scans and 1 patient without sufficient follow-up duration prior to post-baseline assessment.

BOR, best overall response; mCRPC, metastatic castration-resistant prostate cancer; NE, not evaluable; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; RECIST; Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Scher HI, et al. *Clin Cancer Res.* 2005;11(14):5223-5232. 2. Lorente D, et al. *Eur Urol Focus.* 2018;4(2):235-244.

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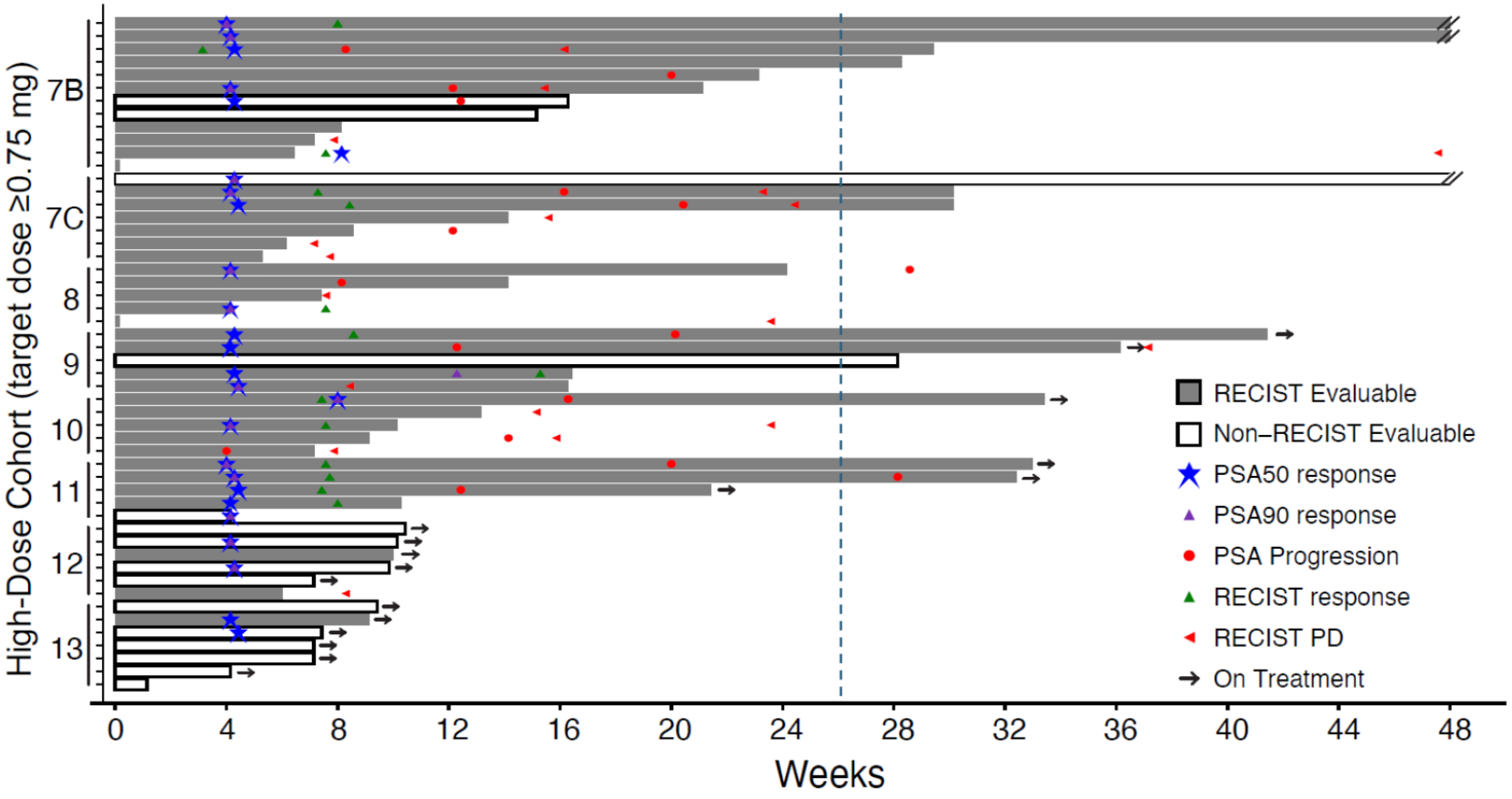
STEAP1xCD3 targeting by xaluritamig: Response durability?



- Nineteen patients from high-dose cohorts (n = 52) remained on treatment at data cutoff
- Of those, 13 patients from high-dose cohorts remained on treatment for > 6 months

Duration of response*

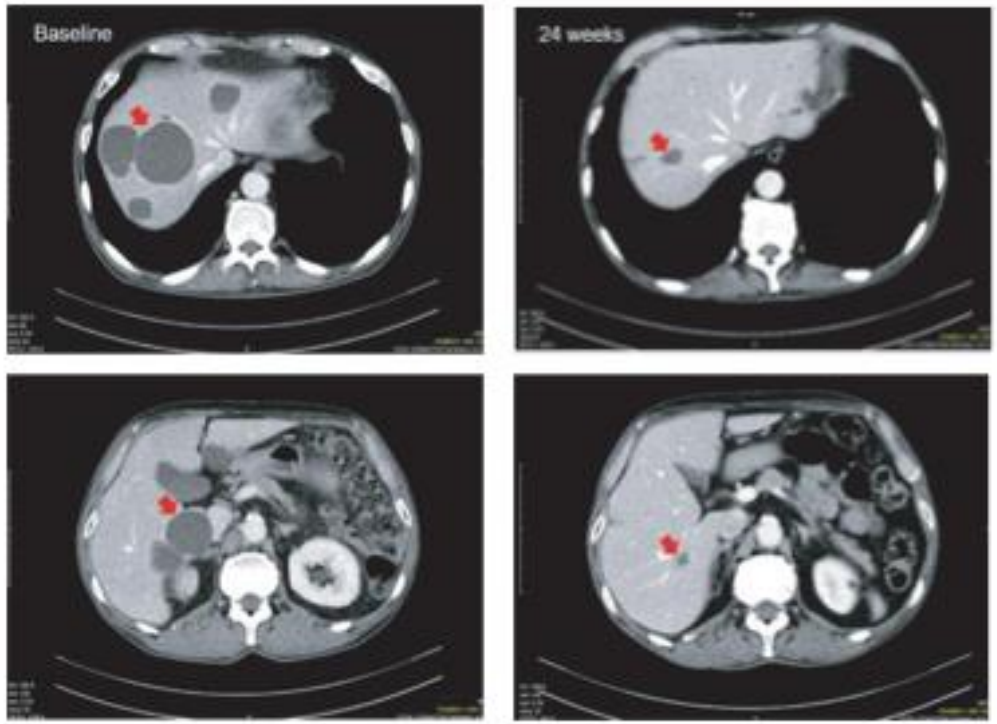
Median, 9.2
(range, 1.9+ to 17.7+) months

n = 16 (confirmed PR)
10/16 still in response

STEAP1xCD3 targeting by xaluritamig: Scans

CT Scan

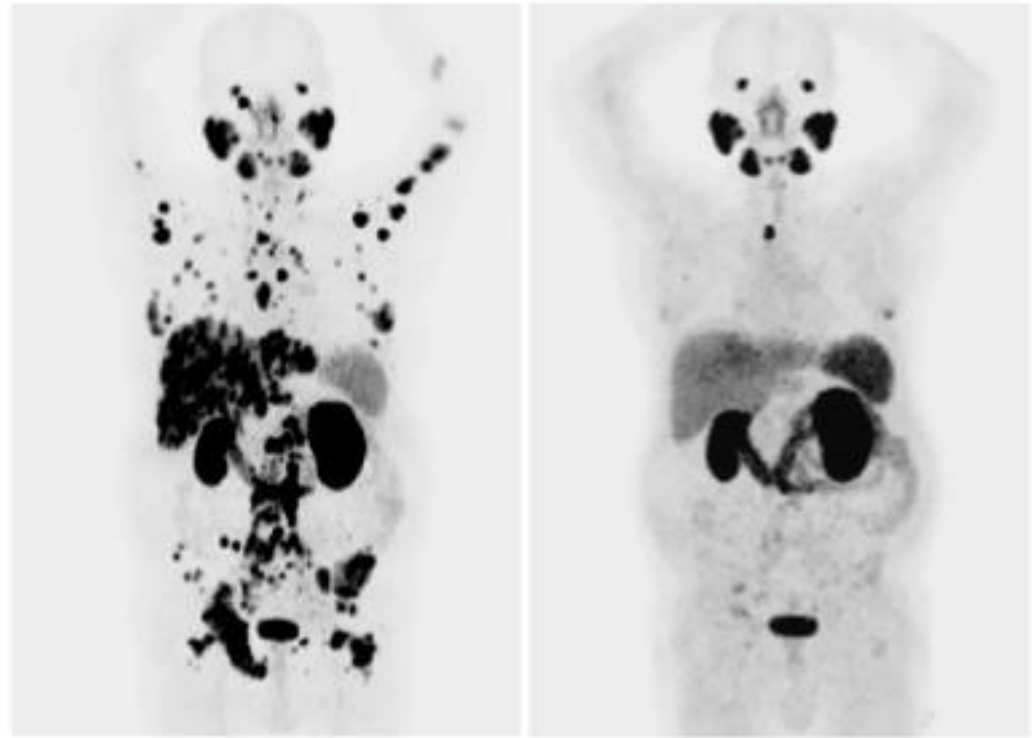
Baseline	Week 24



65-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 11 and achieved a confirmed RECIST and PSA90 response.

PSMA PET Imaging

Baseline	Week 12



56-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 12 and achieved a confirmed PSA90 response (not RECIST evaluable).

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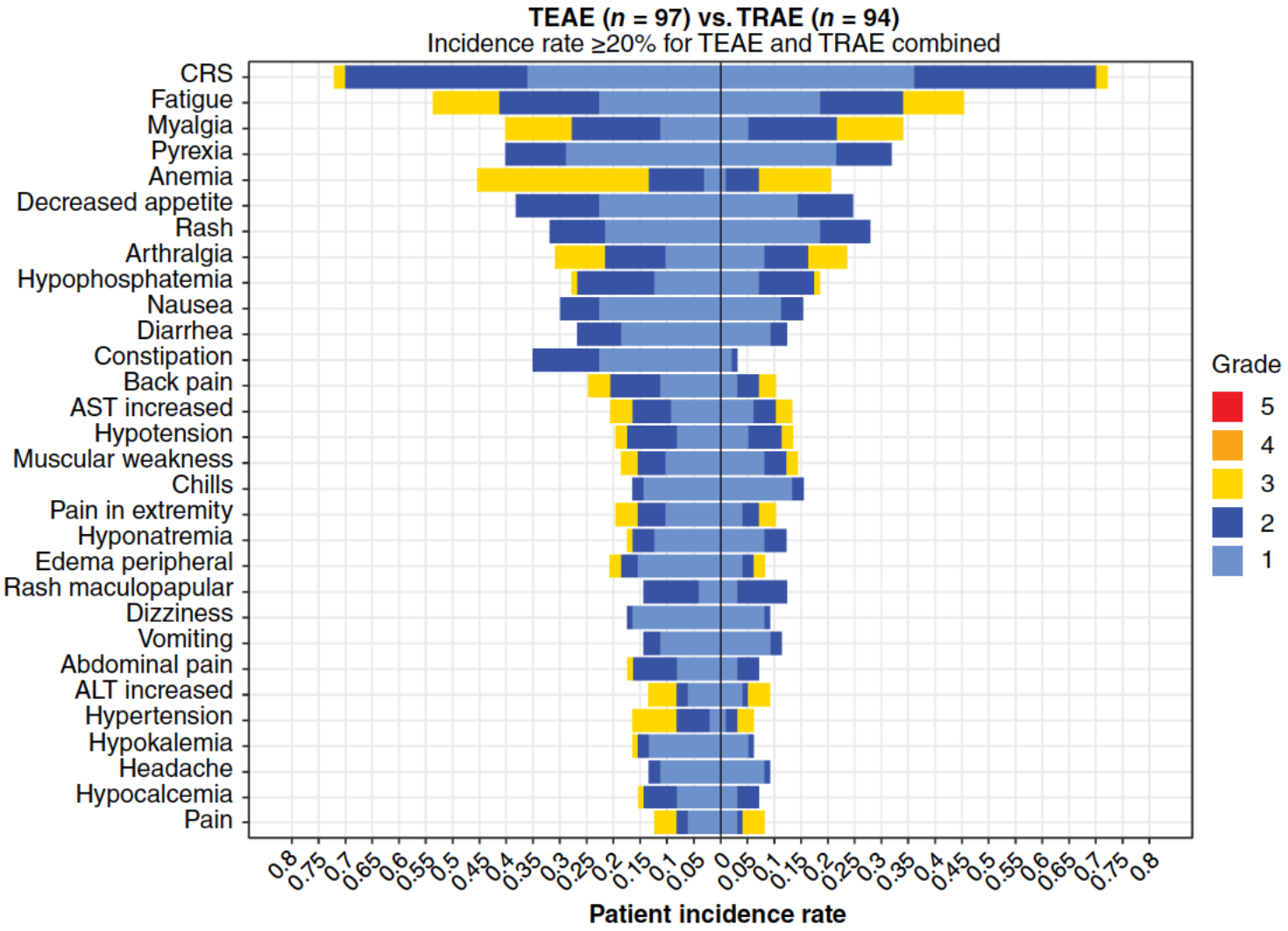
CT, computerized tomography; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSMA PET, prostate-specific membrane antigen positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

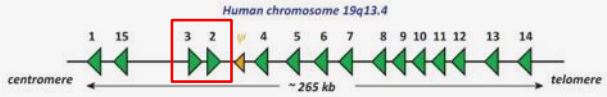
CRS Is Common with Xaluritamig (and other TCE)



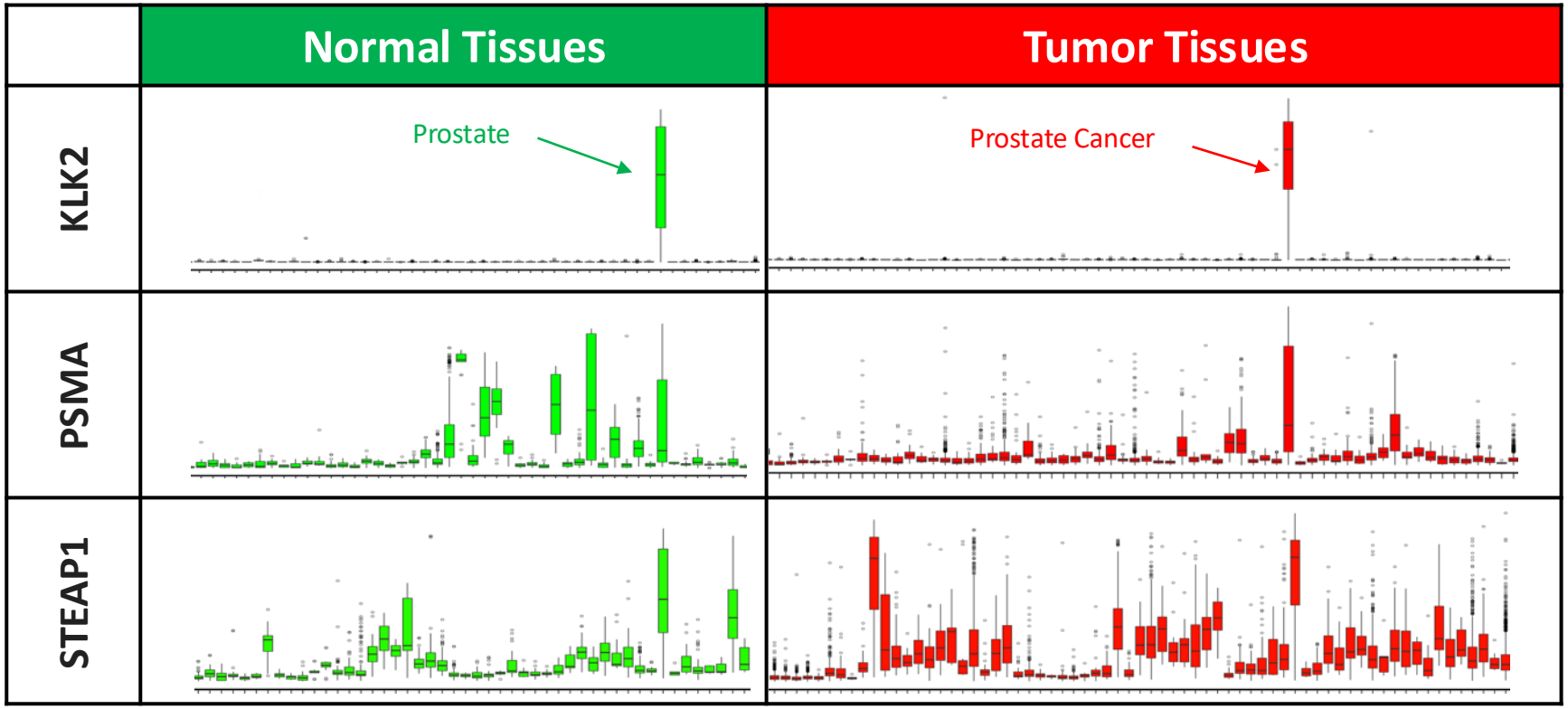
The Target of Pasrimatig is KLK2: A Nearly Perfect PC Antigen

Human Kallikrein-2 (hK2, KLK2)

- Serine protease (activates KLK3/PSA)
- Involved in semen liquefication
- Regulated by AR (colocalizes with KLK3 on chromosome)

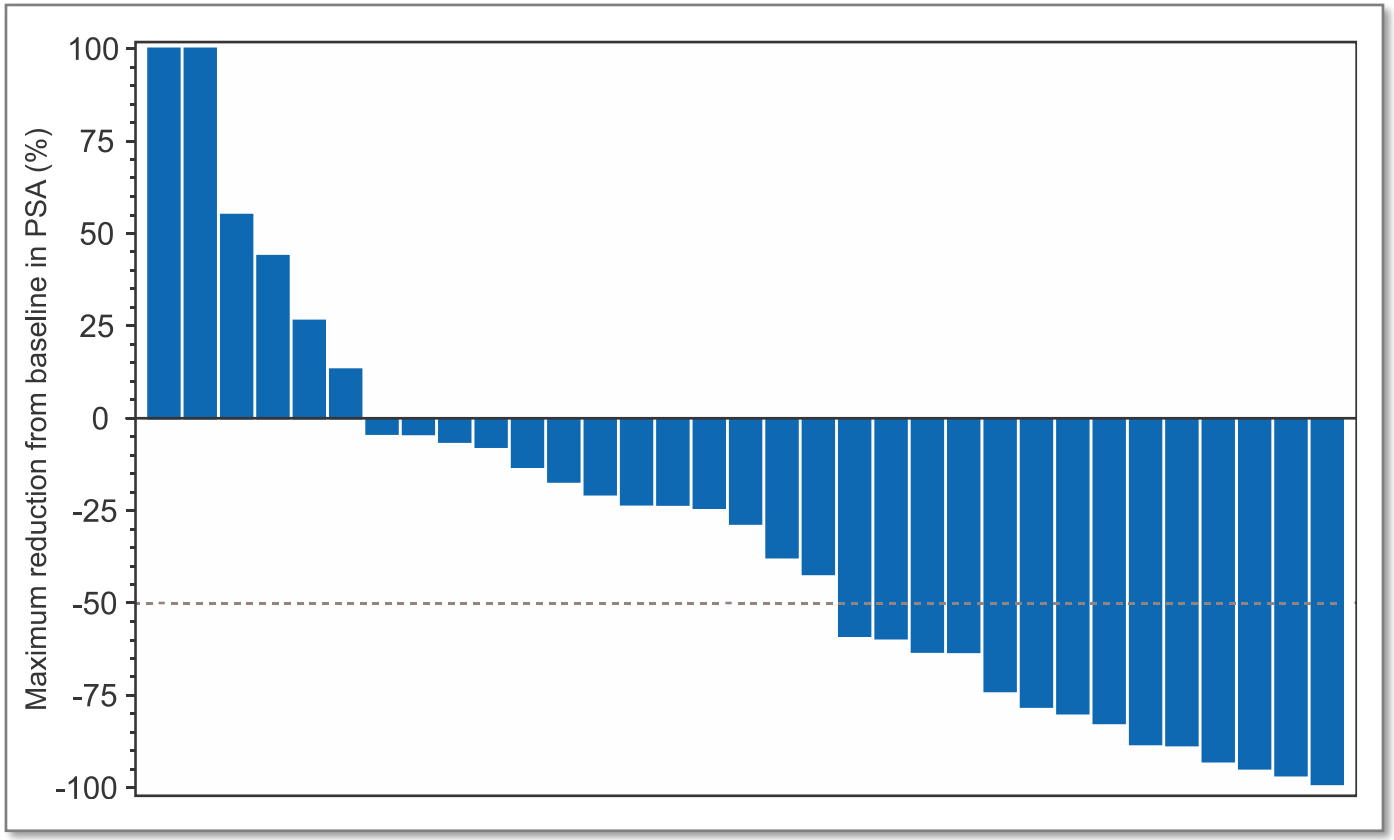


- Internal data confirmed its cell surface expression



Shen, F. Drake C. et al, *Clinical Cancer Research 2025*

Pasritamig Achieved Rapid and Deep Prostate-Specific Antigen Responses



RP2D efficacy population (IV 3.5 mg D1, 18 mg D8, then 300 mg Q6W):

- **PSA decreases** were noted as early as initial step-up doses
- **14/33 (42.4%)** participants achieved **PSA50** at any time
  - **12 (36.4%)** participants achieved **confirmed PSA50**

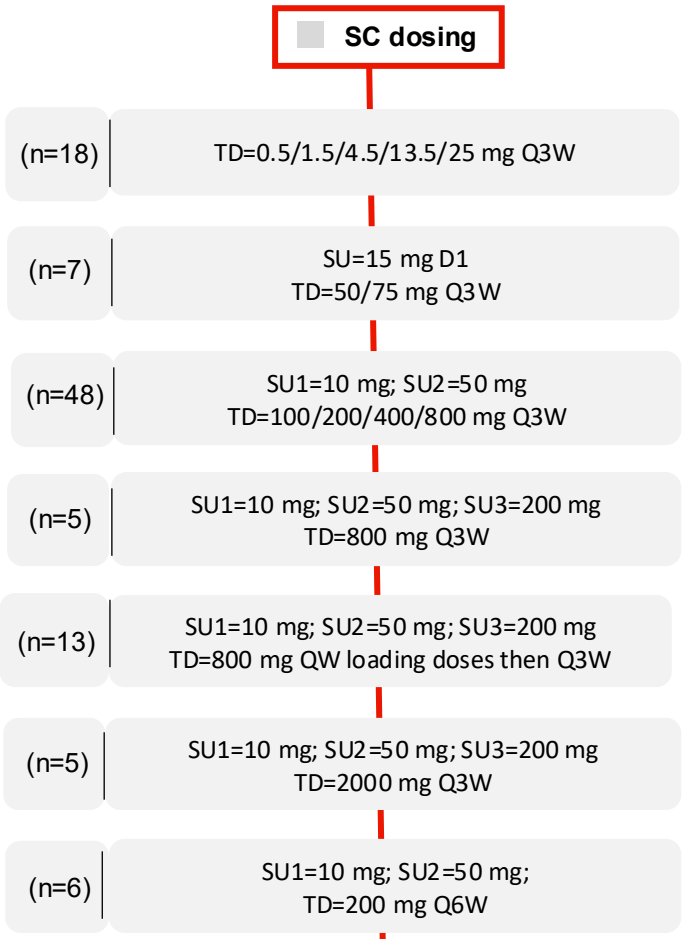
- In the **all-treated population** with measurable disease at baseline (n=84/174), **ORR** was **8.3%** (7/84), not including **1 participant with a CR** who had non-measurable disease at baseline
  - Median (95% CI) **DOR** was **8.9** (3.6, NE) **months**

Data cut-off March 7, 2025. CR, complete response; D, Day; DOR, duration of response; IV, intravenous; NE, not estimable; ORR, overall response rate; PSA, prostate-specific antigen; PSA50, ≥50% decrease from baseline in PSA; RP2D, recommended phase 2 dose.

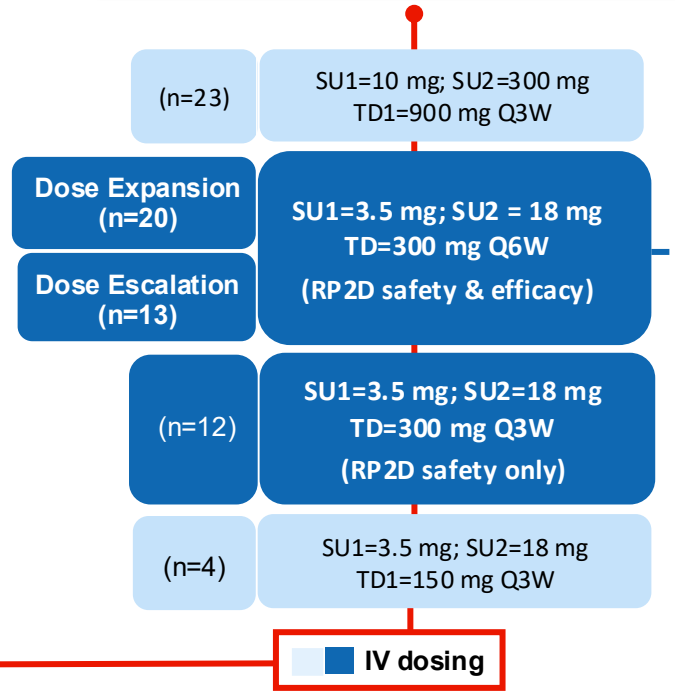
Phase 1, First-in-Human Study (NCT04898634) of Pasritamig: Dose Escalation and Dose Expansion in mCRPC

Key eligibility

- ECOG 0 or 1
- Prior ARPI and/or chemotherapy
- Prior Lu-177 PSMA RLT allowed
- PSA >2 ng/mL and no visceral disease (dose expansion only)



- **Initial dosing SC** with single dose of steroid premedication
- **Transitioned** to **IV dosing** to achieve **higher doses** with **fewer injections**
- **Step-up dosing** introduced **to mitigate CRS**
- **IV dosing** chosen for **RP2D** based on **improved** safety and efficacy profile



Recommended Phase 2 Dose and Schedule

Intravenous

SU1: 3.5 mg Day 1
SU2: 18 mg Day 8
*TD: 300 mg Day 15, then **300 mg Q6W***

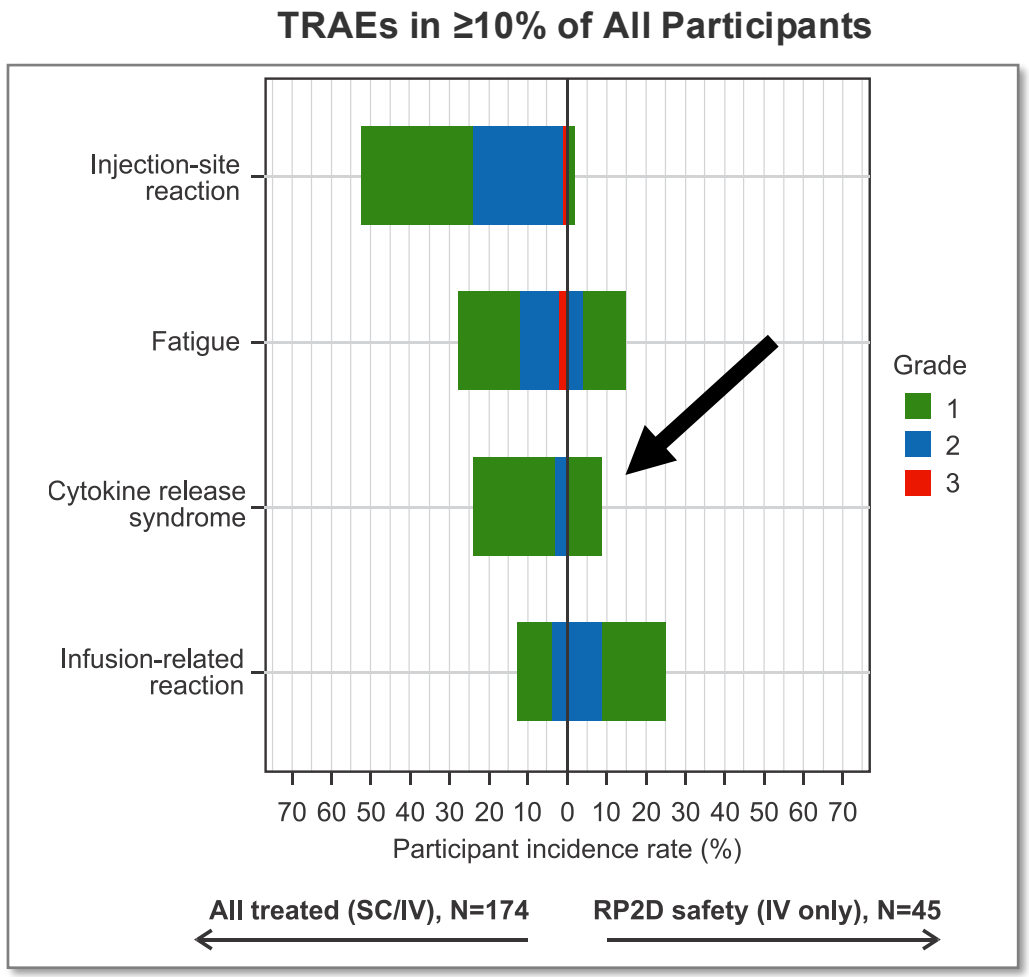
All Outpatient

ARPI, androgen receptor pathway inhibitor; CRS, cytokine release syndrome; ECOG; Eastern Cooperative Oncology Group; IV, intravenous; Lu-177 PSMA RLT, lutetium Lu 177 vipivotide tetraxetan prostate-specific membrane antigen radioligand therapy; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; QW, every week; Q3/6W, every 3/6 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous; SU, step-up dose; TD, treatment dose.

Add QR code here on slide master 0.75" x 0.75"

Presented by C. Baldini at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 30-June 3, 2025; Chicago, IL, USA & Online

CRS is Rare with IV Pasritamig (And Exclusively Grade 1)



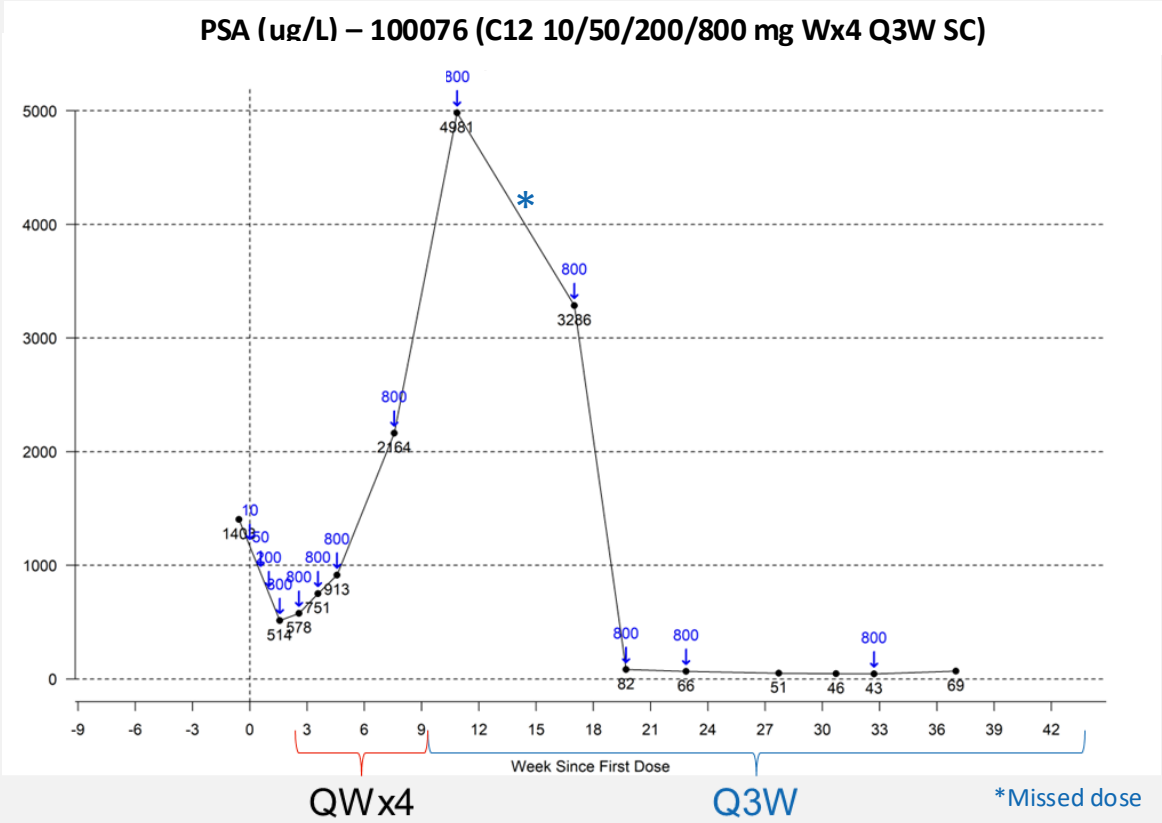
	All-Treated Population (SC/IV) N=174	RP2D Safety Population (IV Only) N=45
Participants with ≥1 TRAE, n (%)	144 (82.8)	**27 (60.0)**
Serious TRAEs, n (%)	12 (6.9)	2 (4.4)[a]
Grade ≥3 TRAEs, n (%)	17 (9.8)	2 (4.4)
TRAEs leading to treatment discontinuation, n (%)	1 (0.6)	0

RP2D safety population (IV 3.5 mg D1, 18 mg D8, 300 mg D15 then Q3W/Q6W):

- **CRS** occurred in 4 pts (8.9%), **all Grade 1** (fever only) and **did not** require tocilizumab
- **IRRs** were seen **in 24.4%** of participants
  - Management was limited to mostly antipyretics; no steroid or tocilizumab was given
- **No** TRAEs led to treatment **discontinuation, dose reduction, ICANS, or death**
- The **only Grade 3** TRAEs were **transient** AST/ALT increases and neutropenia
- **No DLTs**[b]

Data cut-off March 7, 2025. Participants are counted only once for any given event, regardless of the number of times they experienced the event. [a]The serious TRAEs were both Grade 1 CRS hospitalized for observation. [b]1 DLT of transient Grade 3 ALT/AST increase occurred in the all-treated population after SC 50 mg step-up dose; recovered to Grade 1 in 8 days. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; D, Day; DLT, dose-limiting toxicity; ICANS, immune-effector cell associated neurotoxicity syndrome; IRR, infusion-related reaction; IV, intravenous; RP2D, recommended phase 2 dose; SC, subcutaneous; TRAE, treatment-related adverse event.

An Astute Clinical Observation -> Moving from Q1 to Q3 Increased Activity



CRS=Cytokine release syndrome; D=Day; FIH=First-in-human; ISR=Injection site reaction; IV=Intravenous; KLK2= Kallikrein-related peptidase 2; mCRPC= Metastatic castration-resistant prostate cancer; PSA=Prostate-specific antigen, Q1W=Every week; Q3W = Every 3 weeks Q6W=Every 6 weeks; R2PD= Recommended phase 2 dose; SC=Subcutaneous; SU=Step-up; TD=Target dose.

1. Shen et al. *Clin Can Res*. 2025; doi: 10.1158/1078-0432.CCR-25-0950.

Why does 300 mg IV given Q6W increase the frequency of PSA50 responders compared to Q3W?

PSA50 Response	300 mg IV Q3W	300 mg IV Q6W
At any time	4/12 **(33%)**	33/75 **(44%)**
Confirmed at 3W	2/12 **(17%)**	26/75 **(35%)**
Confirmed at 12W	2/12 **(17%)**	21/63 **(33%)**

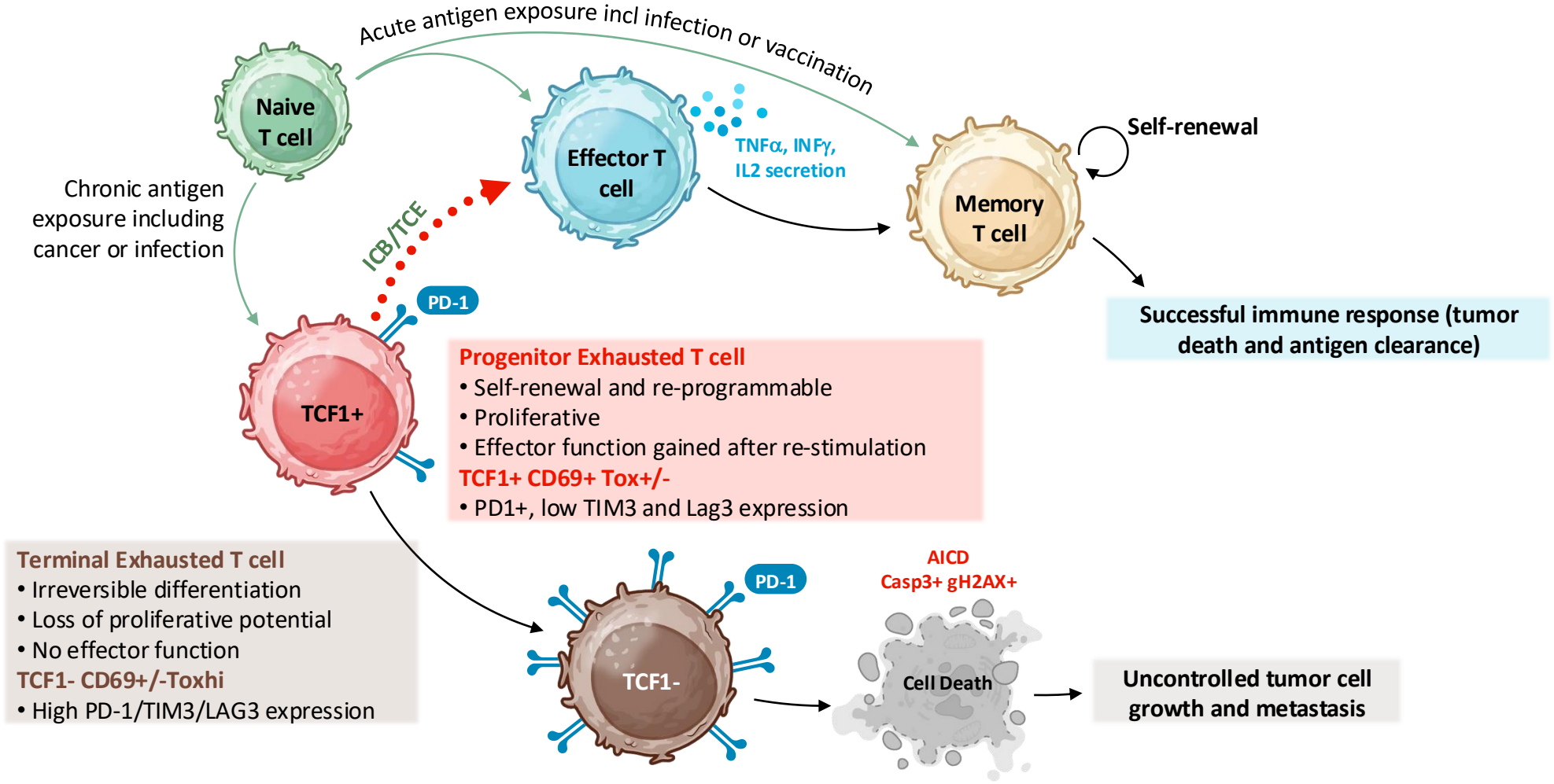
Hypotheses:

1) More frequent dosing induces activation induced cell death (AICD)
2) More frequent dosing induces T cell exhaustion

Clinical Cutoff Date: 04-July-2025

AICD=activation-induced T-cell death; IL2=Interleukin 2; INFg= Interferon gamma; IV=Intravenous; PSA=Prostate-specific antigen; Q3W=Every 3 weeks; Q6W=Every 6 weeks; TNFa=Tumor necrosis factor alpha; W=weeks.

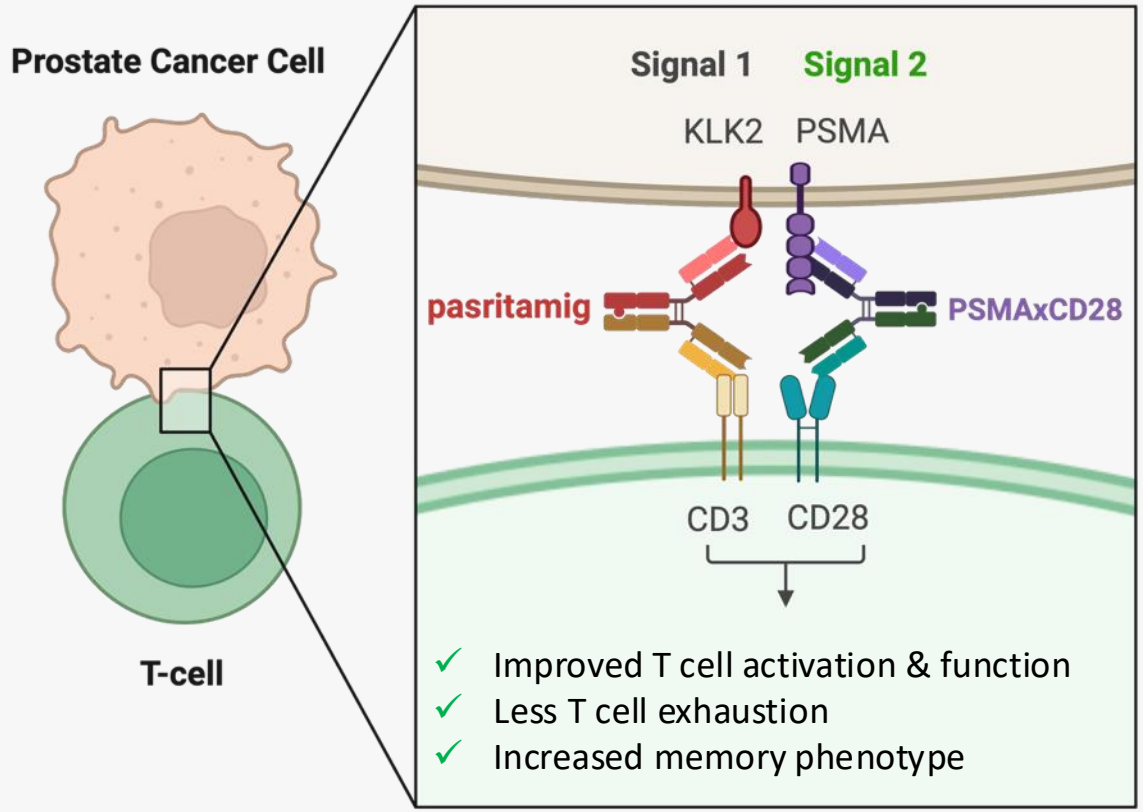
What is the impact of dosing frequency on T-cell exhaustion?



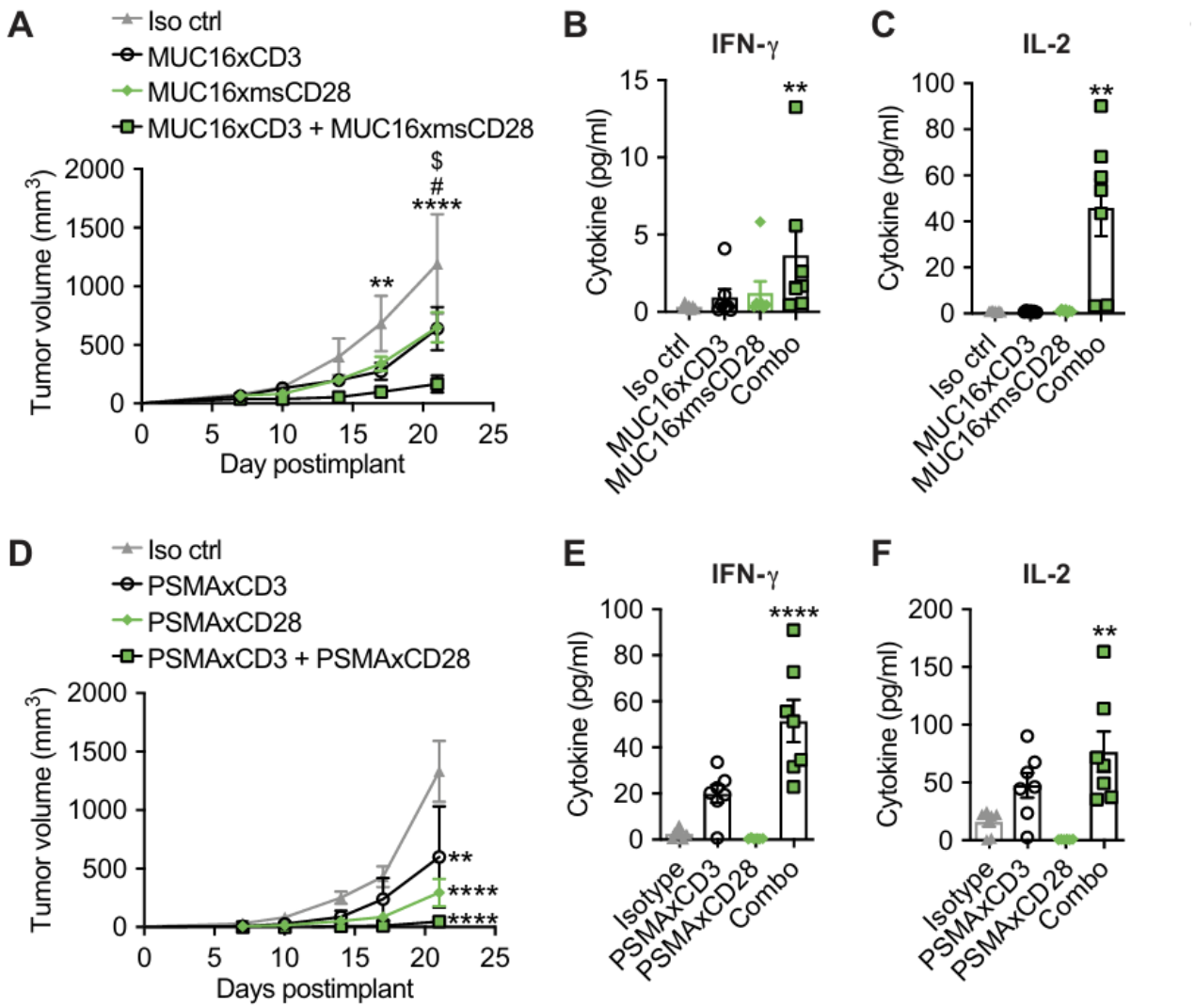
Casp3=Caspase 3; ICB=Immune Checkpoint Blockade; CD69=Cluster of differentiation 69; gH2X=gamma histone 2AX; IL2=Interleukin 2; INFg= Interferon gamma; Lag3=Lymphocyte-activation gene 3; PD-1=Programmed Death-1; TCE=T-cell Engagers; TCF1=T-cell factor 1; TNFa=Tumor necrosis factor alpha; TIM-3=T-cell immunoglobulin and mucin-domain containing-3; Toxhi=High expression of thymocyte selection-associated high mobility group box protein.

Combinations: Pastritamig plus PSMA / CD28

CD3/CD28-based T cell Redirection Therapy



- ✓ Improved T cell activation & function
- ✓ Less T cell exhaustion
- ✓ Increased memory phenotype



Skokos et al. Science Translational Medicine. 2020

TSAxCD28 bispecific enhances TSAxCD3 antitumor efficacy and T cell activation in mouse syngeneic tumor models

TSAxCD28 has limited efficacy on its own, but can markedly enhance tumor killing in conjunction with Signal 1

Only activates CD28 at the tumor site, so should limit systemic toxicity seen with CD28 super agonists

A Phase 1 Study of JNJ-87189401 (PSMA-CD28 Bispecific Antibody) Combined With JNJ-78278343 (KLK2-CD3 Bispecific Antibody) for Advanced Prostate Cancer

Inclusion Criteria:

- Metastatic Prostate AdenoCa
- PSA >2
- Measurable or Evaluable
- ECOG 0 /1
- On ADT, 1 Prior ARSI or taxane

Exclusion Criteria:

- Autoimmune disease in past 12 months
- MI; CVA; CHF in past 6 months

→

JNJ-78278343 (Pasritamig) administered
+
JNJ-87189401 administered

→

Primary Outcome:

- Number of subjects with AEs
- Number of subjects with DLTs

Secondary Outcomes:

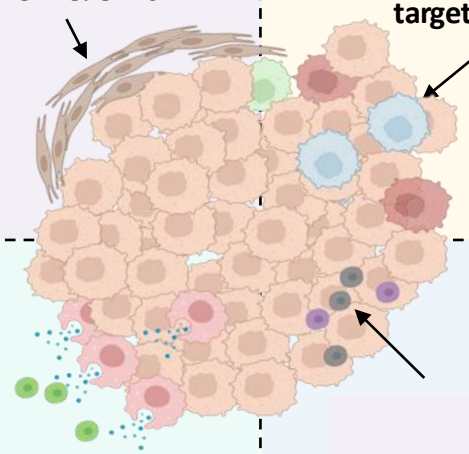
- Serum concentration
- Serum Cytokines
- Serum PSA concentration
- Number of subjects with Antidrug antibodies
- ORR
- PSA response rate
- Duration of response

Potential Pasritamig Combinations to Overcome the Immune-suppressive TME of Prostate Cancer

Physical Barriers

- Pasritamig + Docetaxel (Ongoing)

TCE — Chemo



Tumor Heterogeneity

- Pasritamig + ADC (ongoing)

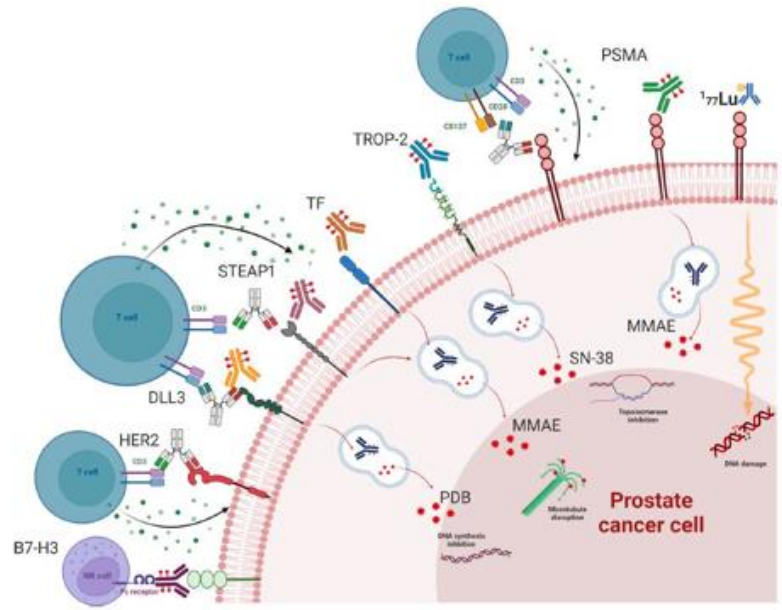
KLK2 — PSMA
TCE — ADC

- Pasritamig + Apalutamide (Ongoing)

KLK2 — ARPI

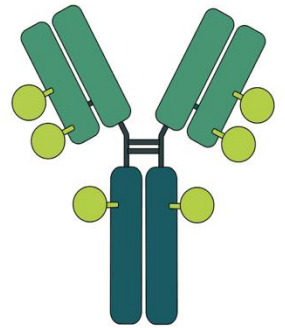
Cell surface protein targeting

- T-cell engagers
- Radiopharmaceuticals
- **Antibody drug conjugates**



DB-1311/BNT324: B7H3 ADC

- As the incidence rate of prostate cancer is increasing,[1] there is a high unmet need for effective therapy for patients with heavily pretreated CRPC[2]
- B7H3 is an immunoregulatory protein that is highly expressed in CRPC and correlates with poor prognosis[3–6]
- B7H3 ADCs have shown early clinical activity in CRPC[7–9]
- DB-1311/BNT324, an investigational, novel B7H3 ADC,[7] has received FDA Fast Track designation for advanced/unresectable or metastatic CRPC that has progressed on or after standard systemic regimens[10]



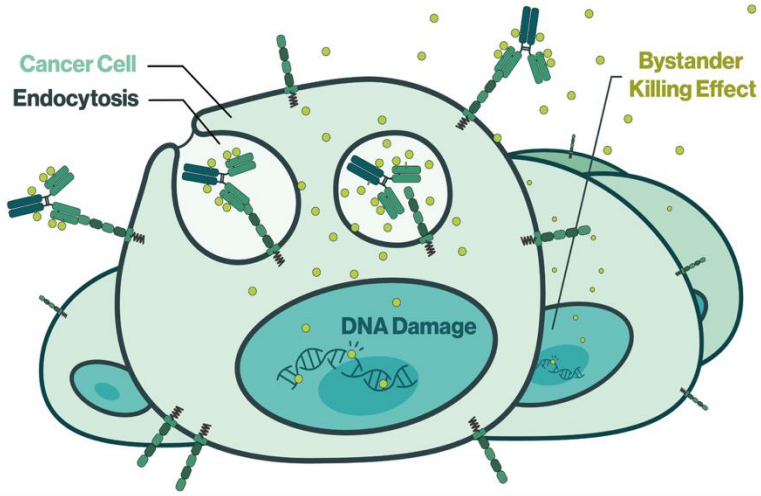
anti-B7H3 ADC

ADC Payload: DNA Topoisomerase I

ADC Target: B7H3 (CD276) Receptor

Key attributes of DB-1311/BNT324:[11]

- Highly potent proprietary topoisomerase I inhibitor payload
- Stable tumor-selective cleavable linker
- Optimized drug-to-antibody ratio: ~6
- Fc silenced (L234A/L235A)
- Selectively endocytosed into the lysosome of B7H3-expressing cells
- Bystander antitumor effect



1. Sherman RL et al. Cancer 2025;131(9):e35833; 2. Narayan V et al. Clin Genitourin Cancer 2024;22(6):102188; 3. Dong P et al. Front Oncol 2018;8:264; 4. Koumprentziotis I-A et al. Vaccines (Basel) 2024;12:54; 5. Pio Fabrizio F et al. Transl Oncol 2024;39:101801; 6. Zang X et al. PNAS 2007;104(49)19458–63; 7. Cheng Y et al. ESMO Asia 2024 57O; 8. Doi T et al. ESMO 2022 453O; 9. de Bono JS et al. ESMO 2024 1654P; 10. https://investors.biontech.de/news-releases/news-release-details/biontech-and-dualitybio-receive-fda-fast-track-designation; 11. Li C et al. AACR 2023 2967.
ADC, antibody–drug conjugate; B7H3, B7 homolog 3 protein; CRPC, castration-resistant prostate cancer; Fc, fragment crystallizable; FDA, US Food and Drug Administration.

DB-1311-O-1001 Study Design (NCT05914116)

Phase 1/2, multicenter, first-in-human study of DB-1311/BNT324 in patients with advanced/metastatic solid tumors unselected for B7H3 expression (N=465)

We present efficacy and safety data from patients with mCRPC treated with DB-1311/BNT324

Key inclusion criteria:

- ≥18 years of age
- ≥1 measurable lesion per RECIST v1.1 (bone-only disease allowed)
- ECOG PS 0–1
- Adequate organ function
- Progressive mCRPC (serum testosterone <50 ng/dL and PD as defined by PCWG3 criteria)

Key exclusion criteria:

- Prior B7H3 targeted therapy
- Prior topoisomerase 1 ADC

Study part/cohort	Additional inclusion criteria	Dose	Status
Phase 1 Dose escalation/backfill		3 mg/kg up to 12 mg/kg IV Q3W	n=27 Complete
Phase 2:			
Cohort 4 (Dose optimization)	• Prior docetaxel; docetaxel rechallenge allowed • Prior NHT	R → 9 mg/kg IV Q3W (n=20) R → 6 mg/kg IV Q3W (n=22)	n=42 Complete
Cohort 11 (Post Lu-177)	• 1–2 lines of systemic chemotherapy, including docetaxel • Prior NHT • Prior Lu-177 radioligand therapy	6 mg/kg IV Q3W	n=4 Enrolling
Cohort 12 (Taxane-naïve)	• Taxane-naïve; prior (neo)adjuvant use >12 months earlier allowed • Prior NHT	6 mg/kg IV Q3W	Enrolling

Primary endpoints:
Investigator-assessed ORR (per RECIST v1.1 [soft tissue] and PCWG3 [bone metastases]) and safety

Secondary endpoints include:
DCR, DOR, rPFS

- **73 patients with mCPRC in current analysis**

Data cut-off: March 4, 2025. DB-1311/BNT324 treatment continued until disease progression/ unacceptable toxicity (treatment beyond progression was allowed). ADC, antibody–drug conjugate; B7H3, B7 homolog 3 protein; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; Lu-177, Lutetium-177; mCRPC, metastatic castration-resistant prostate cancer; NHT, novel hormone therapy; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival.

Baseline and Disease Characteristics

73 patients (USA: 43.8%; Australia: 28.8%; East Asia: 27.4%)
Median treatment duration: 4.8 months (range 0.7–12.9); 36 patients remain on treatment

n (%)		Overall* (N=73)	6 mg/kg (n=38)	9 mg/kg (n=33)
Age (years), median (range)		70 (45–84)	72 (45–84)	69 (56–82)
Race[†]	White	39 (53.4)	20 (52.6)	18 (54.5)
	Asian	22 (30.1)	11 (28.9)	11 (33.3)
	Black	9 (12.3)	6 (15.8)	3 (9.1)
Ethnicity	Hispanic	3 (4.1)	2 (5.3)	1 (3.0)
ECOG PS	0	21 (28.8)	10 (26.3)	9 (27.3)
	1	52 (71.2)	28 (73.7)	24 (72.7)
Site of metastasis	Bone	64 (87.7)	34 (89.5)	28 (84.8)
	Bone only	23 (31.5)	13 (34.2)	8 (24.2)
	Lymph node	35 (47.9)	18 (47.4)	17 (51.5)
	Liver	17 (23.3)	6 (15.8)	11 (33.3)
	Lung	16 (21.9)	10 (26.3)	6 (18.2)

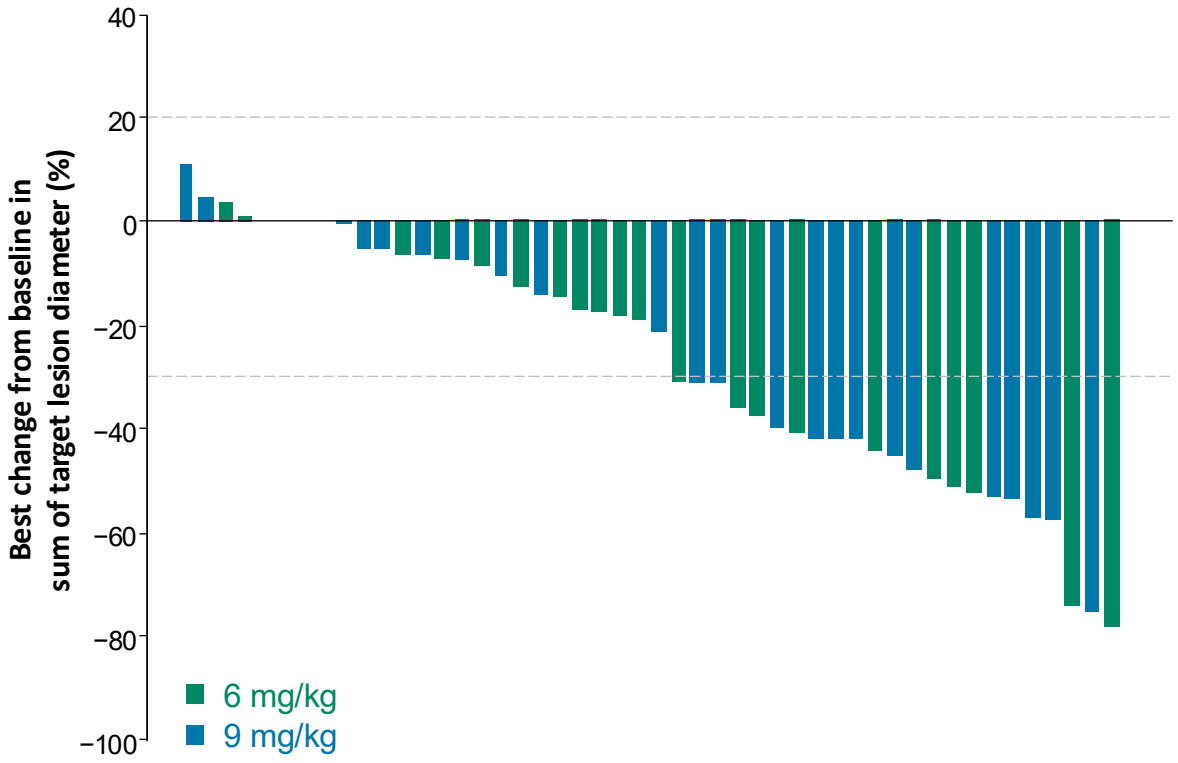
n (%)		Overall* (N=73)	6 mg/kg (n=38)	9 mg/kg (n=33)
Prior lines[‡]	Median (range)	4 (1–14)	4 (2–14)	3 (1–9)
	1	2 (2.7)	0	2 (6.1)
	2	11 (15.1)	4 (10.5)	7 (21.2)
	3	18 (24.7)	6 (15.8)	11 (33.3)
	4	15 (20.5)	10 (26.3)	5 (15.2)
	≥5	24 (32.9)	16 (42.1)	7 (21.2)
Prior treatment	NHT	70 (95.9)	36 (94.7)	32 (97.0)
	1	38 (52.1)	17 (44.7)	19 (57.6)
	2	24 (32.9)	15 (39.5)	9 (27.3)
	≥3	8 (11.0)	4 (10.5)	4 (12.1)
	Docetaxel	68 (93.2)	34 (89.5)	32 (97.0)
	Cabazitaxel	29 (39.7)	17 (44.7)	12 (36.4)
	Lu-177	16 (21.9)	12 (31.6)	3 (9.1)
	Platinum	15 (20.5)	11 (28.9)	4 (12.1)
	IO	12 (16.4)	7 (18.4)	4 (12.1)
	PARPi	10 (13.7)	5 (13.2)	5 (15.2)

Data cut-off: March 4, 2025. Median follow-up: 5.9 months (range 0.1–15). *Includes 3 mg/kg (n=1) and 12 mg/kg (n=1). [†]Not shown Native Hawaiian (n=1) or Other (n=2). [‡]Information on the number of prior lines was missing for 3 patients. IO, immunotherapy; PARPi, poly-ADP ribose polymerase inhibitor.

Tumor Response

Encouraging antitumor activity in heavily pretreated mCRPC

	Overall (N=52)	6 mg/kg (n=24)	9 mg/kg (n=28)
ORR, % [95% CI]	**42.3** [28.7, 56.8]	**41.7** [22.1, 63.4]	**42.9** [24.5, 62.8]
BOR,* n (%)			
CR	0	0	0
PR	22 (42.3)	10 (41.7)	12 (42.9)
SD	25 (48.1)	12 (50.0)	13 (46.4)
PD	1 (1.9)	0	1 (3.6)
cORR, % [95% CI]	**30.8** [18.7, 45.1]	**29.2** [12.6, 51.1]	**32.1** [15.9, 52.4]
Pending confirmation, n	5	3	2
DCR, % [95% CI]	**90.4** [79.0, 96.8]	**91.7** [73.0, 99.0]	**89.3** [71.8, 97.7]
mDOR,† months [95% CI]	**ne** [4.0, ne]	**ne** [4.2, ne]	**ne** [4.0, ne]



Data cut-off: March 4, 2025. *BOR was missing for 4 patients. Evaluable for tumor response defined as having measurable disease at baseline per RECIST v1.1 and ≥1 post-baseline assessment or treatment discontinuation. Tumor responses were assessed using both RECIST v1.1 and PCWG3 criteria. †DOR was calculated in patients with a confirmed response (n=14).

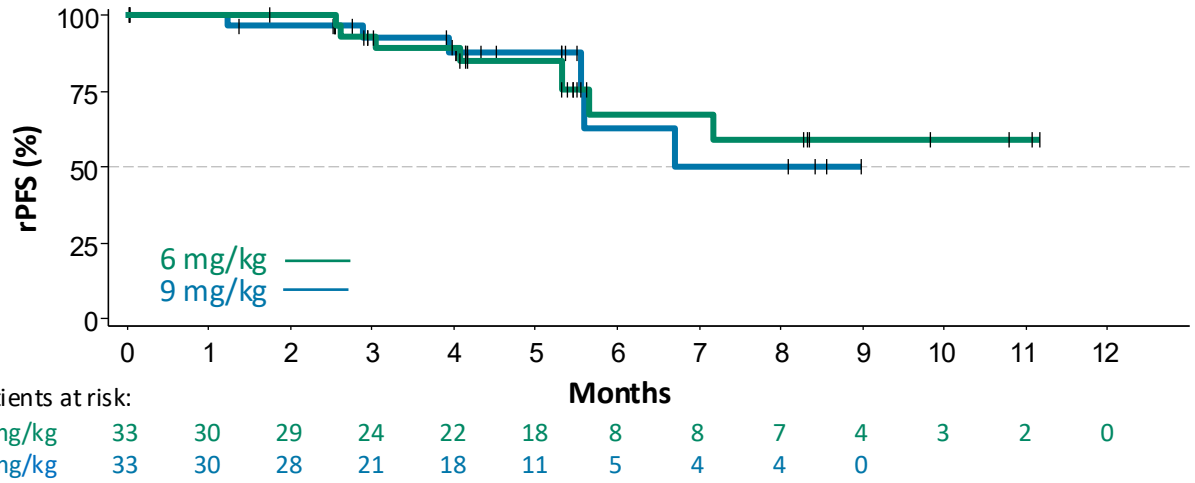
BOR, best overall response; CI, confidence interval; (c)ORR, (confirmed) objective response rate; CR, complete response; DCR, disease control rate; (m)DOR, (median) duration of response; ne, not estimable; PR, partial response; SD stable disease.

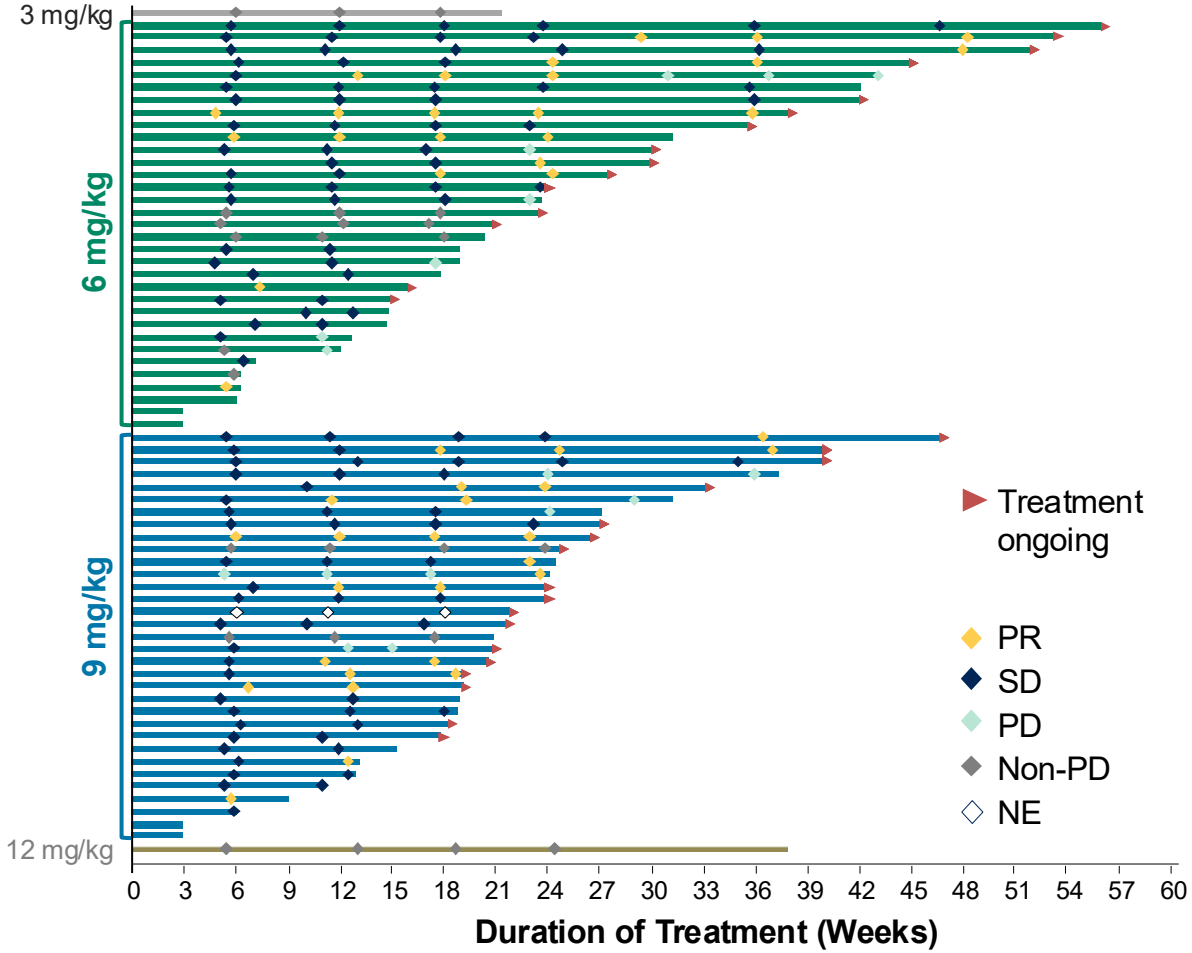
Dr Andrew Parsonson; #5015

Radiographic PFS

Early signs of durable antitumor activity in heavily pretreated mCRPC

	Overall* (N=68)	6 mg/kg (n=33)	9 mg/kg (n=33)
Median rPFS			
Months [95% CI]	**ne** [5.7, ne]	**ne** [5.7, ne]	**ne** [5.6, ne]
rPFS events, n (%)	14 (20.6)	8 (24.2)	6 (18.2)
rPFS rate, %			
6-month	**67.7**	**67.1**	**62.7**
9-month	58.0	58.7	ne





Data cut-off: March 4, 2025. rPFS not yet mature. *Includes 3 mg/kg (n=1) and 12 mg/kg (n=1). Treatment beyond progression was allowed if the investigator considered the patient may continue to benefit from further treatment. Evaluable for rPFS defined as having baseline efficacy assessment and ≥1 post-baseline assessment or treatment discontinuation. NE, not evaluable.

Dr Andrew Parsonson; #5015

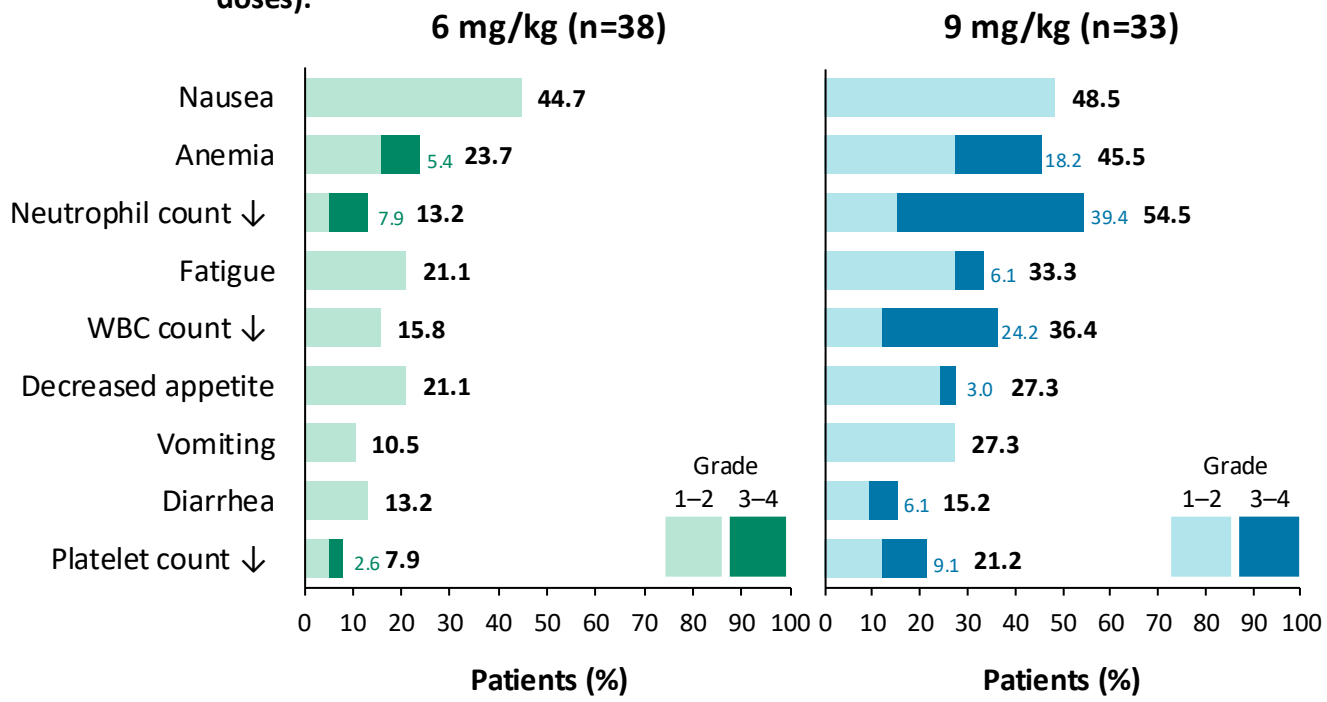
TRAEs in CRPC and Overall Population

Gastrointestinal and hematologic events, primarily Grade 1–2, were the most common TRAEs

Hematologic TRAEs occurred more frequently with 9 mg/kg but did not lead to treatment discontinuation

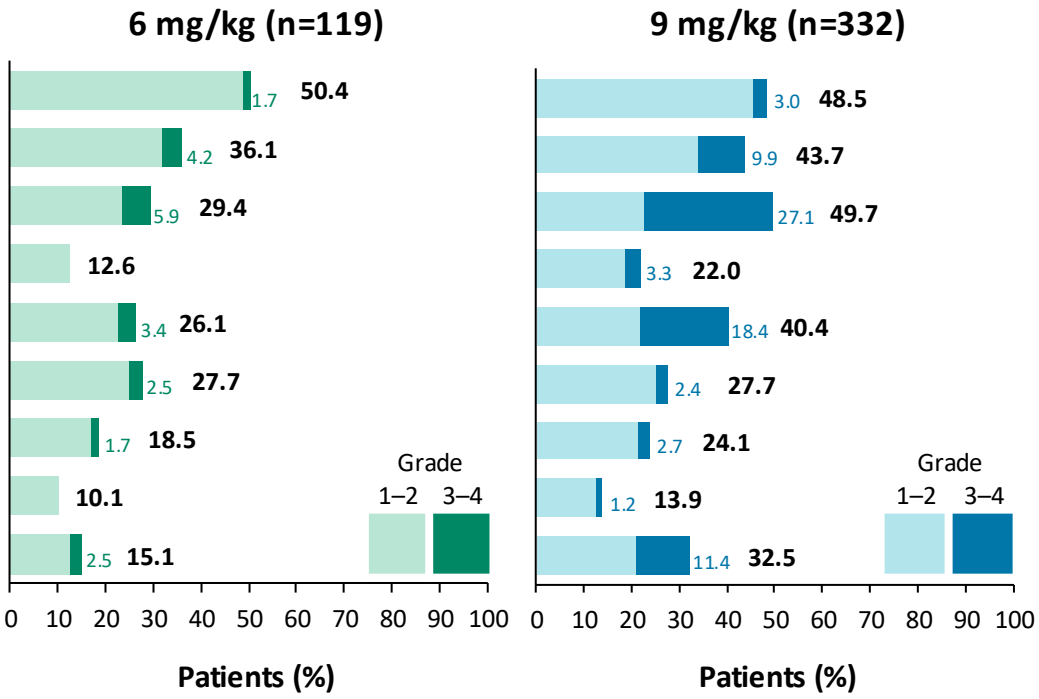
TRAEs in ≥10% of patients with CRPC (across all doses):

CRPC Population



ILDs/pneumonitis reported in 4 patients, all Grade 1.

Overall Population



ILDs/pneumonitis reported in 5 patients receiving 6 mg/kg and 15 receiving 9 mg/kg, all Grade 1–2 except 2 Grade 3 events in two patients receiving 9 mg/kg.

Data cut-off: March 4, 2025. ILD, interstitial lung disease; WBC, white blood cell.

Dr Andrew Parsonson; #5015

Conclusions

DB-1311/BNT324 showed encouraging efficacy and a manageable safety profile in patients with heavily pretreated CRPC

- In patients with heavily pretreated CRPC, ORR was 42.3%, DCR was 90.4%, 6-month rPFS rate was 67.7%. Outcomes were similar by dose (6 mg/kg or 9 mg/kg)
- Outcomes appeared better in earlier treatment lines
  - Encouraging antitumor activity was also observed in later lines and regardless of number of prior NHTs, type of prior treatment, or metastatic site (caveat small sample size)
- Low discontinuation rates for both 6 mg/kg and 9 mg/kg despite higher Grade ≥3 TRAEs with 9 mg/kg
- Gastrointestinal and hematologic toxicities were the most common TRAEs
  - Hematologic TRAEs occurred more frequently with 9 mg/kg, but did not lead to treatment discontinuation
- Cohort 11 (CRPC after Lu-177) and Cohort 12 (taxane-naïve CRPC) are currently enrolling patients
- Further development of DB-1311/BNT324 in prostate cancer is warranted and is being planned

DB-1311/BNT324 is also being evaluated in combination with BNT327, an anti-PD-L1 x VEGF-A bispecific antibody, in SCLC and NSCLC (NCT06892548) and in HCC, cervical cancer, melanoma, and HNSCC (NCT06953089)

Acknowledgments

- The authors would like to thank the patients and their families, along with the staff, research coordinators, and investigators at each participating institution
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- Medical writing assistance was provided by Aurora O'Brate of BioNTech Pharmaceuticals Spain SLU, Barcelona, Spain, and Lily Zhang of Duality Biologics, Shanghai, China. Editorial support was provided in accordance with Good Publication Practice guidelines

Key Takeaway Points

1

DB-1311/BNT324 (B7H3 ADC) showed encouraging efficacy and a manageable safety profile in patients with heavily pretreated CRPC

2

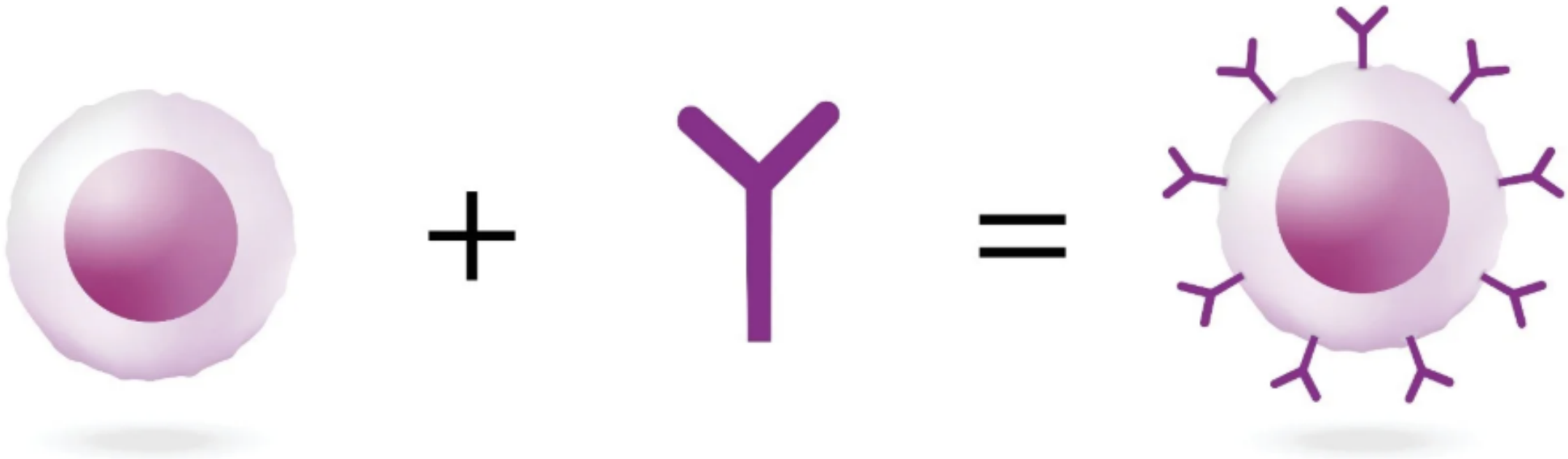
While outcomes appeared better in earlier treatment lines, encouraging activity was also observed in later lines and regardless of type of prior treatment, or metastatic site

3

Study is currently enrolling post Lu-177 CRPC (Cohort 11) and taxane-naïve CRPC (Cohort 12)

Further development of DB-1311/BNT324 in prostate cancer is warranted

CAR T-cell therapy



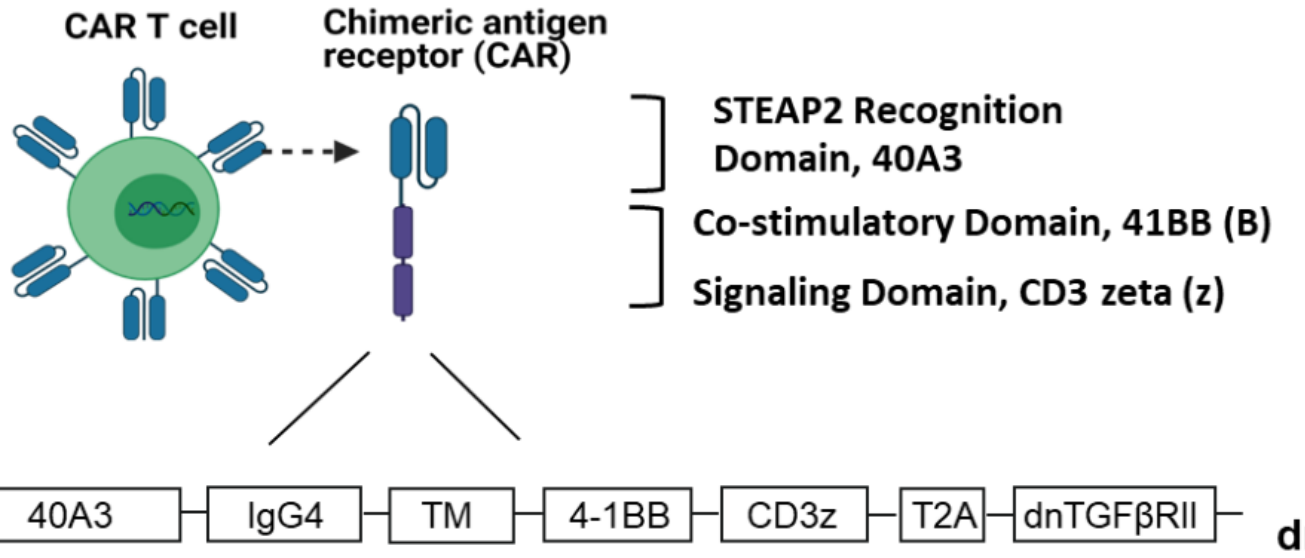
T-cell

CAR
(chimeric antigen receptor)

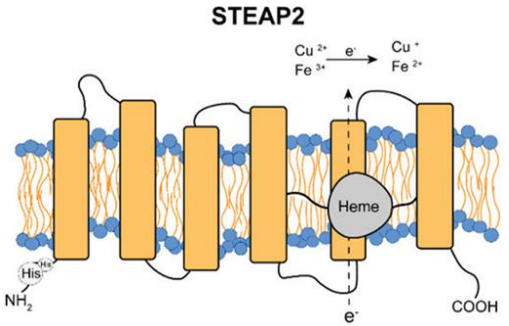
CAR T-cell

A Phase I/II Open Label Study to Evaluate the Safety, Cellular Kinetics, and Efficacy of AZD0754, a Chimeric Antigen Receptor (CAR) T-cell Therapy Directed Against STEAP2, in Adult Participants with Metastatic Prostate Cancer: APOLLO

The AZD0754 (40A3) STEAP2 CAR Construct



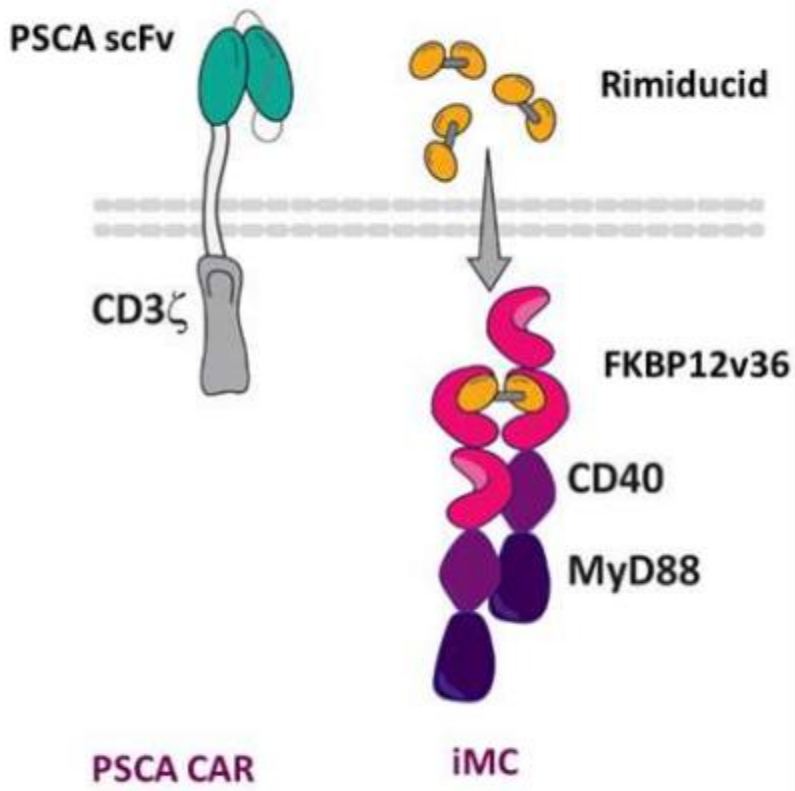
40A3Bz dnTGFβRII



six-transmembrane epithelial antigen of the prostate 2

STEAP2 is a metalloreductase highly expressed on the cell surface of prostate tumours

BPX-601: a two-component inducible GoCAR-T cell



1st generation CAR: Directs specificity and cytotoxicity against PSCA-expressing tumors

iMC: Molecular switch that replaces natural T cell costimulation with inducible signaling from MyD88 and CD40

- Increases proliferation, persistence, survival, and cytotoxicity of adoptively transferred CAR-T cells
- Stimulates endogenous immunity (adjuvant effects):
  - Secretion of pro-inflammatory cytokines
  - Upregulation of costimulatory molecules

Rimiducid: A synthetic small-molecule dimerizer that mediates the oligomerization of iMC and activation of signaling

iMC co-activation controls GoCAR-T cell proliferation, functional persistence, and production of immunomodulatory cytokines with administration of rimiducid

nature communications
Article
https://doi.org/10.1038/s41467-024-53220-6

PSCA-targeted BPX-601 CAR T cells with pharmacological activation by rimiducid in metastatic pancreatic and prostate cancer: a phase 1 dose escalation trial

Mark N. Stein[1,12], Ecaterina E. Dumbrava[2,12] ✉, Benjamin A. Teply[3], Usama S. Gergis[4], Martin E. Guiterrez[5], Ran Reshef[1], Sumit K. Subudhi[2], Céline F. Jacquemont[6], Joseph H. Senesac[6], J. Henri Bayle[6], Charity D. Scripture[6], Monica S. Chatwal[7], Mehmet A. Bilen[8], Walter M. Stadler[9] & Carlos R. Becerra[10,11]

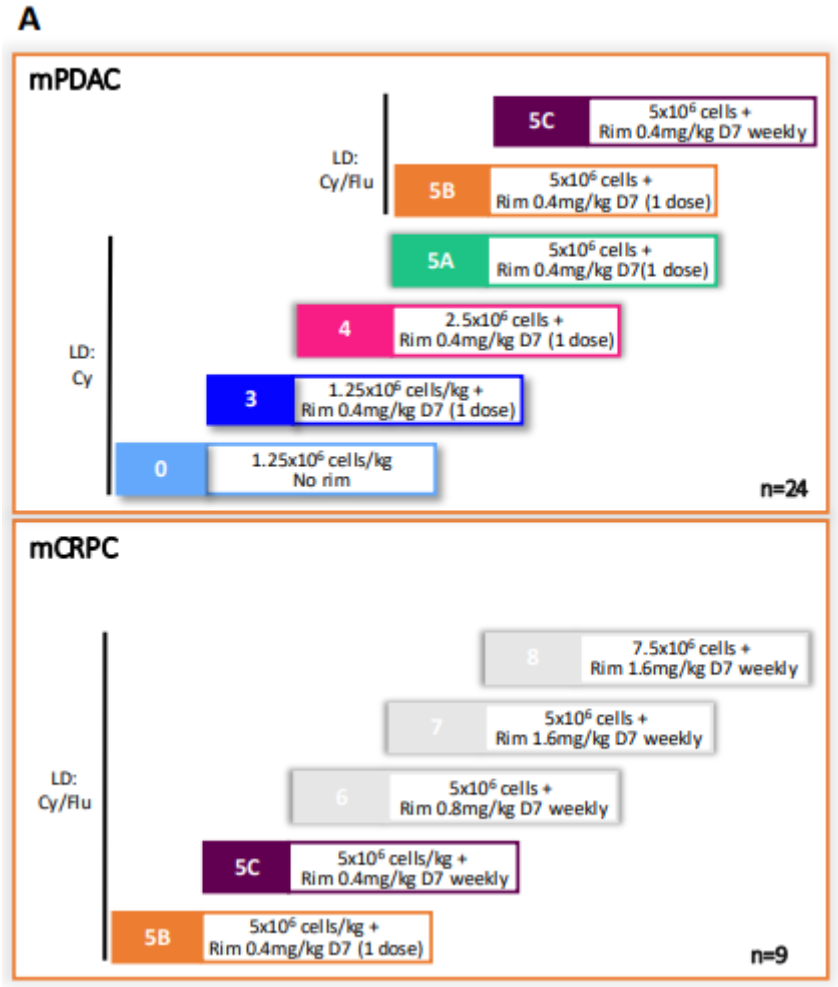
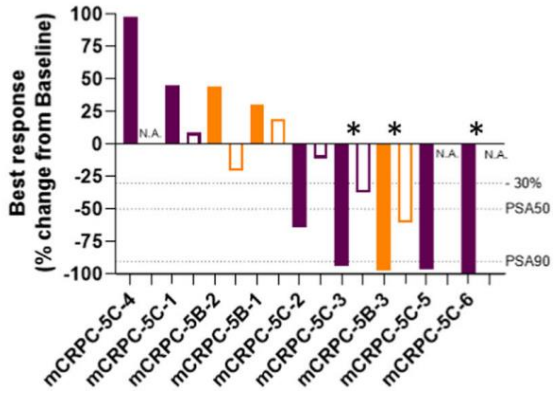
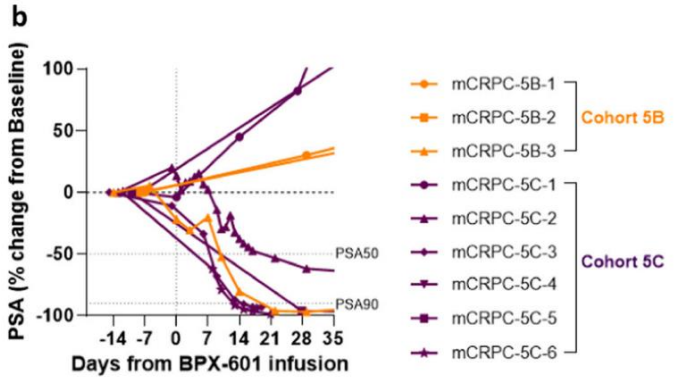


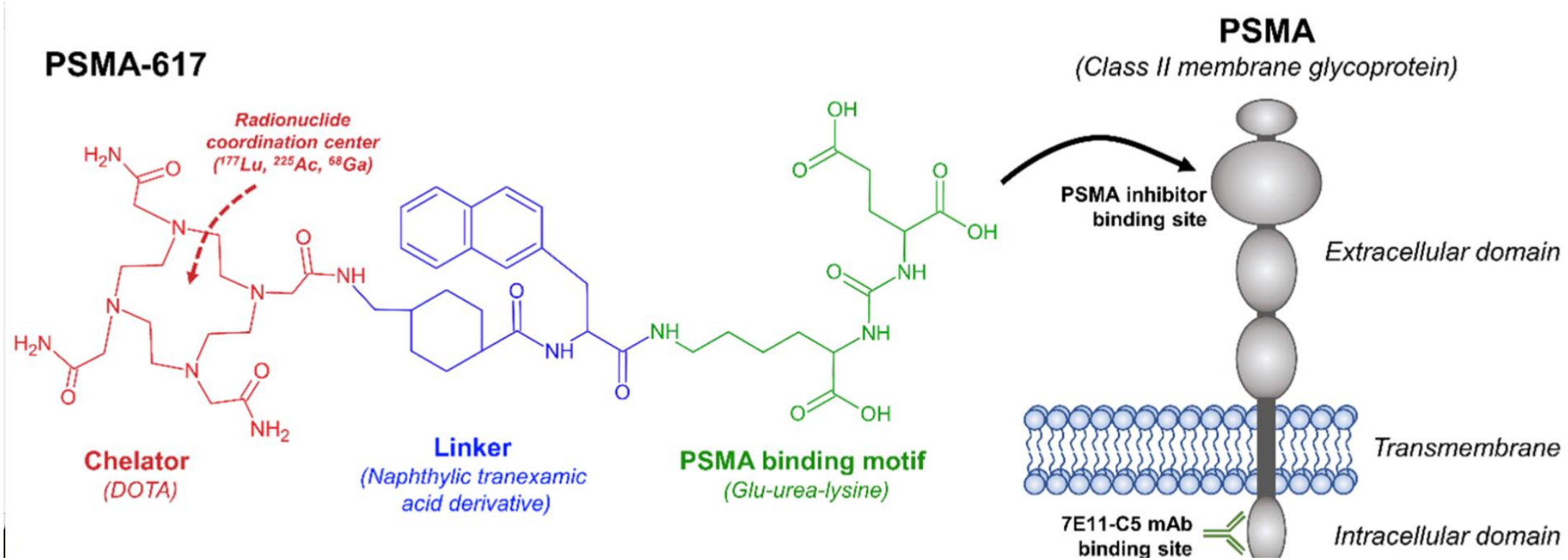
Table 1 | Efficacy evaluation by tumor type[a]

Variable	mPDAC patients (*n* = 20)	mCRPC patients (*n* = 6)
Best overall response		
CR, *n* (%)	0	0
PR, *n* (%)	0	1 (16.7%)[a]
uPR, *n* (%)	0	1 (16.7%)
SD, *n* (%)	12 (60%)	4 (66.7%)
PD, *n* (%)	8 (40%)	0
ORR, *n* (%)	0	1 (16.7%)
DCR, *n* (%)	12 (60%)	6 (100%)





Targeting PSMA – folate hydrolase present in 90% + of CPSC FDA approved in CRPC (Lu-177)



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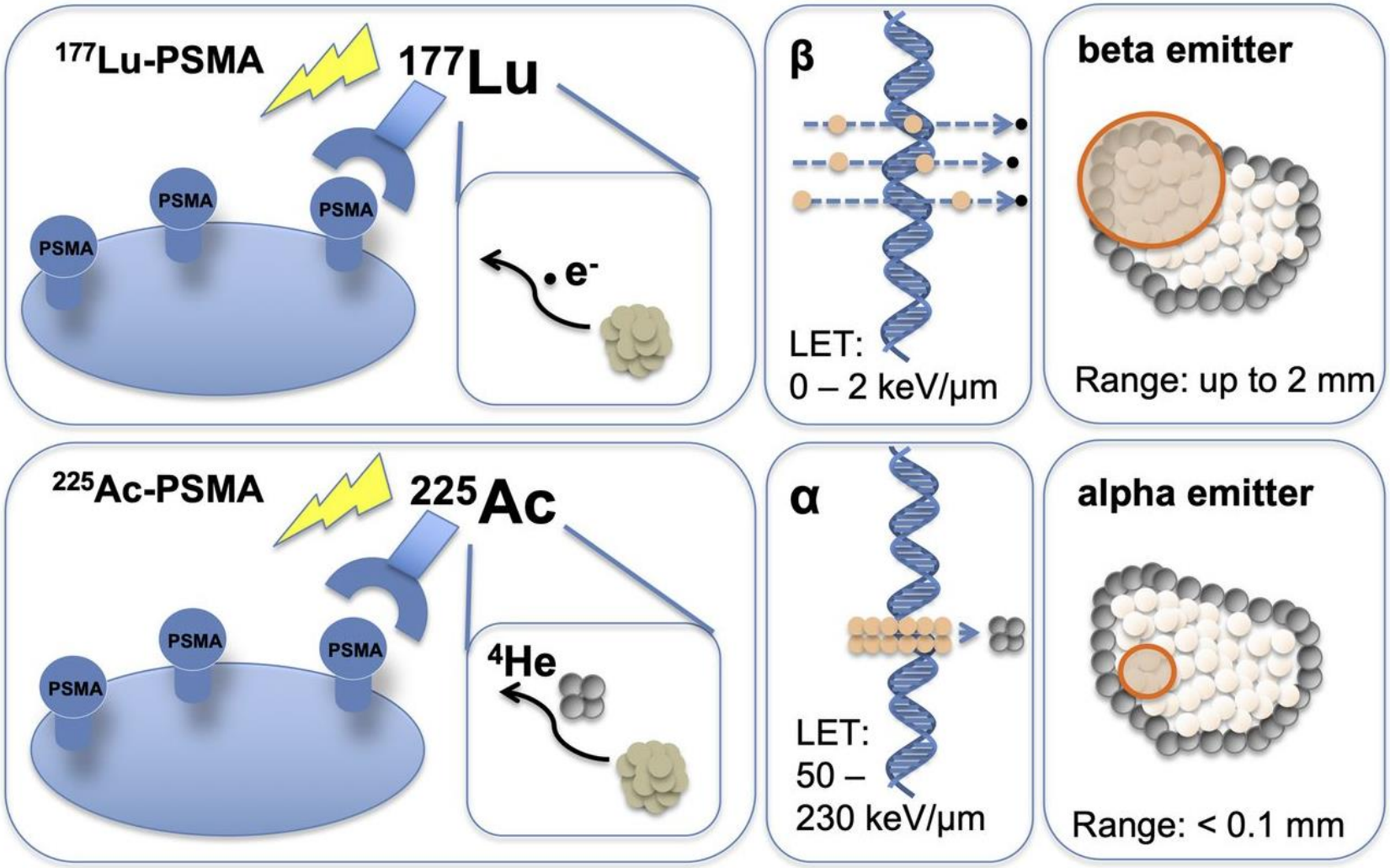
Plichta KA et al Int. J. Mol. Sci. 2021, 22(22), 12095

Alpha particles vs Beta particles



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Feuerecker et al of Nuclear Medicine May 2023, 64 (5) 685-692;

^{212}Pb – The Ideal Isotope for Alpha Therapy?

	Alpha-emitting			Auger	Beta-emitter
	^{212}Pb Lead	^{225}Ac Actinium	^{211}At Astatine	^{161}Tb Terbium	^{177}Lu Lutetium
LET	**High LET**	High LET	High LET	Medium LET	Low LET
T1/2 and emission	T1/2 = **10.6 hrs** **1α & 2β-**	T1/2 = 10 days 4α & 2β-	T1/2 7.2 hrs 1α	T1/2 = 6.9 days 1β- & 2x Auger	T1/2 = 6.7 days 1β-
Recoil	**Limited** ~70% of ^{212}Bi retained within ^{212}Pb chelators	Significant release of progeny from DOTA cage	Limited	Low	Low
Manufacturing and Source Material	**Generator production** ^{228}Th or ^{224}Ra sources	Complex - ^{229}Th decay, ^{232}Th spallation, cyclotron production - ^{226}Ra targets	Medium energy cyclotrons using a ^{209}Bi target	High-flux nuclear reactor using a ^{160}Gd target	Nuclear reactor through neutron activation of ^{176}Lu or ^{176}Yb
Imaging and dosimetry	**Feasible SPECT imaging for dosimetry**	? SPECT imaging	Feasible SPECT imaging for dosimetry	Feasible SPECT imaging for dosimetry	Feasible SPECT imaging for dosimetry

Lead
-easy to make from local generator

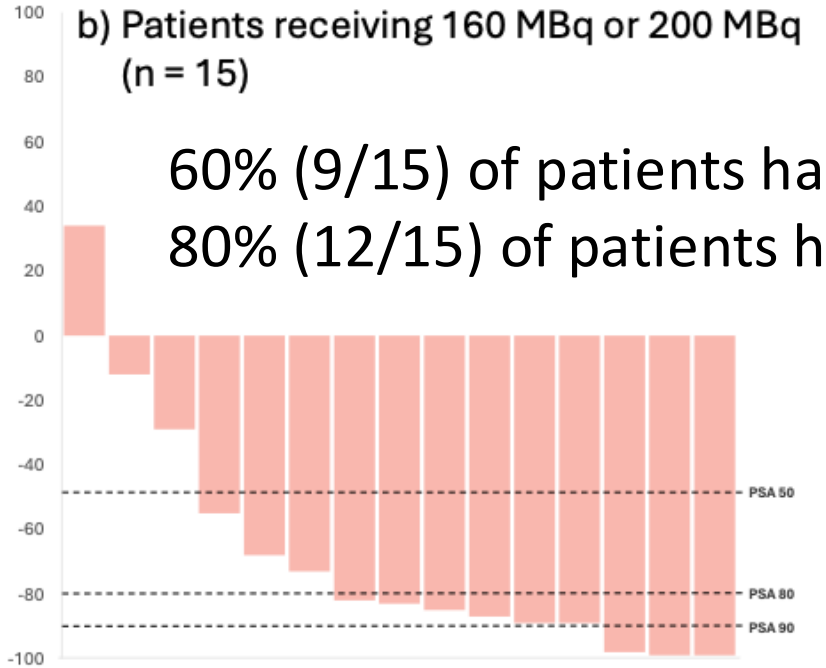
-less toxicity due to short half life

-easier to combine with other agents (lymphocyte sparing)

-can accurately measure dose using PB203

ESMO 2025 -- Results from the phase Ib dose escalation of 212Pb-ADVC001 in PSMA-positive metastatic castration-resistant prostate cancer (mCRPC): The theraPb trial

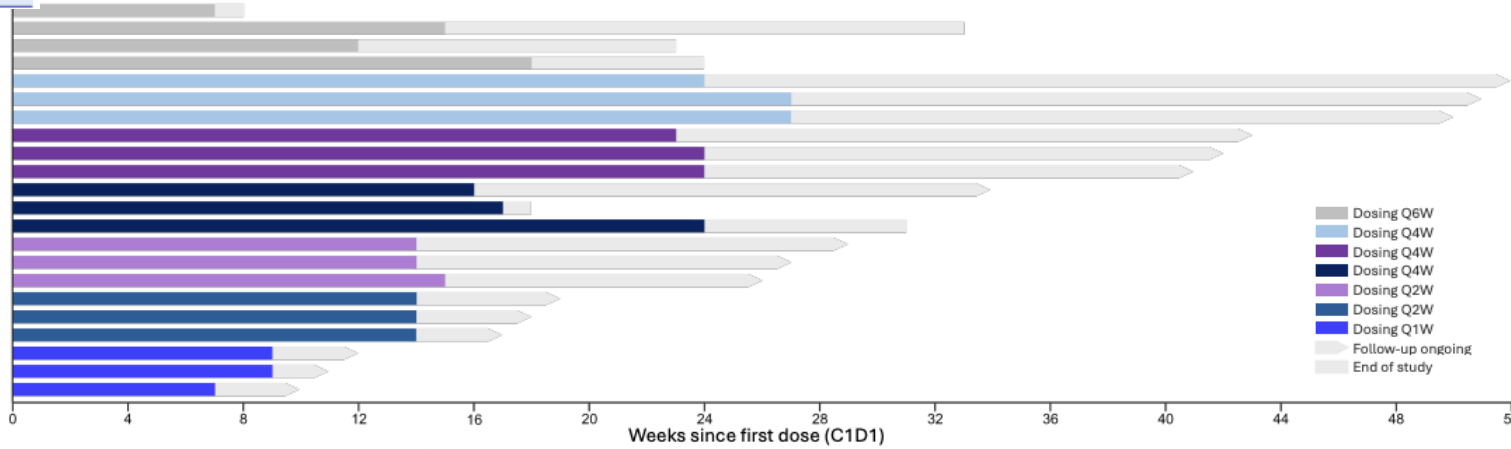
		All (n = 22)
Age, median (range), years		73 (59–88)
ECOG, n (%)	0	5 (23%)
	1	17 (77%)
Gleason Score at diagnosis, n (%)	≥ 8	12 (55%)
	Unknown	1 (5%)
Lines of ARPi, n (%)	1	20 (91%)
	≥ 2	2 (9%)
Lines of chemotherapy, n (%)	0	6 (27%)
	1	8 (36%)
	2 or 3	8 (36%)
Other systemic antineoplastic tx*, n (%)	PARPi	3 (14%)
	Other	1 (5%)
Total number of prior systemic therapies for prostate cancer*	1 or 2	11 (50%)
	≥ 3	11 (50%)
PSA (ng/mL), median (range)		45 (1–438)
Location of metastases, n (%) on PSMA PET/CT (BICR)	Bone	19 (86%)
	Node	12 (55%)
	Visceral	8 (36%)
PSMA PET parameters, median (range)	SUV_{mean}	8.9 (5.5–27.1)
	PSMA-avid TTV (mL)	229 (4–1751)



60% (9/15) of patients had a PSA80 response

80% (12/15) of patients had a PSA50 respons

gure 5: Duration of treatment and follow-up, by cohort



Duration of treatment defined as from C1D1 until 28 days post last dose

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SUMMARY

- NOVEL T CELL ENGAGERS HAVE PROMISING ACTIVITY ALONE AND IN COMBINATIONS
- ANTIBODY DRUG CONJUGATES ARE IN DEVELPOMENT
- CAR-Ts ARE STILL UNDER INVESTIGATION IN PROSTATE CANCER
- RADIOLIGAND THERAPY MAY BE USEFUL ALONE OR IN COMBINATION WITH IMMUNE THERAPY