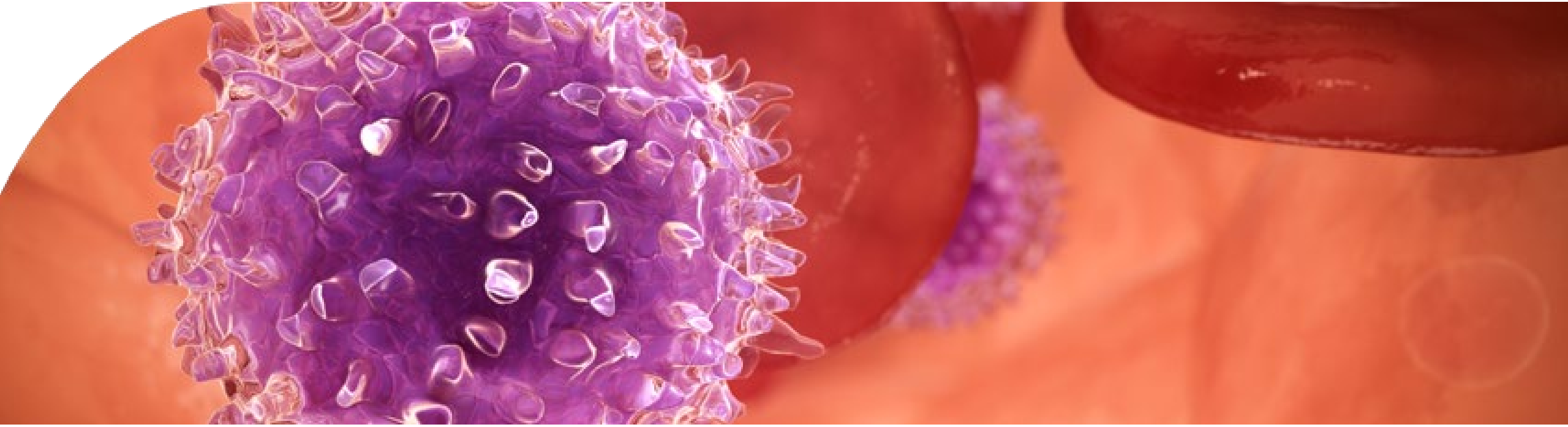


Bispecific Breakthroughs: T-Cell Engagers and Xaluritamig in Prostate Cancer Therapy

Judd Englert, MD, PhD
Vice President, Global Development Oncology

July 25, 2025

AMGEN

Disclosure information

I have the following relevant financial relationships to disclose:

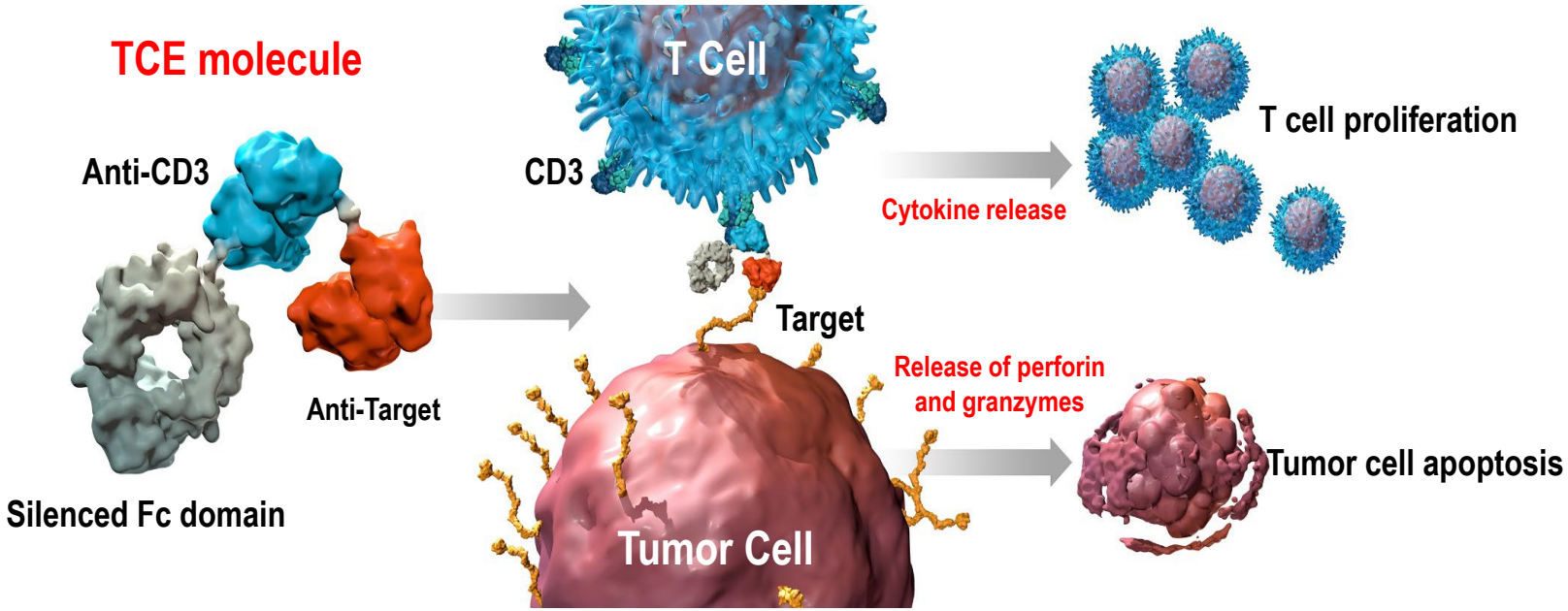
- Employee and shareholder of Amgen, Inc.

What are T-cell Engagers?

Bispecific biologic molecules engineered with one binding domain directed against a tumor-associated antigen on the cancer cell surface and the other against an antigen on T-cells, most often CD3.

Clinical Advantages

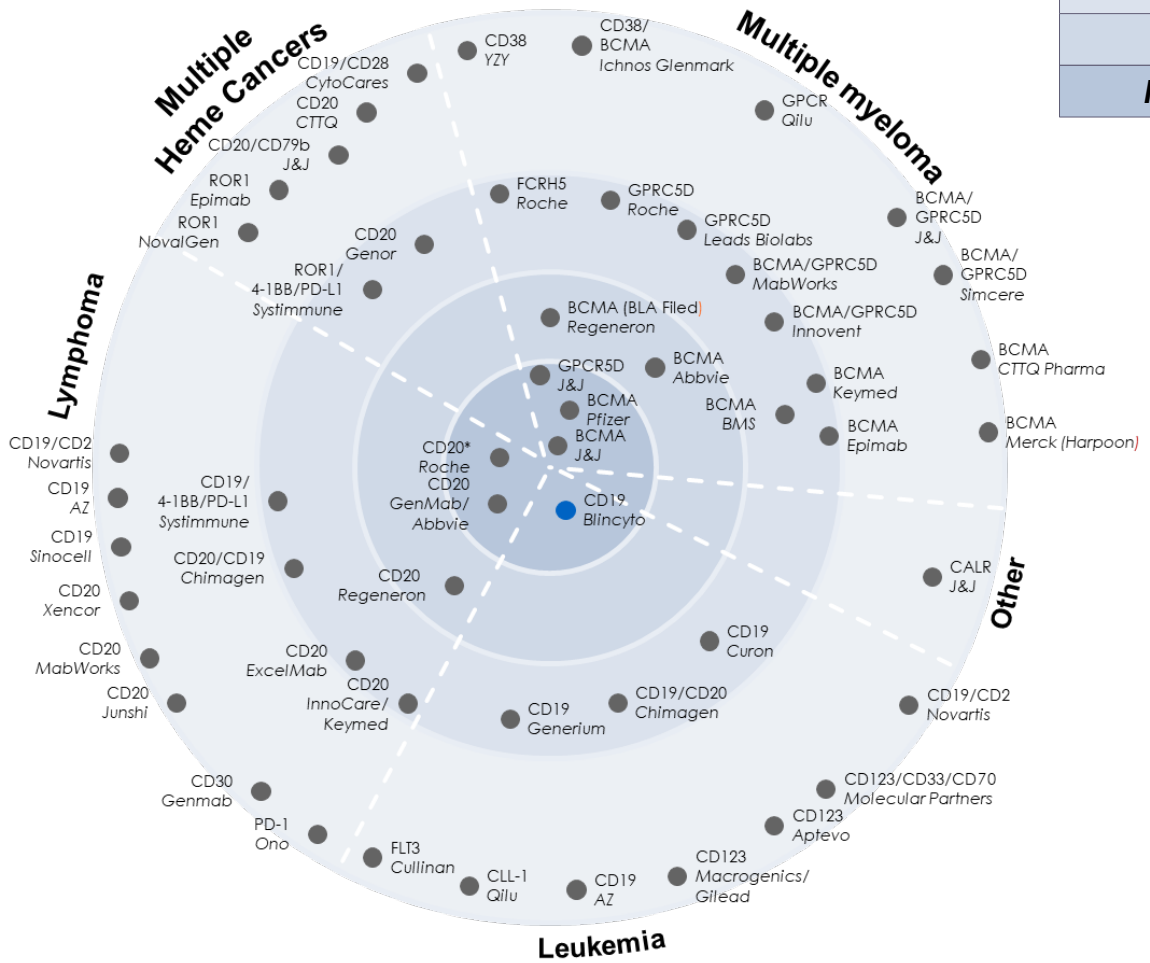
- Off-the-shelf availability
- Rapid onset of action
- Doses can be both modified and repeated



A targeted approach to harness the body's own T-cells to recognize and destroy cancer cells by redirecting naive T cells to target and eliminate tumor cells with high specificity and potency.

T Cell Engager Clinical Trial Landscape is Expanding in Both Hematologic Malignancies and Solid Tumors, including Prostate

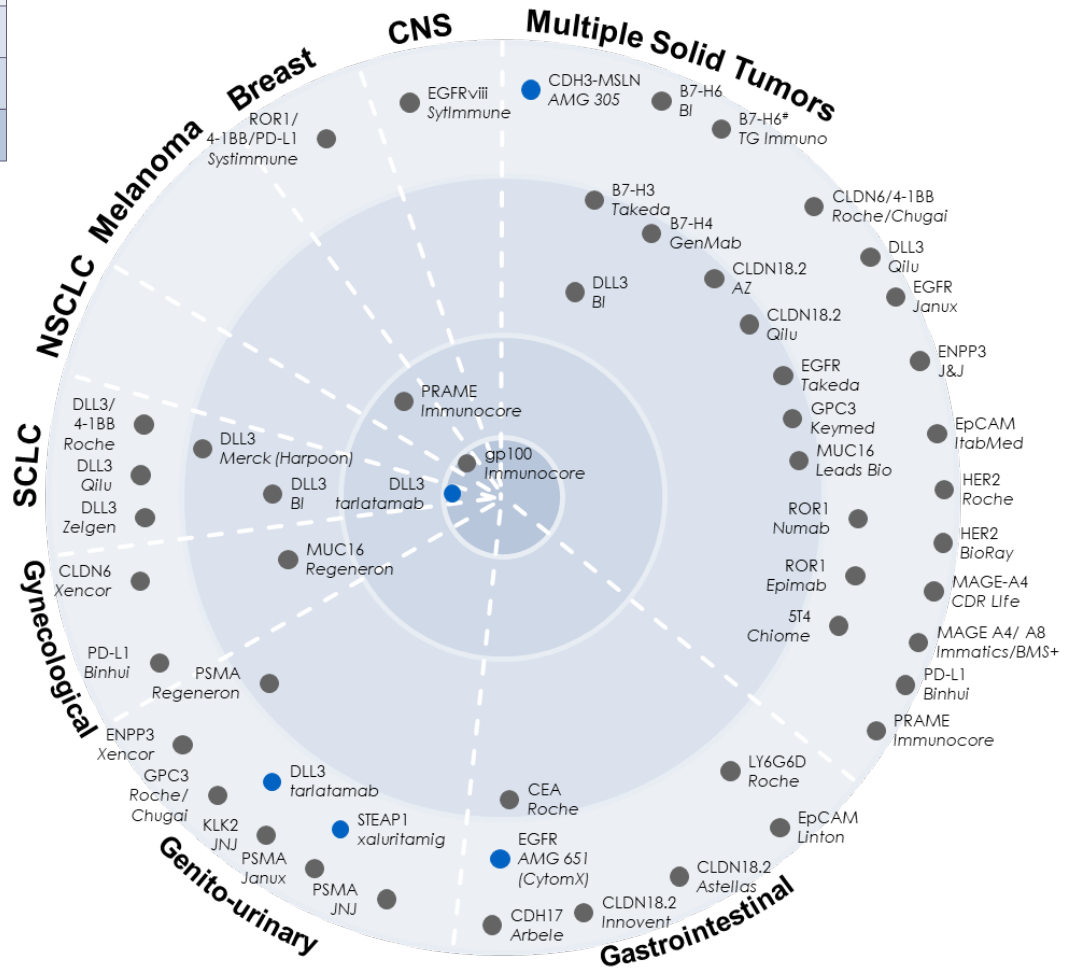
HEMATOLOGIC MALIGNANCIES



Phase I
Phase II
Phase III
Marketed

- Amgen
- Other

SOLID TUMORS



Source: BEACON Dataset (July 2024). Note: all pre-clinical assets were excluded from analysis. Analysis focuses exclusively on CD3xCDXX assets; non-CD3 assets were excluded

US TCE Approvals: 2 out of 9 are for Solid Tumors

Approval Year	Brand Name (Generic Name)	Target	Indication(s)
2014	Blincyto (blinatumomab)	CD19	1. Relapsed or refractory ALL; 2. 1st or 2nd complete remission with MRD ≥ 0.1% 3. CD19-positive Ph-negative B-cell ALL in the consolidation phase of multiphase chemotherapy
2022	**Kimmtrak (tebentafusp-tebn)**	**gp100/HLA-A*02:01**	**HLA-A*02:01-positive unresectable or metastatic uveal melanoma**
2022	Tecvayli (teclistamab)	BCMA	Relapsed or refractory multiple myeloma
2022	Lunsumio (mosunetuzumab)	CD20	Relapsed or refractory follicular lymphoma
2023	Elrexfio (elranatamab)	BCMA	Relapsed or refractory multiple myeloma
2023	Talvey (talquetamab)	GPRC5D	Relapsed or refractory multiple myeloma
2023	Epkinly (epcoritamab)	CD20	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
2023	Columvi (glofitamab)	CD20	Relapsed or refractory DLBCL
2024	**Imdelltra (tarlatamab-dlle)**	**DLL3**	**Extensive-stage small cell lung cancer (ES-SCLC) with disease progression after platinum-based chemotherapy**

Adapted from: www.fda.gov/drugs/news-events-human-drugs/bispecific-antibodies-area-research-and-clinical-applications

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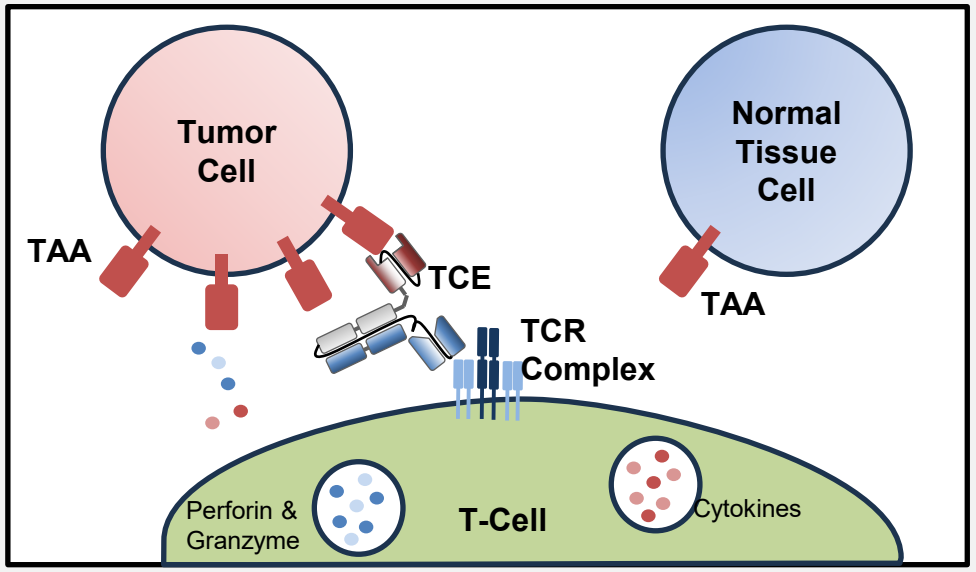
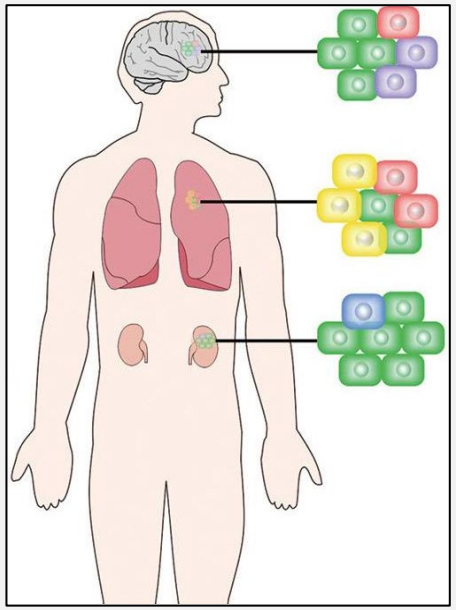
Challenges for T Cell Engagers in Solid Tumors

On Target / Off Tumor Toxicity

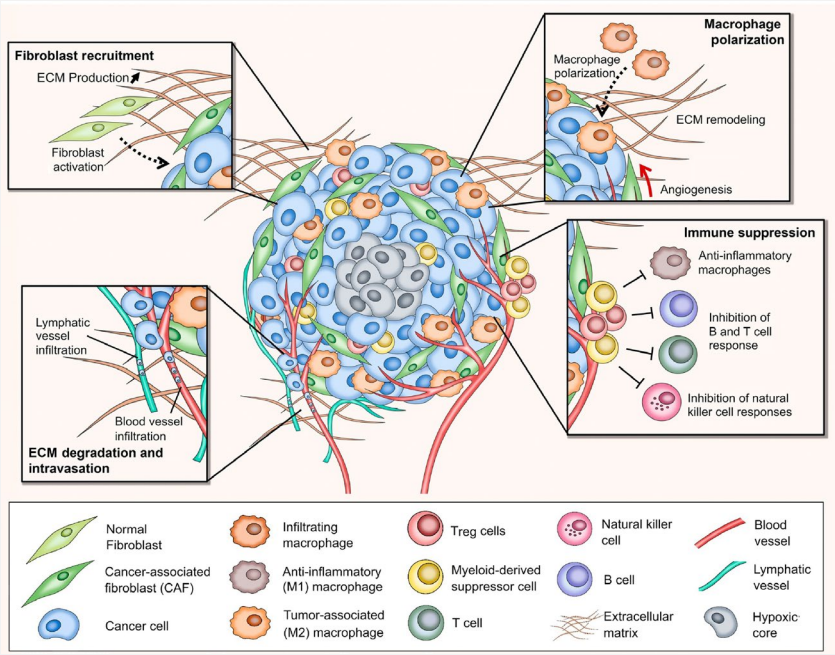


Target and Tumor Heterogeneity



Zhu L, Ann Transl Med 2021

Immunosuppressive TME and T-Cell Availability

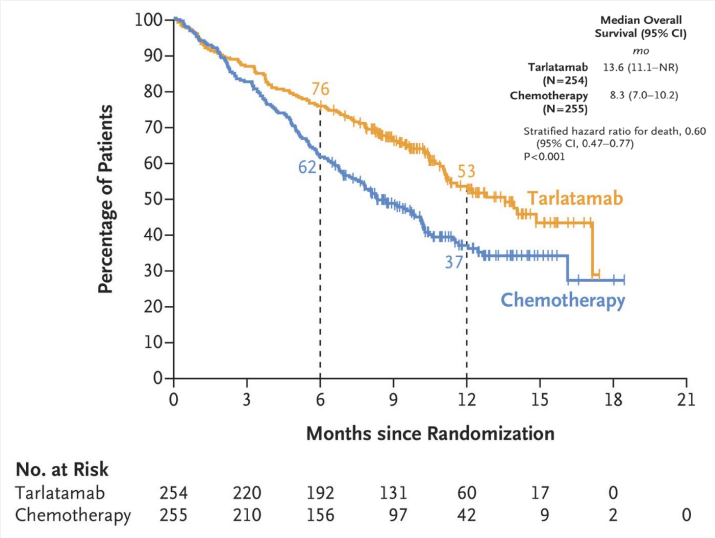


Rodrigues J, Trends in Can 2021

Arvedson T, Annu Rev Cancer Biol 2022
Baeuerle P, Curr Opin Oncol 2022
Shanshal M, Cancers (Basel) 2023

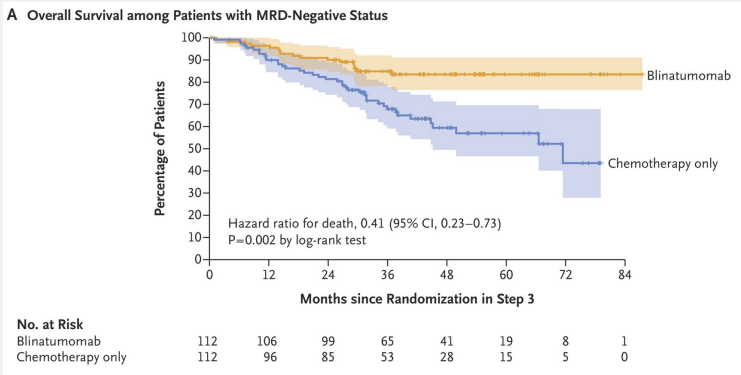
What is the clinical potential for TCEs?

Tarlatamab OS
Target: DLL3
Disease: SCLC



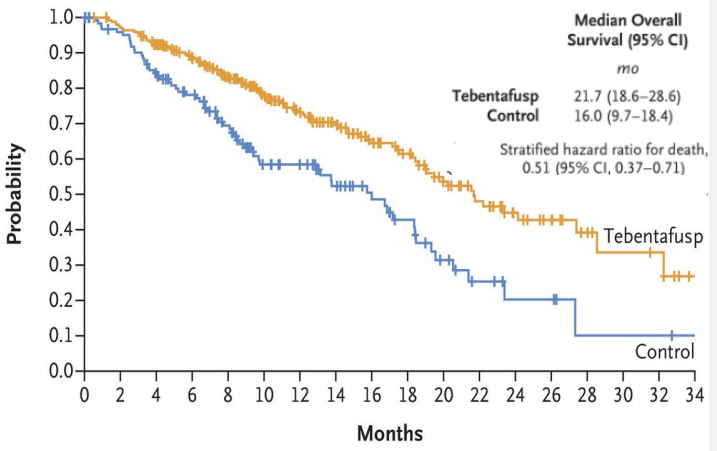
Mountzios G, N Engl J Med 2025

Blinatumomab OS
Target: CD19
Disease: B-Cell ALL



Litzow MR, N Engl J Med 2024

Tebentafusp OS
Target: gp100/HLA-A02:01
Disease: Uveal Melanoma



Nathan P, N Engl J Med 2021

T-cell engagers hold the transformative potential of immunotherapy by offering an elegant strategy to convert "cold" tumors into immunologically active ones and expand the durability and reach of immunotherapy to new tumors

TCEs in Clinical Development for Prostate Adenocarcinoma

Molecule	Target	Sponsor	Phase	Development Status
Xaluritamig (AMG 509)	**STEAP1 × CD3**	**Amgen**	**3**	**Active**
REGN4336	**PSMA x CD3**	**Regeneron**	**1 / 2**	**Active**
REGN5678	**PSMA × CD28**	**Regeneron**	**1 / 2**	**Active**
Pasritamig (JNJ-78278343)	**KLK2 × CD3**	**Janssen**	**1b**	**Active**
JANX007	**PSMA × CD3**	**Janux Therapeutics**	**1b**	**Active**
JNJ-9401 (JNJ-87189401)	**PSMA × CD28**	**Janssen / Xencor**	**1**	**Active**
HPN424	PSMA × CD3	Harpoon Therapeutics	1/2a	Inactive
LAVA-1207	PSMA × Vγ9Vδ2 T cells	LAVA Therapeutics	1/2a	Inactive
AMG 340	PSMA × CD3	Amgen	1	Inactive
Acapatamab AMG 160	PSMA × CD3	Amgen	1	Inactive
Pasotuxizumab (AMG 212 or BAY 2010112)	PSMA × CD3	Bayer / Amgen	1	Inactive
Voxalatamab (JNJ-081)	PSMA × CD3	Janssen	1	Inactive

Adapted from T-cell Engagers in Prostate Cancer. Hage Chehade, Chadi et al. European Urology, Volume 87, Issue 5, 553 - 558

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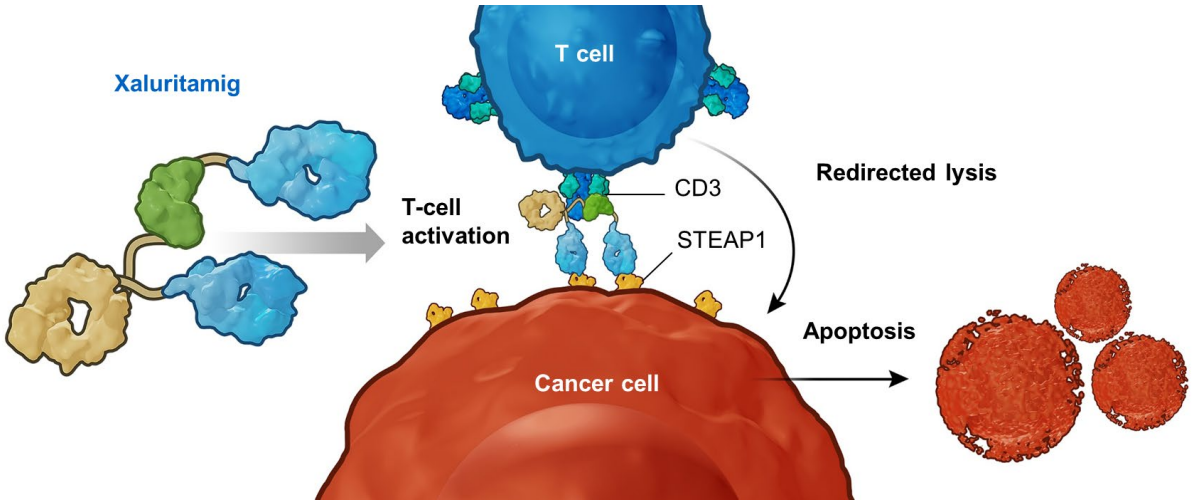
Xaluritamig is a STEAP1-targeted T-cell engager being evaluated for the treatment of prostate cancer

- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival
- Xaluritamig binds CD3 on T-cells and STEAP1 on tumor cells to facilitate T cell–mediated lysis



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

XmAb® is a registered trademark of Xencor, Inc.
STEAP1, six transmembrane epithelial antigen of the prostate.

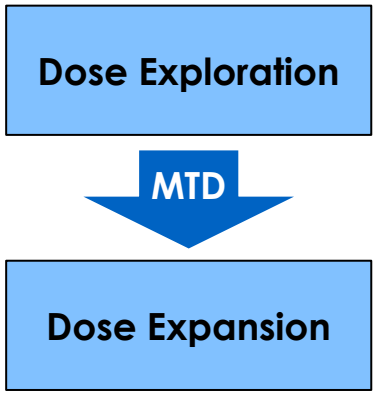
FIH study enrolled a high-risk and heavily pretreated mCRPC population

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



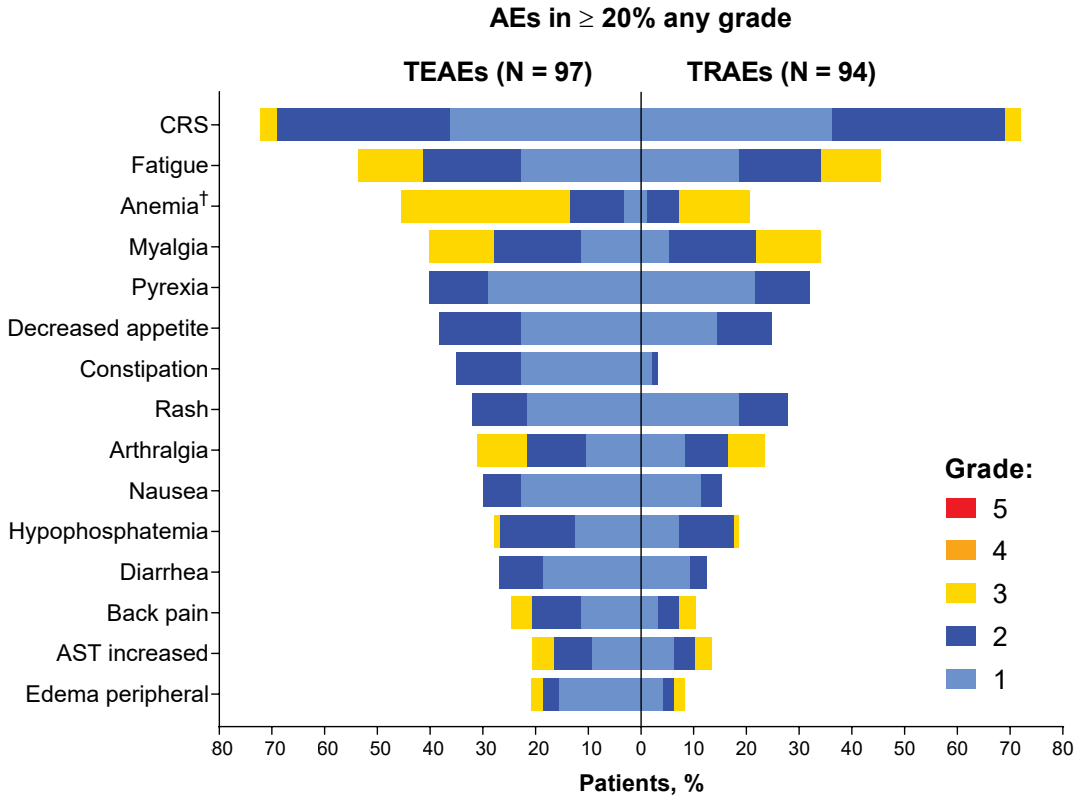
A global, first-in-human, open-label study in patients with advanced prostate cancer (NCT04221542)

Patient Characteristics	All cohorts, Part 1 (N = 97)
Age, median (range), years	67 (40, 86)
Race, n (%)	
White	59 (61)
Asian	32 (33)
Black / African American	5 (5)
ECOG PS 0 / 1, n (%)	45 (46) / 52 (54)
Number of prior lines of therapy†, median (range)	**4 (1, 9)**
≥ 5	27 (28)
Prior taxane, n (%)	**82 (85)**
Prior PSMA-targeting radioligand therapy, n (%)	**4 (4)**
Baseline PSA, ng/mL, median (range)	113.0 (0.2, 5808.9)
Visceral metastases, n (%)	**51 (53)**
Liver	**19 (37)**
Median (range) duration of follow-up, months	8.1 (0.5, 29.2)

Data cutoff March 28, 2023. **Presented at the European Society for Medical Oncology Congress 2023 Annual Meeting, October 20-24, 2023; Madrid, Spain.**
*Patients not eligible or who refused taxanes were allowed without prior taxane treatment.
†Number of prior lines of therapy do not include androgen deprivation therapy and first-generation androgen receptor deprivation therapy.
ECOG PS, Eastern Cooperative Oncology Group performance status; FIH, first-in-human; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen.

The safety profile during dose exploration was generally manageable

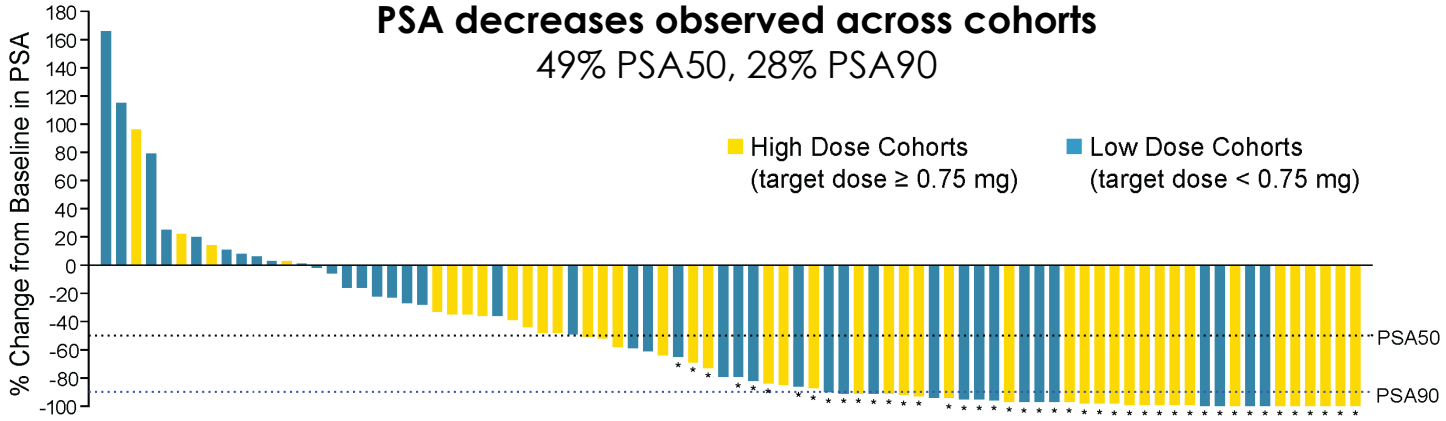
Patient Incidence of TEAEs, n (%)	All cohorts (N = 97)
Any TEAE	97 (100)
Grade ≥ 3	74 (76)
Serious	55 (57)
Related to xaluritamig	94 (97)
Grade ≥ 3	53 (55)
Leading to discontinuation from xaluritamig	18 (19)
Leading to xaluritamig dose interruption (missed doses)	46 (47)
Leading to xaluritamig dose reduction	7 (7)
Serious	38 (39)

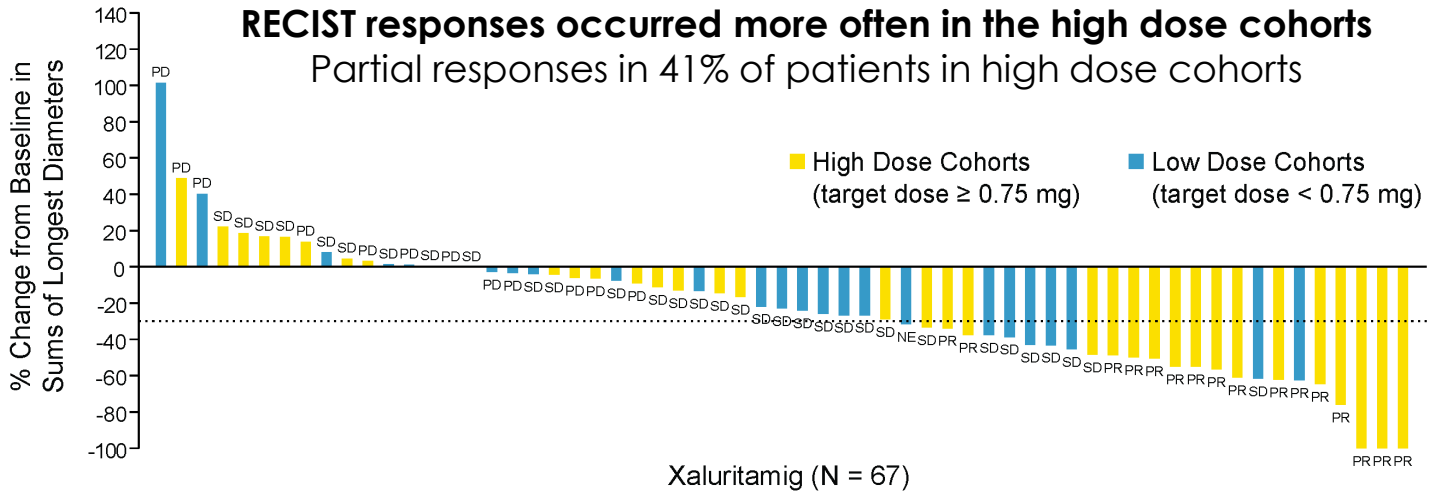


- AEs were generally consistent with the MOA and patient population; with no grade 4/5 events
- TRAEs of musculoskeletal and connective tissue disorders were reported, with 14% being serious

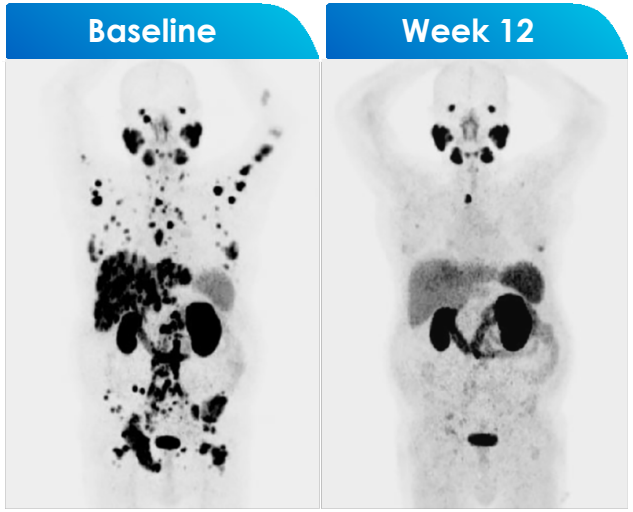
* Presented at the European Society for Medical Oncology Congress 2023 Annual Meeting, October 20-24, 2023; Madrid, Spain. Data cutoff March 28, 2023

PSA and RECIST Responses in FIH Dose-Exploration





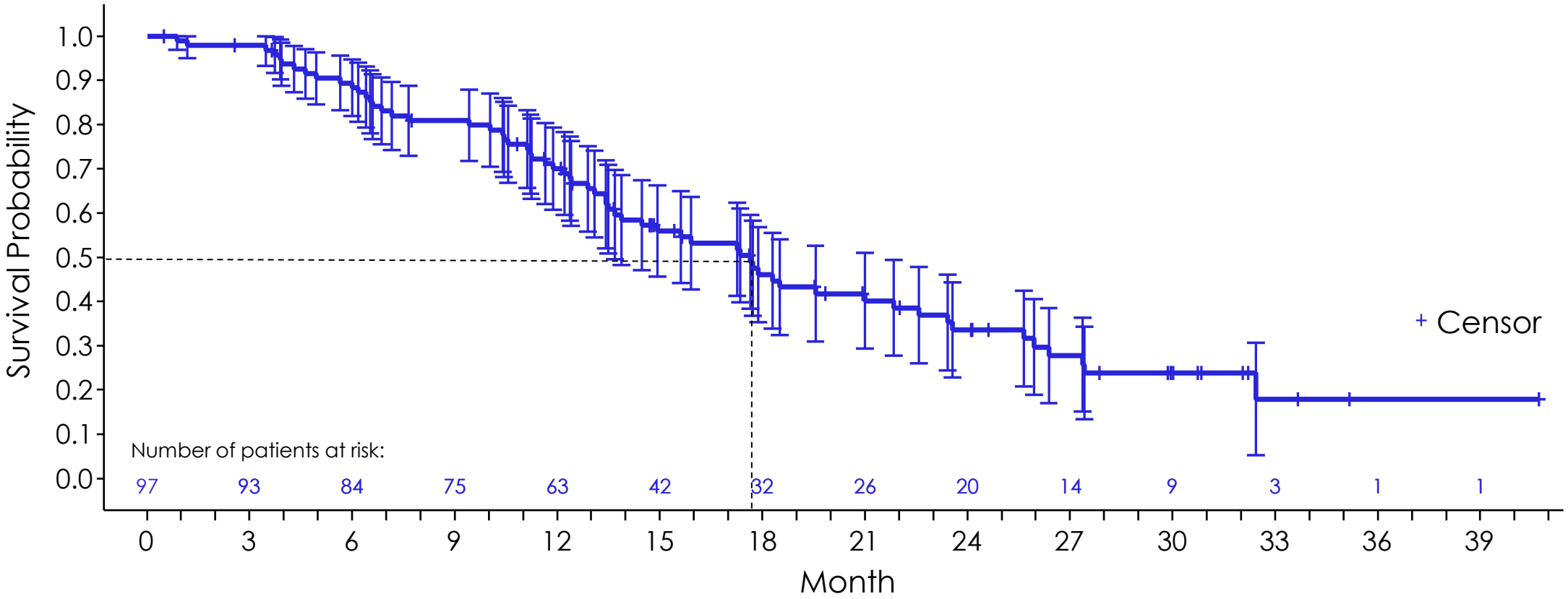
PET Imaging



- 56-year-old heavily pre-treated patient with mCRPC
- Achieved a confirmed PSA90 response (not RECIST evaluable)

CRS, cytokine release syndrome. mCRPC, metastatic castration-resistant prostate cancer. PSA, prostate-specific antigen. RECIST, Response Evaluation Criteria in Solid Tumors.
*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.
Presented at the European Society for Medical Oncology Congress 2023 Annual Meeting, October 20-24, 2023; Madrid, Spain. Data cutoff March 28, 2023

OS Results from Dose-Exploration were Encouraging in a Heavily Pre-Treated and Poor Prognostic Population



- For all patients who received ≥1 dose of xaluritamig (n = 97), at a median (range) follow-up of 27.9 (0.5, 40.8) months, **median OS (95% CI) was 17.7 (13.7, 21.9) months.**
- Median OS (95% CI) for patients in high-dose cohorts (0.75-2 mg target dose, n = 52), who had a median (range) follow-up of 24.6 (0.5, 32.3) months, was comparable at **17.4 (13.7, 25.7) months**.

Presented at the European Society for Medical Oncology Congress 2024 Annual Meeting, Barcelona, Spain.

FIH Dose Expansion Explored 3 Different Doses and Schedules for Optimization

Patients with mCRPC in the expansion phase of this FIH study (NCT04221542) were randomized 1:1:1 to receive IV xaluritamig monotherapy with target dosing regimens of 0.75 mg QW, 1.5 mg QW, or 1.5 mg Q2W, using a 2- or 3-step dosing approach in Cycle 1.

Primary objectives: Safety and tolerability
Secondary objectives: PK, preliminary antitumor activity
Exploratory objectives: PD, immunogenicity

Key inclusion criteria:
- mCRPC progressing on 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 randomized 1:1:1

Planned Target Dose (mg)	Cycle 1 Doses (mg)				Cycle 2+ Dose (mg)
	D1	D8	D15	D22	
0.75	**0.1**	**0.3**	**0.75**	**0.75**	C2D1+ = **0.75** QW
1.5	**0.1**	**0.3**	**1.0**	**1.5**	C2D1+ = **1.5** QW
1.5	**0.1**	**0.3**	**1.0**	**1.5**	C2D1+ = **1.5** Q2W

C1D1 and C1D8 equivalent doses across all cohorts.

Data cut-off date: 30 April 2024. *Patients not eligible or who refused taxanes were allowed without prior taxane treatment. Overall, patients were not to have had more than 2 novel hormonal therapies, 2 taxane regimens, and 2 other systemic anti-cancer treatments (ie, total of 6 prior systemic therapies other than androgen deprivation therapy).
CX, Cycle X; DX, Day X; ECOG, Eastern Cooperative Oncology Group; FIH, first in human; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; QW, weekly; Q2W, every two weeks.
Presented at the European Society for Medical Oncology Congress 2024 Annual Meeting, Barcelona, Spain.

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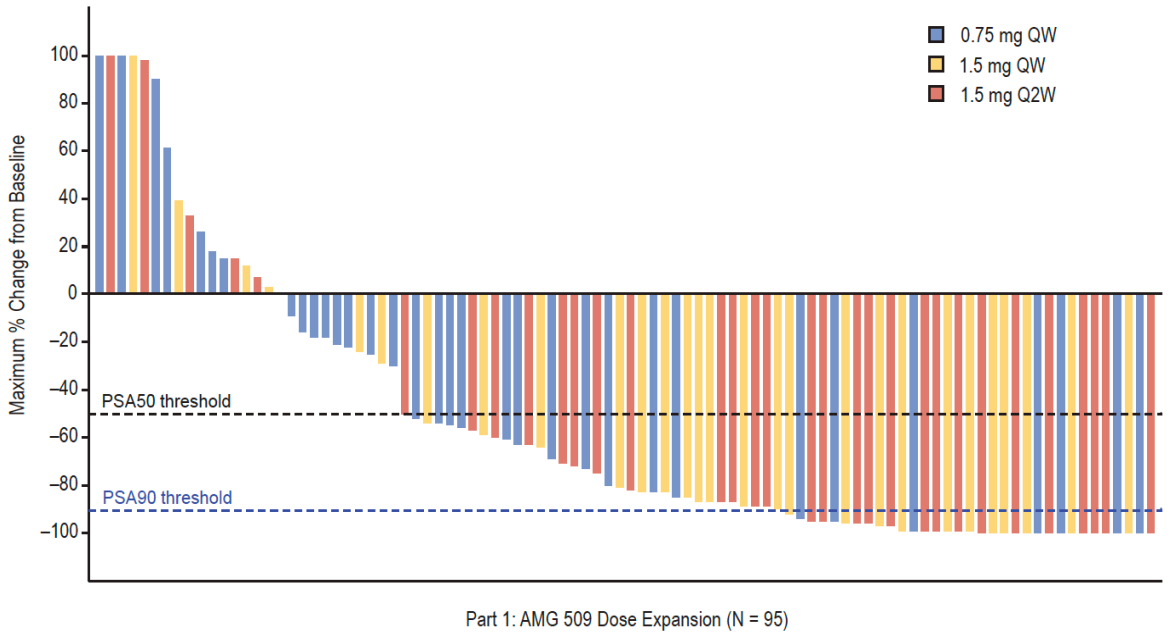
Dose Optimization: Deep and Durable Responses

1.5 mg Q2W was selected as the Pivotal Dose for mCRPC

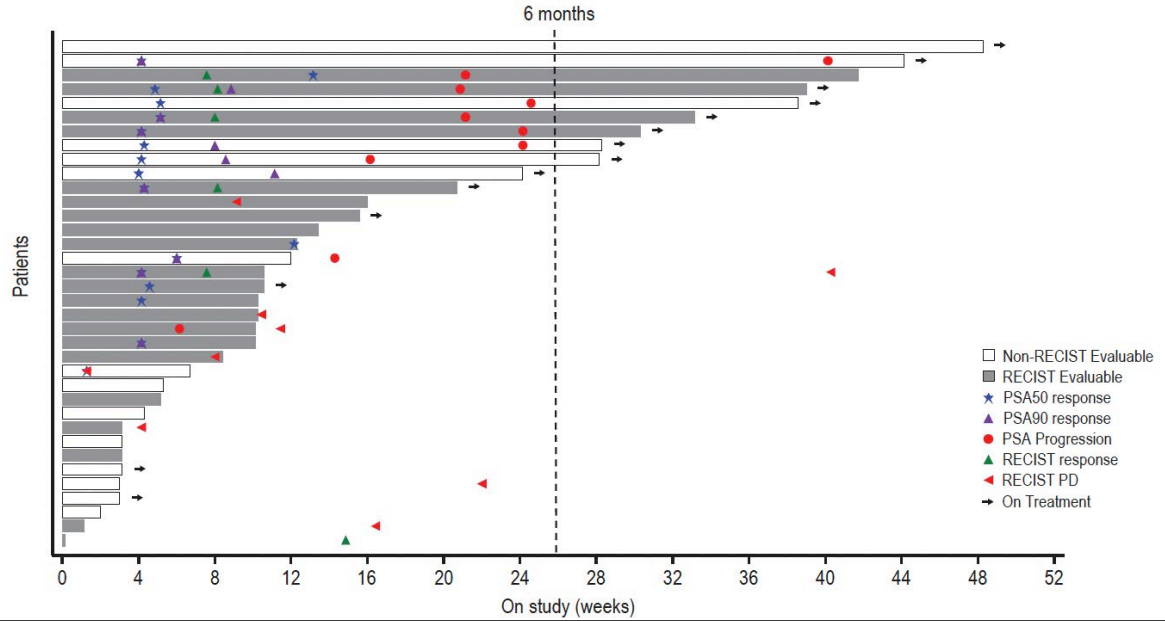
Clinical outcomes: PSA responses are deep

Figure 5: Waterfall Plot of Maximum PSA Reduction



Radiographic and biochemical responses are rapid; while data are immature, durability is encouraging

Figure 6: Swimmer's Plot for Patients Receiving 1.5 mg Q2W Xaluritamig



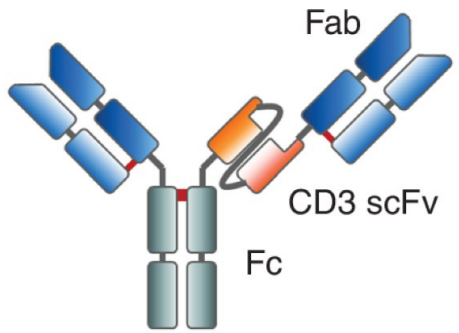
	0.75 mg QW	1.5 mg QW	1.5 mg Q2W	Dose Expansion Total
Prostate-specific antigen (PSA) evaluable	**N = 33**	**N = 30**	**N = 32**	**N = 95**
PSA50 response confirmed, n (%)	12 (36.4)	18 (60.0)	17 (53.1)	47 (49.5)
PSA90 response confirmed, n (%)	7 (21.2)	9 (30.0)	11 (34.4)	27 (28.4)
RECIST evaluable	**N = 27**	**N = 21**	**N = 21**	**N = 69**
Confirmed response (partial or complete response), n (%)	**4 (14.8)**	**4 (19.0)**	**6 (28.6)**	**14 (20.3)**

Presented at the European Society for Medical Oncology Congress 2024 Annual Meeting, September 13-17, 2024; Barcelona, Spain.

What's next? Expanding Targets will Require New Formats

Next-generation approaches aim to widen therapeutic index

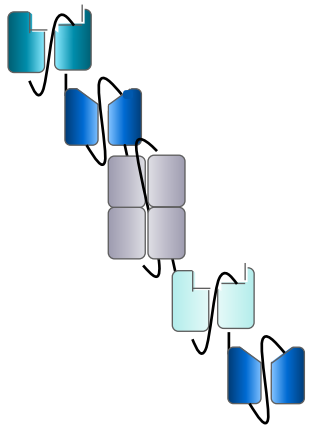
2+1 Single antigen binding



- Increased therapeutic index by preferential targeting to high-expressing tumor cells and reducing binding to low-expressing normal tissues
- ***Example: Xaluritamig (2+1)***

Nolan-Stevaux, Cancer Discov 2023

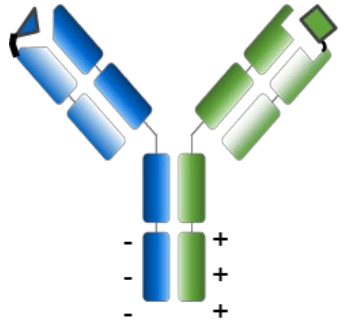
Dual targeting using "AND" TCEs



- Increased specificity and therapeutic index due to requirement to bind 2 targets and CD3

Pham E, Cancer Res 2023 [abstract]

Conditionally activated TCEs



- Designed to be inactive in circulation and activated specifically at tumors

Boustany L, Cancer Res 2022

Conclusions

1. TCEs for solid tumors have lagged behind those for hematologic malignancies, however, recent advances have shown that TCEs (tarlatamab and tebentafusp) can provide clinical benefit and improvements in overall survival in immunologically cold tumors.

2. Xaluritamig is a novel STEAP1 TCE that has demonstrated promising early clinical activity as measured by PSA and RECIST responses in patients with mCRPC
   - Median OS from the FIH of 17.7 months compares favorably to the current standard of care in a heavily-pretreated mCRPC population, indicating that xaluritamig monotherapy has the potential to improve OS in patients with advanced mCRPC.

3. Xaluritamig is the most advanced TCE for prostate cancer with a Ph3 study in mCRPC and initial evaluation ongoing in early disease settings.
   - Phase 3 mCRPC – Initiated 4Q2024
   - Phase 1 BCR – Initiated 3Q2024
   - Phase 1 Neoadjuvant – Initiated 4Q2024