Interim Results From a Phase 1 Study of Xaluritamig (AMG 509), a STEAP1 x CD3 XmAb® 2+1 Immune Therapy, in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Proffered paper presented at ESMO, October 20th, 2023

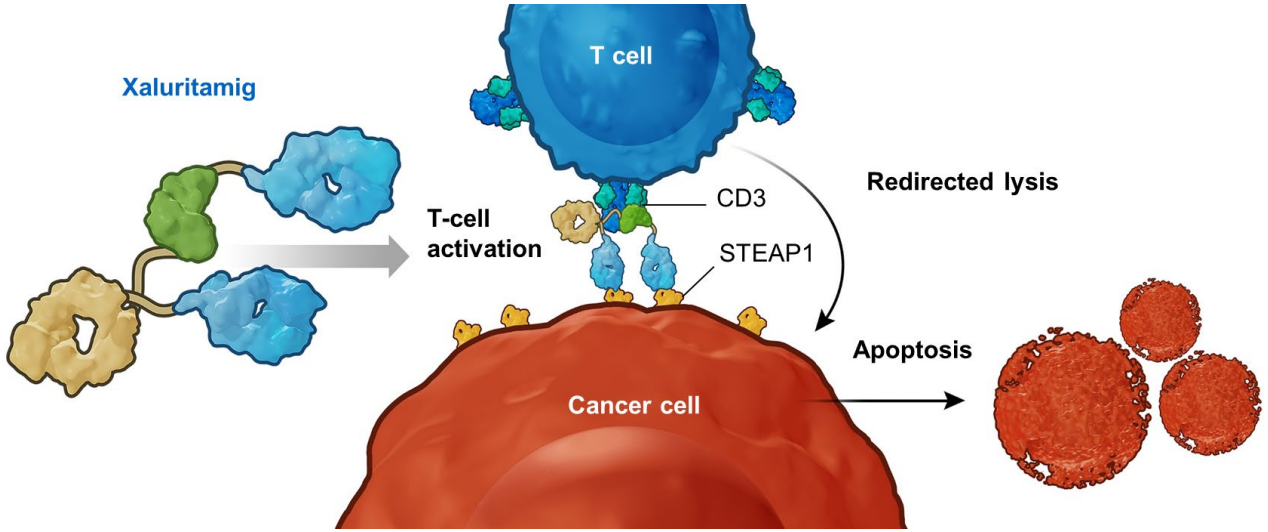
William K. Kelly, Daniel C. Danila, Chia-Chi Lin, Jae-Lyun Lee, Nobuaki Matsubara, Patrick J. Ward, Andrew J. Armstrong, David W. Pook, Miso Kim, Tanya Dorff, Stefanie Fischer, Yung-Chang Lin, Lisa Horvath, Christopher Sumey, Zhao Yang, Gabor Jurida, Jamie Connarn, Hweixian L. Penny, Julia Stieglmaier, Leonard Appleman

AMGEN

SC-AT-NP-00098 10.23

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

- Prostate cancer remains a leading cause of cancer deaths worldwide, and patients with mCRPC have a poor prognosis[1]
- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival[2,3]
- In preclinical studies, xaluritamig showed broad anti-cancer effects in prostate cancer xenograft models[3]



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

XmAb® is a registered trademark of Xencor, Inc.
mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six transmembrane epithelial antigen of the prostate
1. Turco F, et al. Res Rep Urol. 2022;14:339-50. 2. Xu M, et al. Cancers (Basel). 2022;14:4034. 3. Nolan-Stevaux O, et al. Cancer Res. 2020;80(16_Supplement):DDT02-03. 4. Li C, et al. J ImmunoTher Cancer. 2020;8:718.

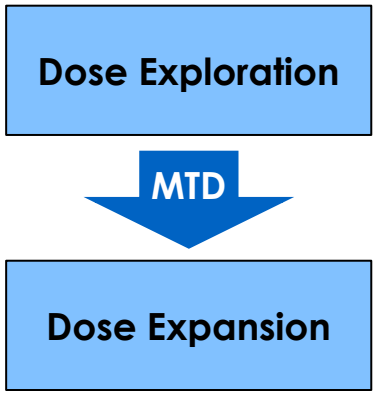
Study design, key eligibility, and baseline demographics

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, n (%)	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.
**Patients not eligible or who refused taxanes were allowed without prior taxane treatment. †One patient (1%) declined to answer.*
‡Number of prior lines of therapy do not include androgen deprivation therapy or 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.

Dose exploration with step-dosing and prophylactic regimen to determine the MTD

Dosing schedule: 28-day cycles; QW dosing (except C7c); treatment until progression* or unacceptable toxicity

Dose exploration guided by BLRM for toxicity

No Step	1-Step	2-Step	3-Step
C1: 0.001 mg **C2:** 0.003 mg **C3:** 0.01 mg **C4:** 0.03 mg **C5:** 0.1 mg **C6:** 0.3 mg	**C7a:** 0.1 → 0.3 mg **C8:** 0.3 → 1.0 mg **C10:** 0.1 → 1.0 mg	**C7b:** 0.1 → 0.3 → 1 mg **C7c:** 0.1 → 0.3 → 1 mg (Q2W) **C9:** 0.1 → 0.3 → 0.75 mg	**C11:** 0.1 → 0.3 → 1 → 1.5 mg **C12:** 0.1 → 0.3 → 0.75 → 1.5 mg **C13:** 0.1 → 0.3 → 1 → 2 mg

Premedication adjusted during C7a† →

Not tolerable MTD

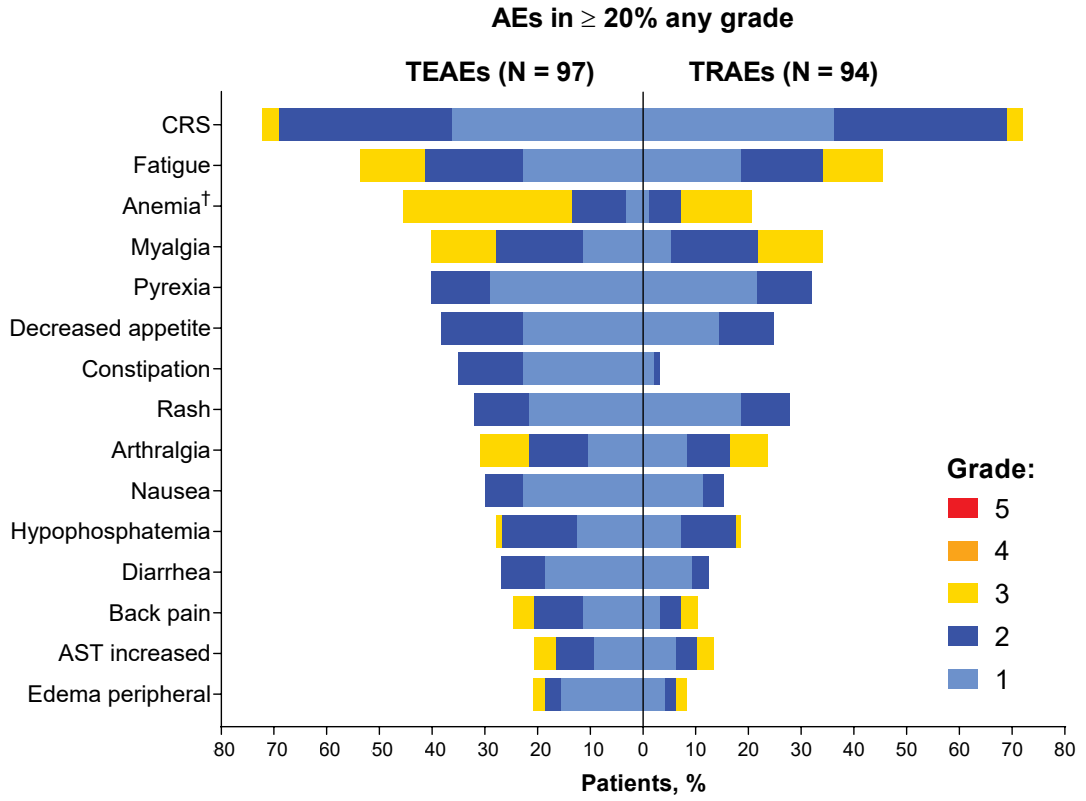
MTD → **Xaluritamig dose expansion**

MTD was identified as 1.5 mg IV QW (3-step, D1 0.1 mg / D8 0.3 mg / D15 1.0 mg / D22+ 1.5 mg)

**Treatment beyond progression was allowed in patients deriving clinical benefit per PCWG3 criteria.*
†Premedication post adjustment: steroids (2 doses) 6–12 hours and 1 hour pre-dose until target dose is reached; acetaminophen and IV hydration 1 hour prior for all doses in cycle 1.
BLRM, Bayesian logistic regression model; C, cohort; D, day; IV, intravenous; MTD, maximum tolerated dose; PCWG3; Prostate Cancer Working Group 3; QW, weekly; Q2W, every 2 weeks.

The safety profile during dose exploration was generally manageable

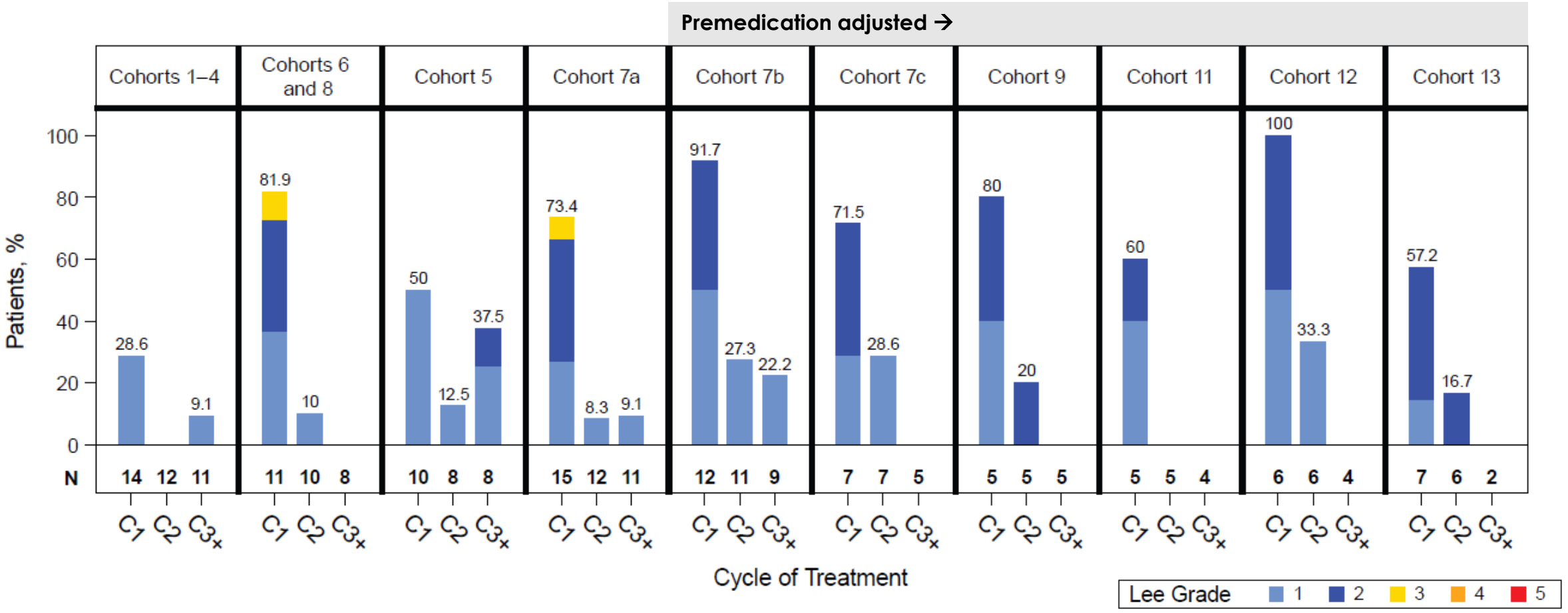
Patient Incidence of TEAEs, n (%)	All cohorts (N = 97)
Any TEAE	97 (100)
Grade ≥ 3	74 (76)
Serious	55 (57)
Related to xaluritamig	94 (97)
Grade ≥ 3	53 (55)
Leading to discontinuation from xaluritamig	18 (19)
Leading to xaluritamig dose interruption (missed doses)	46 (47)
Leading to xaluritamig dose reduction	7 (7)
Serious	38 (39)
DLT-evaluable patients, N	**82**
DLTs, n (%)*	20 (24)



- **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**

**All DLTs were grade 3 and included myalgia (n=3), back pain (n=2), performance status decrease, encephalopathy, CRS, hypotension, hypoalbuminemia, ALT increase, AST increase, fatigue, stomatitis, arthralgia, fasciitis, pharyngitis, QT prolongation, atrial fibrillation, and oropharyngeal pain (n=1 each). † Twenty-four patients required red blood cell transfusion on study.*
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; MOA, mechanism of action; TEAE, treatment-emergent adverse event TRAE, treatment-related adverse event.

CRS consistent with the MOA occurred primarily in cycle 1, was low-grade and manageable



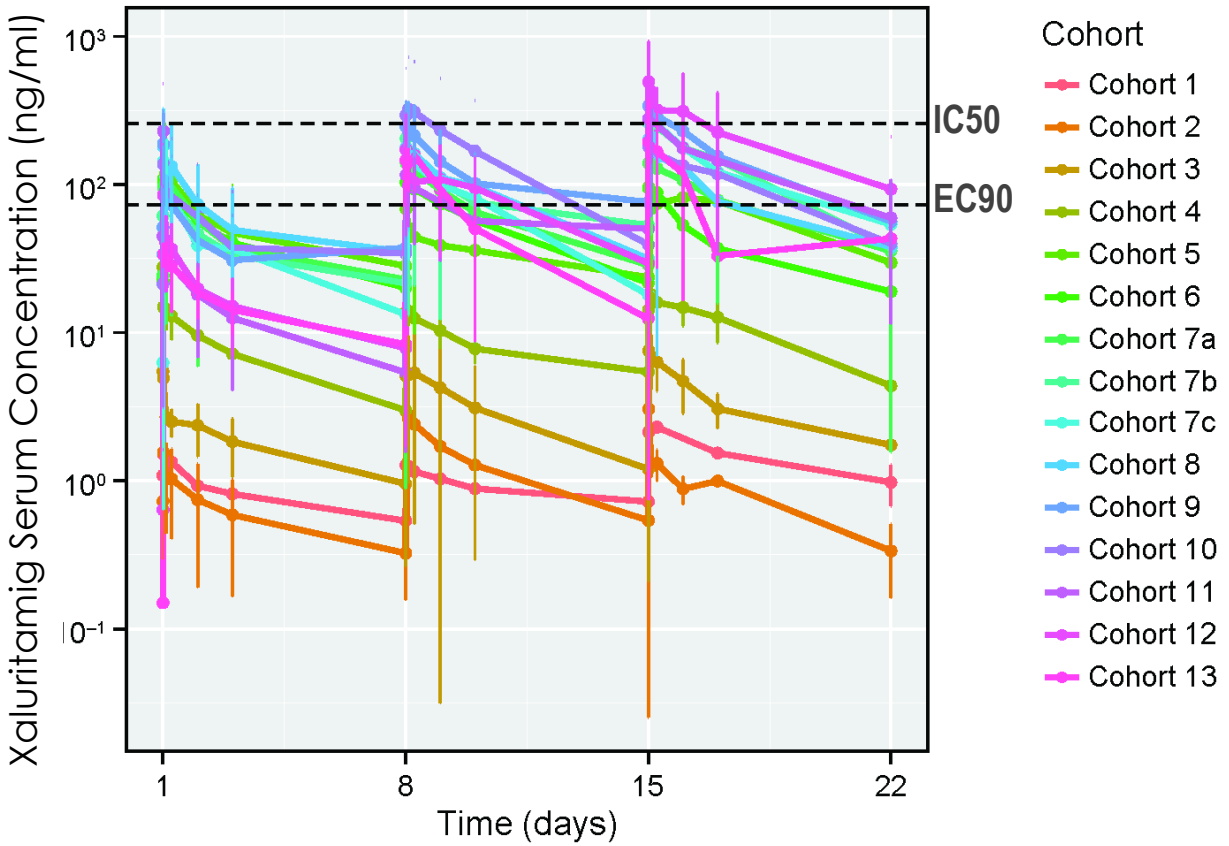
N represents number of patients in the cohort at risk at each timepoint. CRS was graded using Lee 2014 criteria[1]. Cohort 10 was excluded (0.1 mg–1.0 mg) as dosing schedule was adjusted for the remaining patients after initial patients with 10-fold dose increase in 1 step experienced DLTs.

1. Lee D et al. Blood. 2014;124:188-95.

C, cycle; CRS, cytokine release syndrome; MOA, mechanism of action.

PK demonstrated target exposures in the predicted efficacious range

- Mean terminal half-life of approximately 3–4 days
- Dose-proportional increases in exposure were observed
- Cohorts 7b–13 (≥ 0.75 mg target dose) had C_{trough} values above predicted minimum efficacious exposure

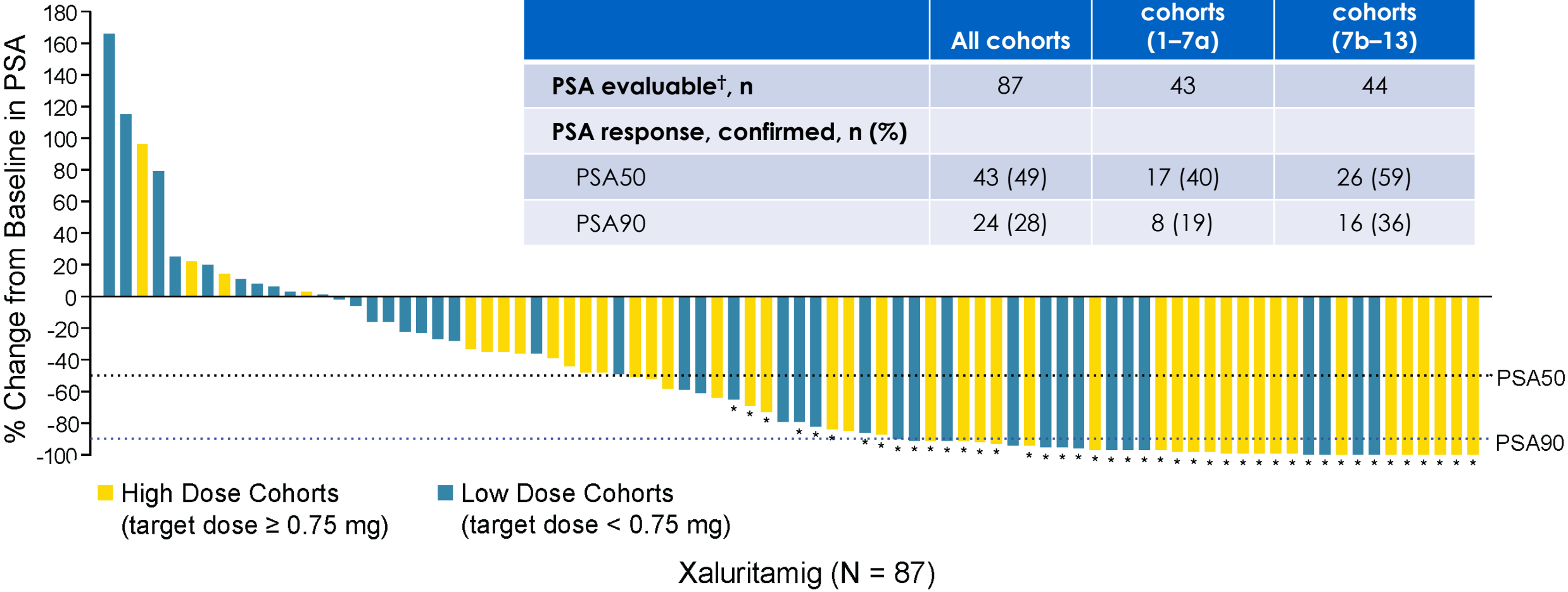


PK findings supported an exploratory evaluation of efficacy by high dose (target dose ≥ 0.75 mg) and low-dose (target dose < 0.75 mg)

Black dotted lines represent lower end of the minimum predicted efficacious exposure based on EC90 for xaluritamig-mediated cell killing in vitro (74 ng/mL) and upper end of the minimum predicted efficacious exposure based on IC50 for xaluritamig-mediated mouse tumor growth inhibition in vivo (259 ng/mL).
C_{trough}, trough concentration; EC, effective concentration; IC, inhibitory concentration; PK, pharmacokinetics.

Confirmed PSA responses were observed across cohorts

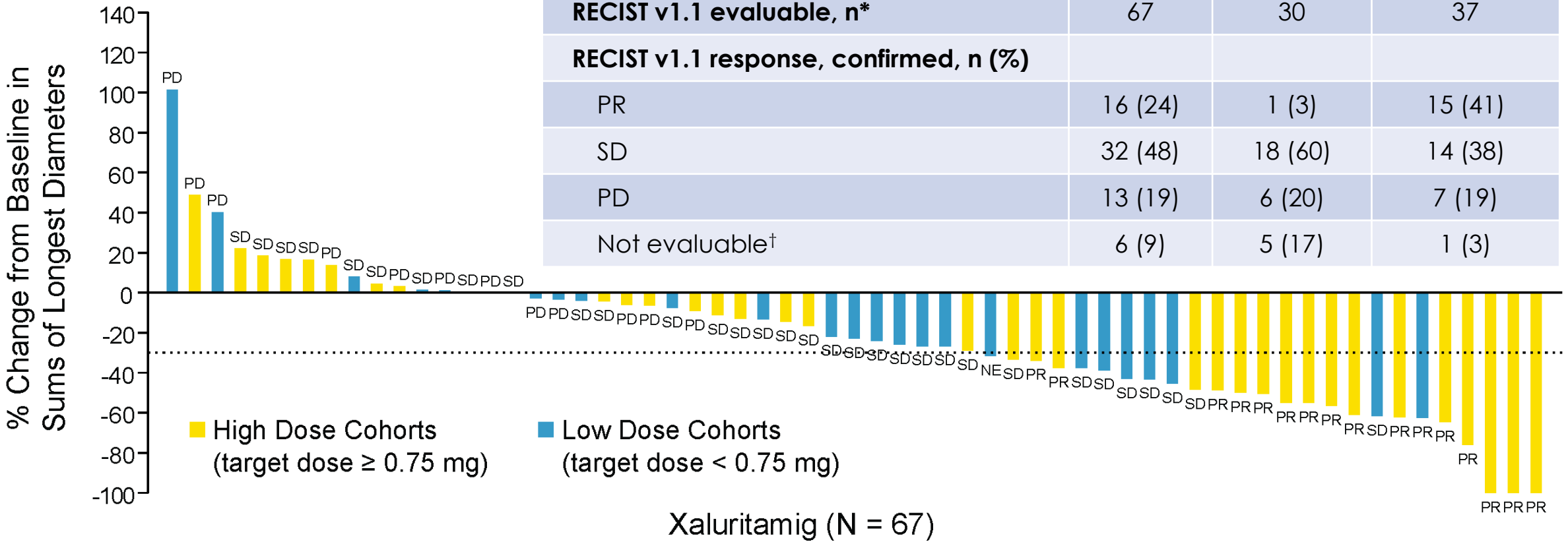
	All cohorts	Low dose cohorts (1–7a)	High dose cohorts (7b–13)
PSA evaluable†, n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)



*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.

Confirmed RECIST responses occurred more often in high dose cohorts

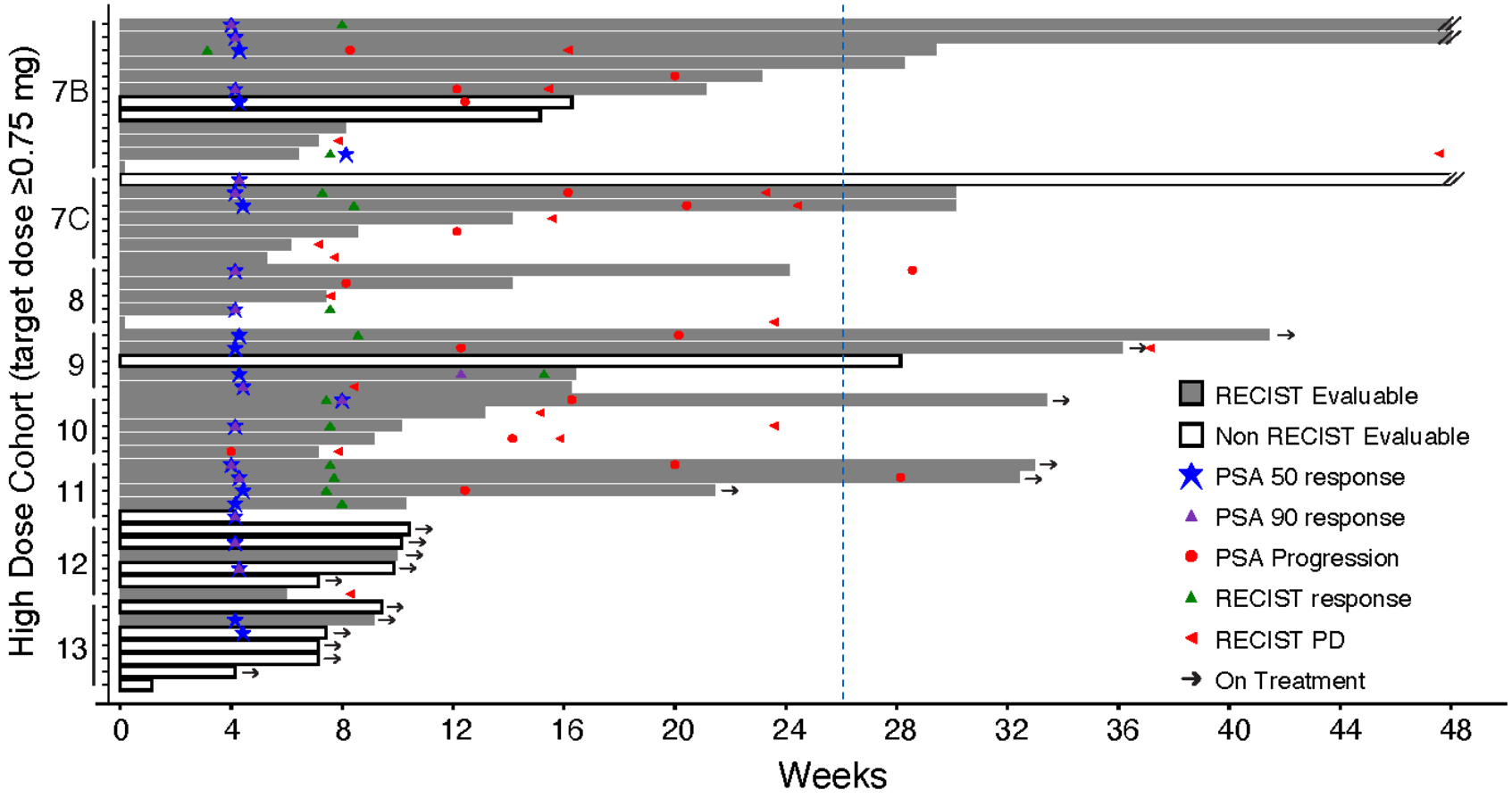
	All cohorts	Low dose cohorts (1–7a)	High dose cohorts (7b–13)
RECIST v1.1 evaluable, n*	67	30	37
RECIST v1.1 response, confirmed, n (%)			
PR	16 (24)	1 (3)	15 (41)
SD	32 (48)	18 (60)	14 (38)
PD	13 (19)	6 (20)	7 (19)
Not evaluable†	6 (9)	5 (17)	1 (3)



*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.

Responses were rapid; preliminary durability encouraging but immature



- 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 of 9.2
(range 1.9+ to 17.7+) months

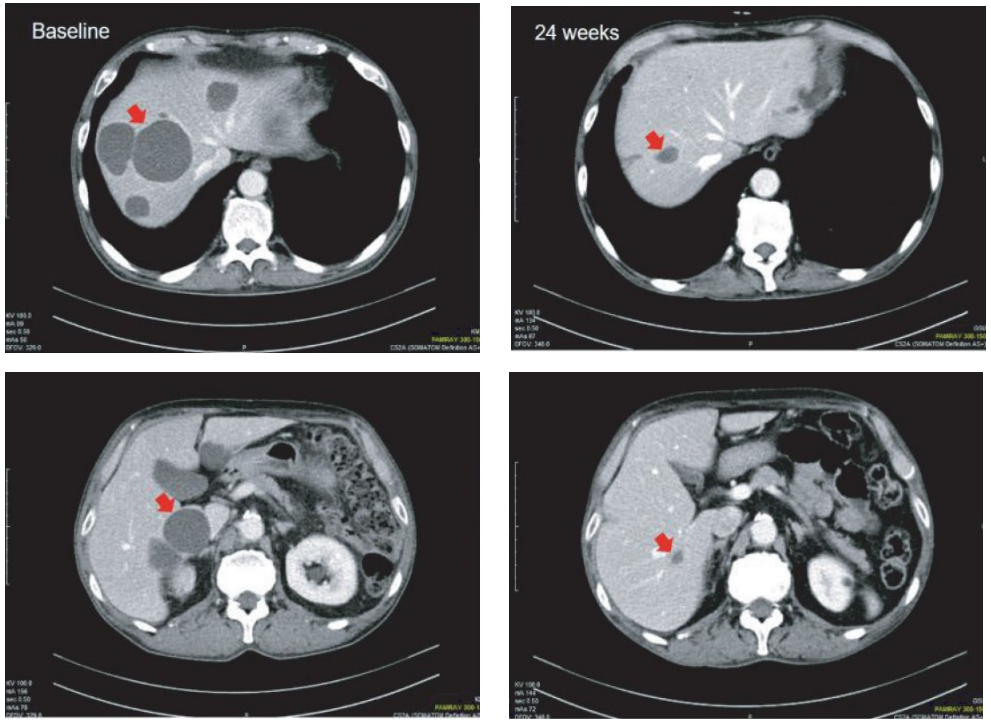
n = 16 (confirmed PR)
10/16 still in response

*+ Indicates censored value. *Includes 15 patients from high-dose cohort and 1 patient from low-dose cohort. Duration of response was measured from first evidence of PR/CR to disease progression or death due to any cause, whichever was earlier. Patients whose treatment was ongoing are noted by an arrowhead. Double parallel lines (//) represent patients who have extended beyond 48 weeks: 1 patient is ongoing treatment at 90 weeks, 1 patient is ongoing treatment at 84 weeks, and 1 patient ended treatment at 58 weeks.*
CR, complete response; PD, progressive disease; PR, partial response; PSA, prostate specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors

Anti-tumor activity has been observed against both soft tissue and bone disease

CT Scan

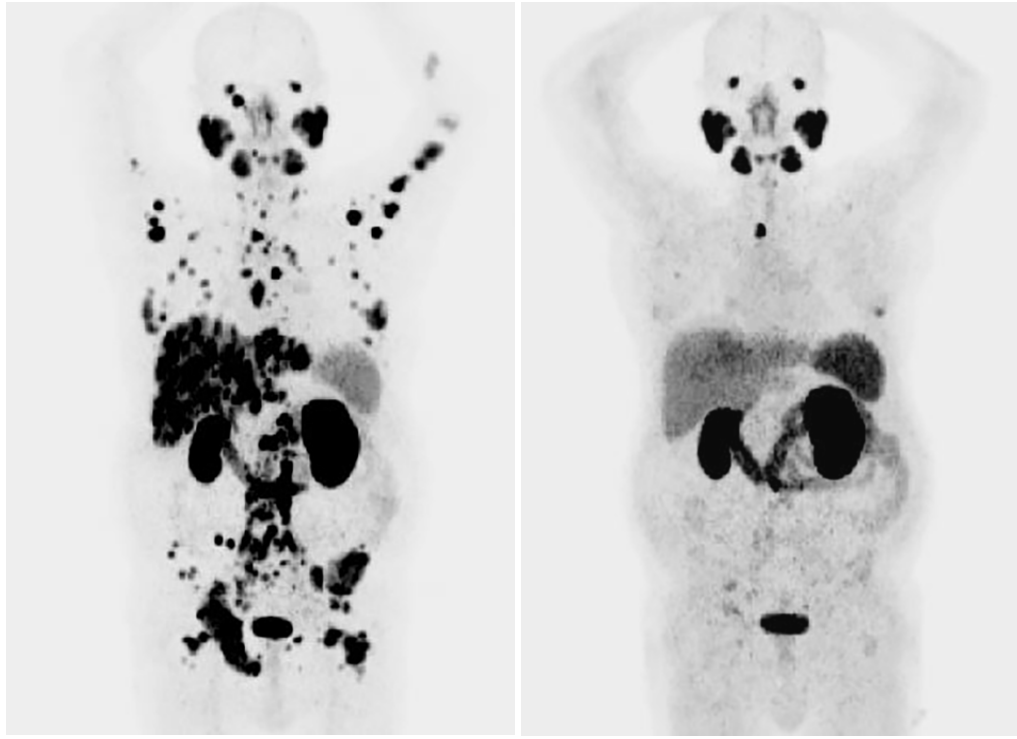
Baseline	Week 24



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).

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

Conclusions

- Xaluritamig is the first clinical T cell engager targeting STEAP1

- The MTD was established utilizing step-dosing and premedication
  - 1.5 mg IV QW (3-step, D1 0.1 mg / D8 0.3 mg / D15 1.0 mg / D22+ 1.5 mg)

- The safety profile was clinically manageable with CRS that was generally low grade and primarily in cycle 1

- Observed encouraging antitumor activity in heavily pre-treated patients with mCRPC
  - PSA50 response: 49% (Total) 59% (High-dose)
  - PSA90 response: 28% (Total) 36% (High-dose)
  - RECIST ORR: 24% (Total) 41% (High-dose)

- Dose expansion and optimization is currently ongoing to advance further development of xaluritamig as both a monotherapy and in combination

CRS, cytokine release syndrome; D, day; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PSA, prostate-specific antigen; QW, weekly; RECIST; Response Evaluation Criteria in Solid Tumors; STEAP1, six transmembrane epithelial antigen of the prostate 1.