Poster #: 1598P

Xaluritamig, a STEAP1 × CD3 XmAb® 2+1 Immune Therapy, in Patients With Metastatic Castration-Resistant Prostate Cancer: Initial Results From Dose Expansion Cohorts in a Phase 1 Study

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Xaluritamig Summary

- In this randomized dose-optimization study, xaluritamig monotherapy 1.5 mg Q2W demonstrated the most favorable efficacy and safety profile among the 3 regimens (0.75 mg QW, 1.5 mg QW, 1.5 mg Q2W) examined in patients with heavily-pretreated mCRPC. These encouraging efficacy data compare favorably to the standard of care.[5,6]
- Xaluritamig monotherapy has a manageable safety profile, consistent with MOA, and a majority of events were transient and reversible, as previously described.[3] Grade 3 adverse events, such as CRS and musculoskeletal events, allowed treatment continuation in most patients. CRS rates were similar across all regimens and most CRS events occurred in Cycle 1 (no grade 4/5 CRS*).
- A Q2W dosing schedule demonstrated an overall more favorable safety profile, notably with a lower incidence of musculoskeletal inflammatory events, including a lower rate of grade 2/3 events.
- Taken together, these results validate STEAP1 as a promising target in prostate cancer and identify xaluritamig 1.5 mg Q2W as the recommended dose for a phase 3 trial (plans ongoing) in patients with mCRPC.

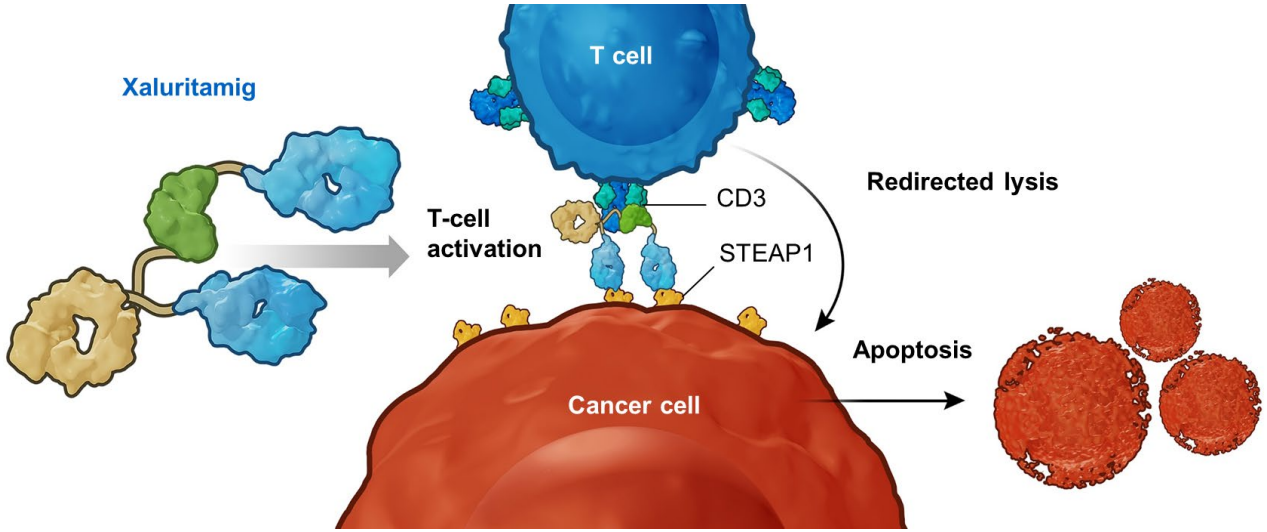
	0.75 mg QW	1.5 mg QW	1.5 mg Q2W	Total
PSA50, n/N (%)	12/33 (36.4)	18/30 (60.0)	17/32 (53.1)	47/95 (49.5)
PSA90, n/N (%)	7/33 (21.2)	9/30 (30.0)	11/32 (34.4)	27/95 (28.4)
ORR, n/N (%)	4/27 (14.8)	4/21 (19.0)	6/21 (28.6)	14/69 (20.3)

**CRS grade per Lee DW, Gardner R, Porter DL, et al. Blood 2014;124:188-195 CRS, cytokine release syndrome; mCRPC, Metastatic Castration-Resistant Prostate Cancer; MOA, mechanism of action; ORR, overall response rate; PSA, Prostate-specific antigen; PSA50, PSA decline of 50%-100% from baseline; PSA90, PSA decline of 90%-100% from baseline; QW, weekly; Q2W, every 2 weeks.*

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

- Xaluritamig is a novel bispecific XmAb® T-cell engager* targeting STEAP1-expressing cells such as in prostate cancer.[1,2]
- The monotherapy dose exploration results demonstrated encouraging efficacy and a manageable safety profile in patients with metastatic castration-resistant prostate cancer (mCRPC).[3]
- Here, using a data cutoff of April 30, 2024, we present initial results from a randomized dose expansion study comparing three regimens to further evaluate the efficacy and safety of xaluritamig and to identify the optimal regimen for future studies.

Figure 1: Xaluritamig (AMG 509): XmAb® 2+1 T-cell engager designed to facilitate T-cell-mediated lysis of STEAP1-expressing cells[1-3]



Developed pursuant to a research collaboration with Xencor, Inc. mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six-transmembrane epithelial antigen of the prostate 1.

Methods

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. There were no formal statistical hypotheses tested.

Figure 2: Dose Expansion Study Design

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.*

Results

Baseline demographics characterize a heavily-pretreated and high-risk patient population

Table 1: Patient Baseline Characteristics and Follow-up

Patient Characteristics	0.75 mg QW (N = 35)	1.5 mg QW (N = 35)	1.5 mg Q2W N = 36	Dose Expansion Total (N = 106)
Age, median (range), years	66 (37, 84)	71 (58, 82)	67 (56, 86)	67 (37, 86)
Race, Caucasian / Asian / African American, %	80.0 / 11.4 / 5.7	71.4 / 22.9 / 5.7	61.1 / 30.6 / 2.8	70.8 / 21.7 / 4.7
ECOG PS 0 / 1, n (%)	16 (45.7) / 19 (54.3)	16 (45.7) / 19 (54.3)	13 (36.1) / 22 (61.1)	45 (42.4) / 60 (56.6)
Number of prior lines of therapy for mCRPC,‡ median (range)	3.5 (1, 6)	3 (1, 7)	3 (1, 6)	3 (1, 7)
>3, n (%)	17 (48.6)	16 (45.7)	14 (38.9)	47 (44.3)
Prior taxane, n (%)	31 (88.6)	29 (82.9)	31 (86.1)	91 (85.8)
≥2 taxanes, n (%)	15 (42.9)	23 (65.7)	14 (38.9)	52 (49.1)
Prior PSMA-targeting radioligand therapy, n (%)	9 (25.7)	6 (17.1)	4 (11.1)	19 (17.9)
Visceral metastases, n (%)	20 (57.1)	18 (51.4)	20 (55.6)	58 (54.7)
Liver, n (%)	12 (34.3)	10 (28.6)	9 (25.0)	31 (29.2)
PSA, median (range), ng/mL	145.3 (4.0, 3757.6)	82.9 (1.4, 5154.8)	94.8 (5.0, 7508.0)	98.5 (1.4, 7508.0)
Lactate dehydrogenase, median (range), U/L	286 (117, 3143)	242 (136, 1195)	256 (166, 2834)	257 (117, 3143)
Hemoglobin, median (range), g/L	114 (86, 147)	109 (88, 145)	111 (82, 150)	112 (82, 150)
Alkaline phosphatase, median (range), U/L	149 (42, 1443)	106 (40, 966)	143 (1, 947)	122 (1, 1443)
Duration of follow-up, median (range), months	7.8 (0.3, 11.8)	5.9 (0.3, 11.1)	6.5 (0.7, 11.6)	6.3 (0.3, 11.8)

‡Number of prior lines of therapy do not include androgen deprivation therapy or first-generation androgen receptor deprivation therapy. ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; PS, performance status; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QW, weekly; Q2W, every two weeks.

Dose expansion safety/PK profiles are consistent with dose exploration

- Generally, the safety profile was manageable, reversible, and consistent with the MOA and patient population, with no fatal treatment-related adverse events (TRAE), as previously described.[3]
- Serious TRAEs in 64 patients (60.4%) included musculoskeletal (n = 23), CRS (n = 19), and infections (n = 9).
- Seventeen (16.0%) patients discontinued due to TRAEs, including musculoskeletal (n = 4), infections (n = 2), and CRS (n = 2).
- Other frequently reported TRAEs included rash (35.8%; 5.7% grade ≥3), anemia (34.0%; 17.0% grade ≥3), and fatigue (32.1%; 9.4% grade ≥3).
- PK observed in dose expansion was consistent with that observed in dose escalation.
- Overlapping exposure (C_{max} and AUC) was observed at the 0.75 mg and 1.5 mg target doses during Cycle 1.

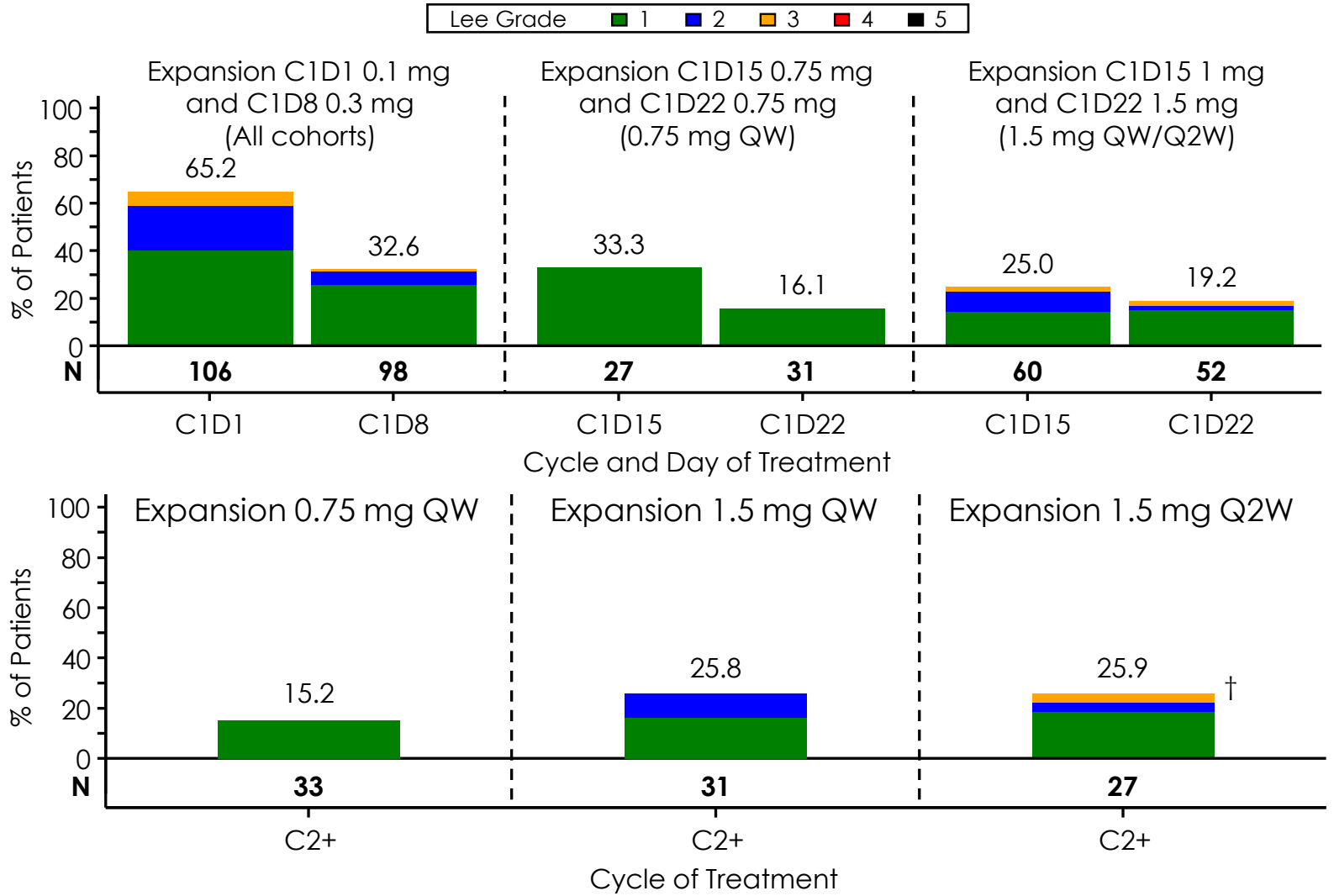
Table 2: Treatment-related Adverse Events (TRAEs)

TRAEs by category, n (%)	0.75 mg QW (N = 35)	1.5 mg QW (N = 35)	1.5 mg Q2W (N = 36)	Dose Expansion Total (N = 106)
All TRAEs	34 (97.1)	35 (100.0)	35 (97.2)	104 (98.1)
Grade 1	1 (2.9)	1 (2.9)	0 (0)	2 (1.9)
Grade 2	8 (22.9)	8 (22.9)	6 (16.7)	22 (20.8)
Grade 3	20 (57.1)	24 (68.6)	26 (72.2)	70 (66.0)
Grade 4	5 (14.3)	2 (5.7)	3 (8.3)	10 (9.4)

Coded using MedDRA V27.0. CTCAE v5; CRS per Lee DW, Gardner R, Porter DL, et al. Blood 2014;124:188-195). AE, adverse event; AUC, area under the curve; Cmax maximum concentration; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; MOA, mechanism of action; PK, pharmacokinetics; QW, weekly; Q2W, every two weeks; TRAE, treatment-related adverse event. Table contains worst grade of AEs.

CRS profile is consistent across expansion dose cohorts

Figure 3: CRS in Cycle 1 (top) and Cycle 2 and Beyond (bottom)

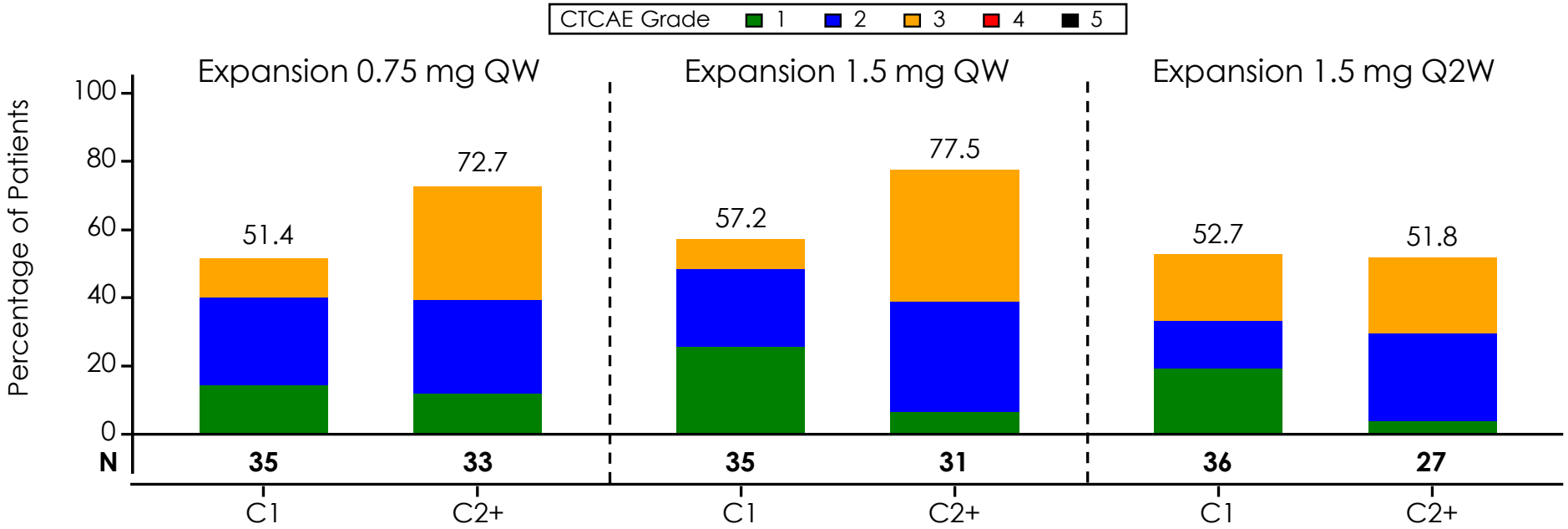


- CRS was the most common TRAE; overall, it was observed in 80 patients (75.5%).
- CRS was most frequent in Cycle 1, with a majority of events occurring Cycle 1 Day 1; CRS was mostly grade 1/2, with few grade 3 (9.4%) events and no grade 4/5 events (grade per Lee 2014).*[4]
- Overall, similar CRS profiles were seen across all 3 dosing regimens.

*Coded using MedDRA V27.0. *CRS grade per Lee DW, Gardner R, Porter DL, et al. Blood 2014;124:188-195. †Representing 1 patient at each grade in C3+. CX, Cycle X; CRS, cytokine release syndrome; DX, Day X; MedDRA, Medical Dictionary for Regulatory Activities; QW, weekly; Q2W, every two weeks; TRAE, treatment-related adverse event.*

Q2W dosing schedule is associated with lower rates of musculoskeletal events

Figure 4: Musculoskeletal Inflammatory AEs

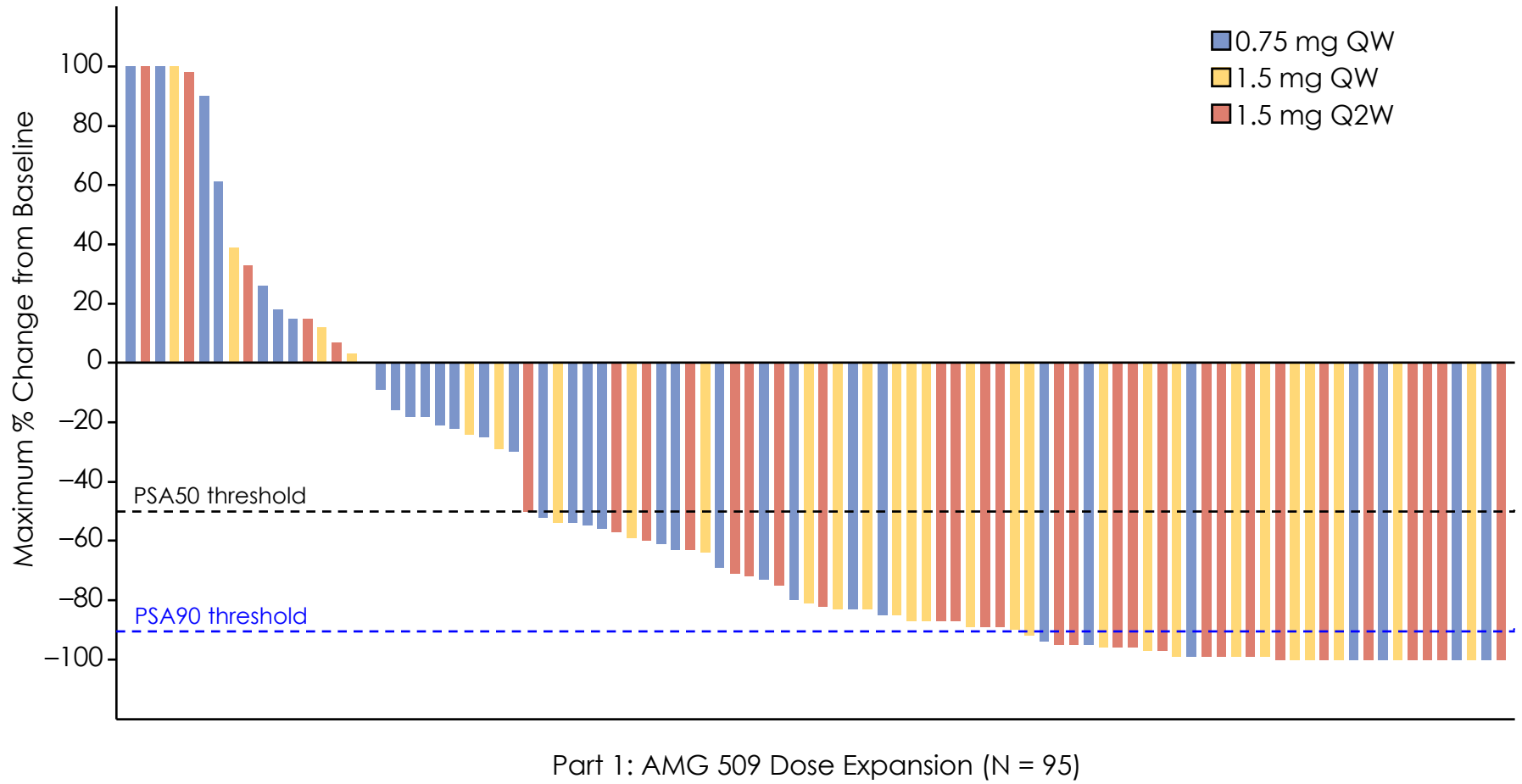


- Musculoskeletal inflammatory TRAEs, primarily myalgia, arthralgia, and muscle weakness, were reported by 81 patients (76.4%); 37.7% were grade 3. Overall, rates were lowest in the 1.5 mg Q2W cohort (69.4% vs 74.3% in 0.75 mg QW and 85.7% in 1.5 mg QW) and grade 2/3 events were less common after Q2W dosing was implemented (Cycle 2+ Q2W vs QW).
- Discontinuation rate due to musculoskeletal events was low due to improvement/resolution with dose reductions/temporary dosing holds.
- Detailed treatment guidance for TRAEs (including indications for dose hold/reduction, steroids and/or tocilizumab) has been incorporated into the protocol, which is expected to further improve the musculoskeletal AE profile.

Coded using MedDRA V27.0. CTCAE v5. AE, adverse event; CX, Cycle X; CTCAE, Common Terminology Criteria for Adverse Events; QW, weekly; Q2W, every two weeks; TRAE, treatment-related adverse event. Musculoskeletal events included myalgia, muscle weakness, myofascitis, myositis, arthralgia, soft tissue swelling, genital edema/swelling, scrotal swelling, orbital swelling, periorbital edema/swelling.

Clinical outcomes: PSA responses are deep

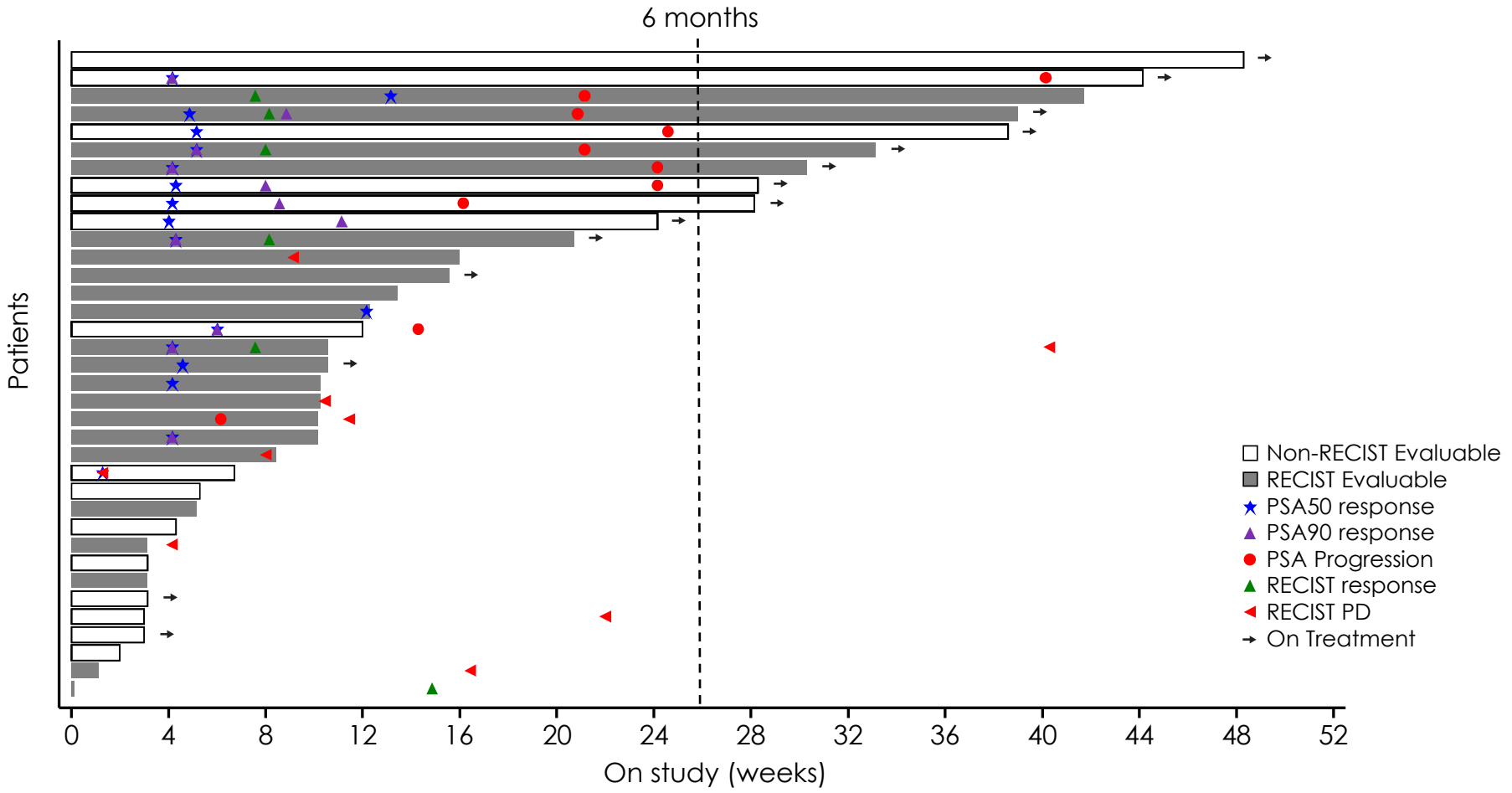
Figure 5: Waterfall Plot of Maximum PSA Reduction



Changes shown here reflect maximum PSA reduction at a single assessment; PSA50 and PSA90 rates reported elsewhere in this poster required a second consecutive confirmatory PSA assessment. Median (range) duration of follow-up was 7.8 (0.3, 11.8) months for 0.75 mg QW, 5.9 (0.3, 11.1) months for 1.5 mg QW, and 6.5 (0.7, 11.6) months for 1.5 mg Q2W. Data are from enrolled patients (PSA N = 95, RECIST v1.1 N = 69) who received ≥1 dose of study drug, had measurable PSA/baseline disease, and had the opportunity for ≥8 weeks of follow-up. PSA, prostate-specific antigen; PSA50, PSA decline of 50%-100% from baseline; PSA90, PSA decline of 90%-100% from baseline; QW, weekly; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

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



Median (range) duration of follow-up for patients receiving 1.5 mg Q2W was 6.5 (0.7, 11.6) months. Data are from enrolled patients (N = 36) who received ≥1 dose of study drug, had measurable PSA/baseline disease, and had the opportunity for ≥8 weeks of follow-up. PD, progressive disease; PSA, prostate-specific antigen; PSA50, PSA decline of 50%–100% from baseline; PSA90, PSA decline of 90%-100% from baseline; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Xaluritamig efficacy summary

Table 3: Comparison of Efficacy Outcomes Among the 0.75 mg QW, 1.5 mg QW, and 1.5 mg Q2W Regimens

	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)**
Confirmed complete response, n (%)	0 (0.0)	0 (0.0)	1 (4.8)	1 (1.4)
Confirmed partial response, n (%)	4 (14.8)	4 (19.0)	5 (23.8)	13 (18.8)
Stable disease, n (%)	10 (37.0)	14 (66.7)	10 (47.6)	34 (49.3)
Progressive disease, n (%)	12 (44.4)	1 (4.8)	4 (19.0)	17 (24.6)
Not evaluable, n (%)	1 (3.7)	2 (9.5)	1 (4.8)	4 (5.8)

- Efficacy includes PSA50 response up to 60%, PSA90* up to 34%, and ORR up to 29%, in keeping with response rates seen in the exploratory phase high-dose cohorts (0.75–2.0 mg) of PSA50 59%, PSA90 36%, and ORR 41%.[3]
- In the dose expansion, in patients with liver metastases† evaluable for PSA response (n = 28), findings include PSA50 36%, PSA90 11%; of RECIST evaluable (n = 30), ORR was 13%.

**Patients with PSA90 responses were also captured in the PSA50 response group. †A total of 31 patients (29% of total) had liver metastases at baseline. Median (range) duration of follow-up was 7.8 (0.3, 11.8) months for 0.75 mg QW, 5.9 (0.3, 11.1) months for 1.5 mg QW, and 6.5 (0.7, 11.6) months for 1.5 mg Q2W. Summary of confirmed PSA response and objective response per RECIST 1.1 both by investigator assessment. PSA50 and PSA90 rates included those with a second consecutive confirmatory PSA assessment. ORR, overall response rate; PSA, Prostate-specific antigen; PSA50, PSA decline of 50%–100% from baseline; PSA90, PSA decline of 90%–100% from baseline; QW, weekly; Q2W; every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.*

Xaluritamig duration of response

Table 4: Duration of Response Among the 0.75 mg QW, 1.5 mg QW, and 1.5 mg Q2W Regimens

	0.75 mg QW	1.5 mg QW	1.5 mg Q2W	Dose Expansion Total
Duration of follow-up, median (range), months	7.8 (0.3, 11.8)	5.9 (0.3, 11.1)	6.5 (0.7, 11.6)	6.3 (0.3, 11.8)
PSA50 responders	**N = 12**	**N = 18**	**N = 17**	**N = 47**
Duration of PSA50 response, n (%)				
≥3 months	5 (41.7)	8 (44.4)	10 (58.8)	23 (48.9)
≥6 months	2 (16.7)	1 (5.6)	1 (5.9)	4 (8.5)
Radiographic Progression-Free Survival (PFS) evaluable	**N = 35**	**N = 35**	**N = 36**	**N = 106**
PFS, median (range), months	8.3 (0.0+, 11.1)	5.6 (0.0+, 8.3)	7.8 (0.0+, 10.3+)	7.8 (0.0+, 11.1)
Kaplan-Meier estimate, %				
3 months	61.0	92.2	73.6	74.8
6 months	52.3	43.8	56.3	52.3
RECIST responders	**N = 4**	**N = 4**	**N = 6**	**N = 14**
Duration of objective response, n (%)				
≥3 months	2 (50)	3 (75)	5 (83.3)	10 (71.4)
≥6 months	2 (50)	1 (25)	3 (50)	6 (42.9)

- Median (range) treatment duration was 14 (1–50) weeks; 29 (26%) completed ≥6 months of treatment.

Study Limitations

- The dosing regimens evaluated in this randomized dose expansion were not powered to demonstrate definitive differences in safety and efficacy; thus, the assessment of differences in these signals is based on emerging trends.
- Durability of response and other time to event endpoints are not fully mature, as median (range) follow-up was 6.3 (0.3, 11.8) months, and endpoints may evolve with longer follow-up.
- Racial diversity was limited, with enrollment being 70.8% Caucasian, 21.7% Asian, and 4.7% African American.

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