

Adaptive dosing in phase 1 study of alpitatug satetraxetan, an actinium-225-labeled antibody targeting human Kallikrein-2 for metastatic castration-resistant prostate cancer

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Key Takeaway

The efficacy of alpi-sat was maintained with an adaptive dosing regimen, though GRID dosing did not fully mitigate safety concerns

Conclusions

Targeting KLK2 with alpi-sat, an α-emitting RLT, with GRID demonstrated clinical activity, with the greatest activity reported in patients in the chemo-naïve cohort receiving a dose of 250 µCi

Despite less frequent adaptive dosing with GRID, hematologic and pulmonary toxicity was observed, even after a single dose of this long–half-life RLT

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Introduction

- Alpitatug satetraxetan (alpi-sat) is a first-in-class anti-human kallikrein-2 (hK2/KLK2) antibody–based actinium-225 (²²⁵Ac) radioligand therapy (RLT)^{1,2}
- Alpi-sat preferentially binds to the membrane-associated form of KLK2, which is highly expressed on prostate cancer cells, and delivers α-particle radiation to prostate tumor cells^{1–4}
- Preclinical studies demonstrated in vitro KLK2-targeted internalization of the anti-KLK2 antibody and in vivo antitumor activity of alpi-sat⁴
- In the first-in-human study, alpi-sat elicited deep and durable responses (46% PSA50 at doses ≥150 µCi every 8–12 weeks) in heavily pretreated metastatic castration-resistant prostate cancer during dose escalation⁵
- We report on an adaptive dosing schedule (guided response interval dosing [GRID]) designed to mitigate ²²⁵Ac-related adverse events while preserving antitumor activity

Methods

- Figure 1** illustrates the Part 1 dose-escalation study design, including the adaptive dosing schedule
- First GRID dose of alpi-sat was 200 or 250 µCi
- For patients with initially stable or decreasing prostate-specific antigen (PSA) levels, up to 2 subsequent 150 µCi doses were permitted ≥12 weeks later upon PSA progression, per PCWG3, for a maximum of 3 doses total
 - Additional retreatment criteria: platelets ≥100×10⁹/L; hemoglobin ≥8 g/dL
- Three groups were evaluated at a dose of 250 µCi:
 - Cohort 2a: Post-chemotherapy (post-chemo, n=19)
 - Cohort 2b: Chemotherapy- and RLT-naïve (chemo-naïve, n=21)
 - Cohort 2c: Post-¹⁷⁷Lu vipivotide tetraxetan RLT and chemotherapy (post-¹⁷⁷Lu-PSMA-617, n=20)
- A chemo-naïve cohort was evaluated at a dose of 200 µCi (n=18)
- Radiographic progression-free survival (rPFS) was assessed using survival analysis

Results

Patients

- As of April 1, 2026, 78 patients received ≥1 dose with GRID; baseline characteristics are shown in **Table 1**

Characteristic	GRID 200 µCi Chemo-naïve (n=18)	Chemo-naïve (n=21)	GRID 250 µCi Post-chemo (n=19)	Post- ¹⁷⁷ Lu-PSMA-617 (n=20)
Age, median (range), years	74.5 (54–89)	74.0 (59–83)	71.0 (54–80)	68.0 (60–81)
Prior cancer-related therapy, n (%)				
Radiotherapy	10 (55.6)	16 (76.2)	14 (73.7)	18 (90.0)
Primary radiotherapy	2 (11.1)	2 (9.5)	6 (31.6)	5 (25.0)
Palliative radiotherapy	6 (33.3)	7 (33.3)	4 (21.1)	10 (60.0)
ARPI	18 (100)	21 (100)	19 (100)	20 (100)
1 ARPI	7 (38.9)	11 (52.4)	3 (15.8)	3 (15.0)
>1 ARPI	11 (61.1)	10 (47.6)	16 (84.2)	17 (85.0)
Taxane-based chemotherapy	0	0	19 (100)	20 (100)
PSA, median (range), µg/L	7.8 (1.6–119.9)	32.0 (1.7–797.9)	68.6 (11.6–1221.0)	85.6 (9.7–1300.0)
Platelets, median (range), 10 ⁹ /L	222.0 (174–344)	201.0 (117–362)	231.0 (135–620)	192.5 (156–311)
Hemoglobin, median (range), g/dL	12.8 (9.7–15.1)	11.7 (9.5–14.5)	11.2 (8.6–13.7)	10.8 (9.6–13.4)
Extent of disease, n (%)				
Bone	13 (72.2)	17 (81.0)	16 (84.2)	19 (95.0)
Soft tissue	13 (72.2)	17 (81.0)	16 (84.2)	15 (75.0)
Visceral	5 (27.8)	5 (23.8)	6 (31.6)	9 (45.0)
Lymph node	7 (38.9)	11 (52.4)	13 (68.4)	11 (55.0)
Other	2 (11.1)	3 (14.3)	1 (5.3)	2 (10.0)

ARPI, androgen receptor pathway inhibitor; GRID, guided response interval dosing; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Efficacy

- For patients in the chemo-naïve cohort receiving 250 µCi GRID, PSA50 rates were 42.9%, with durable clinical benefit after 1 or 2 doses (median [range] time to treatment discontinuation, 10.1 [1.4 to 17.9] months; median rPFS, 13.5 months)
- Lower PSA50 rates were observed at 250 µCi in post-chemo (31.6%) and post-RLT cohorts (20.0%) and at 200 µCi (27.8%; **Figure 2**)
- Out of 78 patients in the GRID cohorts, 14 received a second dose; 12 had stable or decreasing PSA with subsequent dose
- The objective response rates (complete response + partial response) in patients with measurable disease at baseline by cohort were: 200 µCi chemo-naïve (18.2%), 250 µCi chemo-naïve (18.2%), 250 µCi post-chemo (13.3%), and 250 µCi post-RLT (11.1%)

Safety

- A summary of safety results is shown in **Table 2**
- Among persistent cytopenias (grade 1 for ≥24 weeks or grade ≥2 for ≥12 weeks), 7 cases of anemia and 5 cases of thrombocytopenia were reported; 1 case each of acute myeloid leukemia (peripheral blasts noted 3 weeks after dosing), myelodysplastic syndrome (MDS), hypocellular marrow, and multiple myeloma (MM) was reported in the chemo-naïve cohort. MDS and MM were retrospectively found to have consistent abnormalities at baseline
- Treatment-related adverse events leading to treatment discontinuation included pneumonitis (n=2), hypoxia (n=1), chronic kidney disease (n=1), myelodysplastic syndrome (n=1, fatal), acute kidney disease (n=1, fatal), and thrombocytopenia (n=1, fatal)
- Grade ≥3 anemia and thrombocytopenia were lower in GRID 250 µCi cohorts (22% and 12%) compared to scheduled 250 µCi cohorts (37% and 30%)

AEs, n (%)	GRID 200 µCi Chemo-naïve (n=18)		Chemo-naïve (n=21)		GRID 250 µCi Post-chemo (n=19)		Post- ¹⁷⁷ Lu-PSMA-617 (n=20)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE (n≥25%)	18 (100)	6 (33.3)	21 (100)	13 (61.9)	19 (100)	14 (73.7)	20 (100)	14 (70.0)
Fatigue	11 (61.1)	1 (5.6)	9 (42.9)	1 (4.8)	6 (31.6)	0	18 (90.0)	1 (5.0)
Thrombocytopenia	6 (33.3)	1 (5.6)	13 (61.9)	3 (14.3)	8 (42.1)	1 (5.3)	14 (70.0)	3 (15.0)
Leukopenia	6 (33.3)	0	13 (61.9)	3 (14.3)	4 (21.1)	0	13 (65.0)	5 (25.0)
Lymphopenia	7 (38.9)	1 (5.6)	10 (47.6)	8 (38.1)	12 (63.2)	7 (36.8)	4 (20.0)	4 (20.0)
Nausea	6 (33.3)	0	13 (61.9)	0	5 (26.3)	0	6 (30.0)	0
Anemia	5 (27.8)	1 (5.6)	9 (42.9)	6 (28.6)	9 (47.4)	2 (10.5)	10 (50.0)	5 (25.0)
Decreased appetite	7 (38.9)	0	10 (47.6)	0	6 (31.6)	0	9 (45.0)	0
Dry mouth	6 (33.3)	0	10 (47.6)	0	6 (31.6)	0	3 (15.0)	0
Diarrhea	6 (33.3)	0	9 (42.9)	0	3 (15.8)	0	4 (20.0)	0
Dyspnea	3 (16.7)	0	5 (23.8)	0	5 (26.3)	1 (5.3)	8 (40.0)	0
Vomiting	1 (5.6)	0	6 (28.6)	0	4 (21.1)	0	7 (35.0)	0
Neutropenia	1 (5.6)	0	6 (28.6)	2 (9.5)	4 (21.1)	0	7 (35.0)	5 (25.0)
Dizziness	3 (16.7)	0	6 (28.6)	0	3 (15.8)	0	7 (35.0)	0
Back pain	4 (22.2)	1 (5.6)	7 (33.3)	1 (4.8)	5 (26.3)	0	3 (15.0)	0
Weight decreased	3 (16.7)	0	7 (33.3)	0	4 (21.1)	0	3 (15.0)	0
Hypokalemia	1 (5.6)	1 (5.6)	2 (9.5)	1 (4.8)	6 (31.6)	1 (5.3)	2 (10.0)	0
Arthralgia	2 (11.1)	0	4 (19.0)	1 (4.8)	2 (10.5)	1 (5.3)	6 (30.0)	2 (10.0)
Dysgeusia	4 (22.2)	0	3 (14.3)	0	3 (15.8)	0	5 (25.0)	0
Pneumonitis	1 (5.6)	0	1 (4.8)	1 (4.8)	2 (10.5)	1 (5.3)	1 (5.0)	0
Serious TEAE/TRAЕ	4 (22.2)/2 (11.1)		9 (42.9)/5 (23.8)		10 (52.6)/1 (5.3)		7 (35.0)/2 (10.0)	
TRAЕ leading to discontinuation	1 (5.6)		2 (9.5)		0		3 (15.0)	
TRAЕ/TRAЕ leading to death	1 (5.6)/1 (5.6)		2 (9.5)/2 (9.5)		1 (5.3)/0		2 (10.0)/0	

AE, adverse event; GRID, guided response interval dosing; ILD, interstitial lung disease; PSMA, prostate-specific membrane antigen; TEAE, treatment-emergent adverse event; TRAЕ, treatment-related adverse event.

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Figure 1: Study design

alpi-sat, alpitatug satetraxetan; ARPI, androgen receptor pathway inhibitor; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP2D, recommended phase 2 dose.

Figure 2: (A) Maximum reduction from baseline in PSA and (B) duration of PSA response

chemo, chemotherapy; GRID, guided response interval dosing; IV, intravenous; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

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Prostate Cancer