185: Mature phase 1 follow up of alpha emitter ^{225}Ac-J591 with ^{177}Lu-PSMA-I&T in metastatic castration-resistant prostate cancer

Gabriel Raab, Tobechukwu Joseph Okobi*, Aaron N. Holmes, Sandra Huicochea Castellanos, Vasilios Avlonitis, Amie Patel, Charlene Thomas, Jones T. Nauseef, Ana M. Molina, Zachary Davidson, Cora N. Sternberg, David M. Nanus, Joe Reginald Osborne, Neil Harrison Bander, Scott T. Tagawa

Weill Cornell Medicine

Background

- **PSMA-Targeting Antibodies**: PSMA may be targeted by antibodies (mAb) or small molecules (SML), with different kinetics and biodistribution (and therefore different predicted toxicities, Table)
- **Alpha vs. Beta Emitters**: α-emitters with higher linear energy transfer over shorter range than β-, offering distinct therapeutic advantages with preclinical and dosimetric rationale for combination (Fig 1b and 1c)
- Small molecules are not retained intracellularly and the combination of antibody with small molecule may enhance intracellular retention, as suggested by preclinical models (Fig 1a).

	Monoclonal Antibody (mAb)	Small-Molecule Ligand (SML)
Size	151 kilodalton	1042 g/mol
Properties	Long circulation time (days)	Short circulation (hours)
Targeting	Target via vasculature	Rapid diffusion to all sites of target expression
Predicted off tumor exposure	Bone marrow, liver (non-specific)	Salivary & lacrimal glands, intestines, kidney (specific off-tumor PSMA targeting)
Predicted toxicities	Infusion reaction, myelosuppression	Nausea, vomiting, xerostomia, renal Injury

Table 1: Comparison of anti-PSMA antibody vs small-molecule.
Both target PSMA+ tumor, different off-tumor distribution → hypothesis that combo better

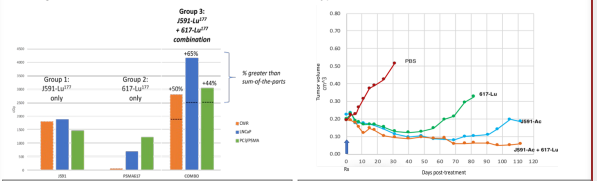


Figure 1A. Xenograft with 3 different PSMA expressing cell lines treated with ^{177}Lu-J591, ^{177}Lu-PSMA-617, or both. Counts at 72 hours displayed with combo demonstrating higher uptake/retention of ^{177}Lu than the sum of parts (synergy). mAb leads to more uptake/retention of SML (data not shown).

Figure 1B: Alpha/Beta Combination: Alpha and beta with different energy and range; 177Lu-J591, 225Ac-J591, or combo administered. Most significant reduction in tumor volume with combination of alpha + beta, including pathologic CR's

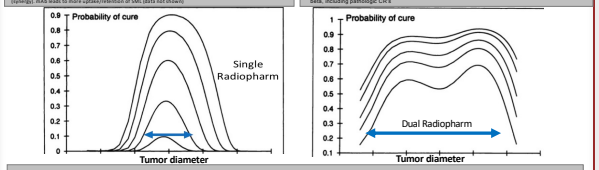


Figure 1C: Dual α (Ac^{225}) + β (Lu^{177}) radionuclide therapy Provides potency & precision of α. Combining α + β particles extends curability range. O'Donaghue J et al.

Methods

Trial Population:
- Progressive mCRPC
- ≥1 prior AR pathway inhibitor (ARPI), prior chemo (or unfit/refused)
- ≥1 lesion with ^{68}Ga-PSMA-11 PET SUVmax >liver (additional PSMA low lesions allowed)

Treatment:
- 177Lu-PSMA-I&T (6.8 GBq) and 225Ac-J591 (30, 35, or 40 KBq/kg); 2nd dose at be administered at 8 weeks.

Primary Outcome:
- Dose-limiting toxicity (DLT)
- Recommended phase 2 dose (RP2D)

Preliminary Efficacy Outcome:
- Overall survival (OS)
- Progression-free survival (PFS)
- PSA response (PSA50)
- Circulating tumor cell (CTC) changes.

*Presenter's Contact Information : Tobechukwu Okobi, rdl9005@nyp.org

Conclusion

The combination of PSMA-targeted alpha (via antibody) plus beta (via small molecule) was feasible. High-grade AEs were rare and no new safety signals emerged with longer term follow-up. Nearly all patients had PSA decline, and 6 had durable disease control off therapy.

Results/Graphs/Data

Primary Endpoint:
Two DLT's at 40 Kbq/Kg: 1 Gr 2 and 1 Gr 3 platelets delaying cycle 2 for >3 weeks
RP2D of 225Ac-J591 was 35 KBq/kg.

Overall, 94% had PSA declines; 64% with >50% decline (Figure below)
Of those with available CTC counts (CellSearch) at baseline and follow up:
4/5 (80%) unfavorable-to-favorable
4/8 (50%) detectable-to-undetectable.

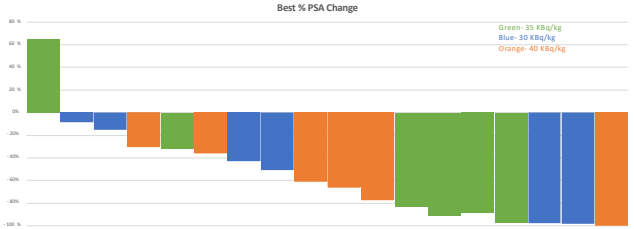


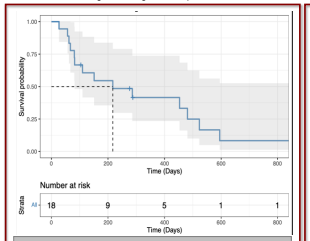
Table 2: Patient Characteristics

Patient Characteristics	N = 18 (6 at each dose level)
Median Age at Treatment	70 (range 55 - 87)
Median PSA (ng/mL)	54.5 (range 2.43 - 9614)
CALGB (Halabi) Risk Category	
Low	4 (22%)
Intermediate	5 (27%)
High	8 (44%)
Prior Therapies	
>1 ARPI	11 (61%)
Chemotherapy	12 (67%)
Sipuleucel-T	5 (28%)
Radium- 223	3 (17%)
Metastatic Sites	
Lymph node Metastasis	9
Visceral Metastasis	4
Bone Metastasis	13
medianSUVMax	48.32 (95% CI 36.34 – 58.16)
medianSUVmean	8.08 (95% CI 7.90 – 9.05)
Baseline CTC	
0/undetectable	3 (17%)
1-4	4 (22%)
5 or greater	11 (61%)

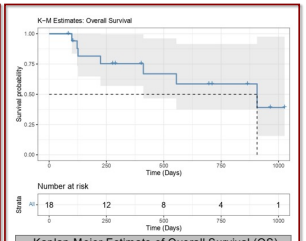
Table 3- Select adverse events by grade and frequency

Adverse Event	Total	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	3 (17%)	3 (17%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia	12 (67%)	9 (50%)	1 (5%)	2 (11%)	0 (0 %)
Anemia	9 (50%)	4 (22%)	2 (11%)	3 (17%)	0 (0 %)
Xerostomia	12 (67%)	11 (61%)	1 (5%)	0 (0%)	0 (0%)
Acute renal failure	2 (11%)	2 (11%)	0 (0%)	0 (0%)	0 (0%)
Pain flare	11 (62%)	9 (50%)	1 (5%)	1 (5%)	0 (0%)
Nausea	10 (56%)	10 (56%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	8 (44%)	8 (44%)	0 (0%)	0 (0%)	0 (0%)

- Above table describes worse AEs for all cohorts while on study. All AEs improved from worst grade with 70% returning to baseline.
- For late AEs (defined as present at last follow up after progression and start of new therapy), neutropenia (Gr 1 in 1 = 6%), anemia (Gr 1 in 1 = 6%, Gr 2 in 5 =28%), renal failure (Gr 1 in 1 = 6%), thrombocytopenia (1 Gr 1, 1 Gr 3, 6% ea). Late AEs were attributed to POD and/or subsequent treatment. No new signals at longer follow-up.



Kaplan-Meier Estimate of progression-free survival (PFS) with median PFS 7.3mo (95% CI 2.7-15.8)



Kaplan-Meier Estimate of Overall Survival (OS) with median OS 29.8 mo (95% CI 7.4- NR)

- With extended follow up, median OS was 29.8 months (95% CI 7.4-NR)
  Currently, 6 patients are confirmed alive at 28 mo median follow-up
- PFS extended analysis:
  At RP2D, 3 of 6 were progression-free at 13, 17 and 18 mo
  1 of 6 treated at dose level 30 KBq/kg remains progression-free at 33 mo follow up

Acknowledgement:
Supported by: The trial was sponsored by Weill Cornell Medicine. Additional funding was provided by NIH, Prostate Cancer Foundation, Department of Defense, POINT Biopharma (provided 177Lu-PSMA-I&T)

Disclosures: Full disclosures are available on the ASCO website, including:
Dr. Tagawa has received honoraria + institutional research funding from POINT Biopharma, Lantheus, Telix, Novartis, Blue Earth, Convergent Therapeutics, Clarity, with his employer (WCM) licensing the drug to Convergent Therapeutics.
Dr. Bander: consulting/advisory role and equity in Convergent Therapeutics.