Results of combined targeting of prostate-specific membrane antigen (PSMA) with alpha-radiolabeled antibody ^{225}Ac-J591 and beta-radiolabeled ligand ^{177}Lu-PSMA I&T: preclinical and initial phase 1 clinical data in patients with metastatic castration-resistant prostate cancer (mCRPC).

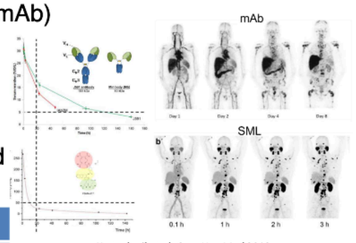
Scott T. Tagawa, Edward Fung, Muhammad O. Niaz, Mahelia Bissassar, Sharon Singh, Amie Patel, Angela Tan, Juana Martinez Zuloaga, Sandra Huicochea Castellanos, Jones Nauseef, Ana M. Molina, Cora N. Sternberg, David M. Nanus, Joseph Osborne Neil H. Bander

Meyer Cancer Center, Weill Cornell Medicine, New York, NY

Weill Cornell Medicine
Meyer Cancer Center

BACKGROUND

- PSMA is overexpressed by most PC cells
- PSMA may be targeted with both antibodies (mAb) and small molecule ligands (SML)
- mAb with long circulating times
- SML with rapid distribution to all PSMA+ sites
- Based upon kinetics and biodistribution, mAb predicted to have more myelosuppression and SML more xerostomia and nausea



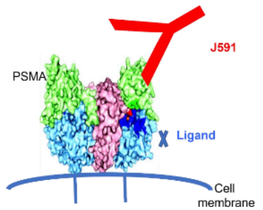
Kratochwil et al, *Sem Nuc Med* 2019

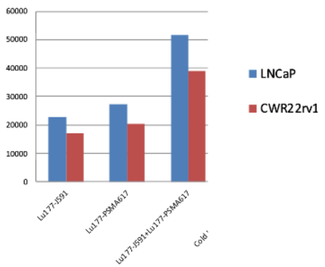
	^{177}Lu-J591	^{177}Lu-PSMA-617	P-Value
Patients (n)	131	50	
Neutropenia (n)	102 (**77.9%**, 21% Gr 4)	2 (4%)	<0.001
Anemia (n)	101 (**77.1%**, 11% Gr 3)	8 (16%)	<0.001
Thrombocytopenia (n)	118 (**90.1%**, 37% Gr 4)	10 (20%)	<0.001
Xerostomia (n)	1 (<1%)	29 (**58%**)	<0.001
Nausea (n)	19 (14.5%)	21 (**42%**)	<0.001

Niaz et al, AUA 2020

Retrospective analysis of prospective trials supports hypothesis / prediction based upon biodistribution

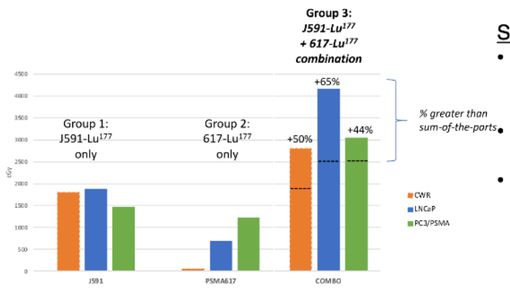
- Alpha emitters have high potency and high range; beta emitters with lower energy and longer range
- mAb J591 and PSMA SML have different, non-competitive binding sites



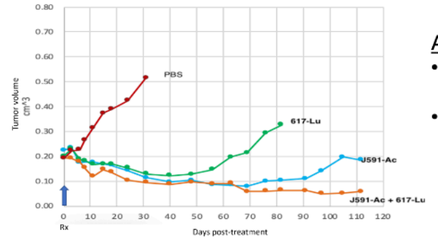


HYPOTHESIS:
Combining mAb and SML targeting plus combining alpha and beta emitters will offer complementary benefits and will be safe and effective.

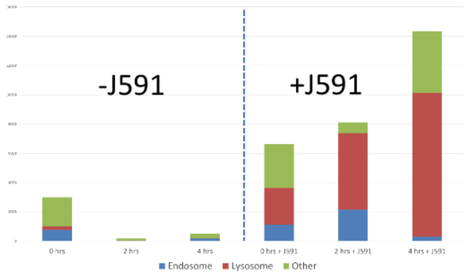
RESULTS



Synergistic Uptake:
- 177Lu-J591, 177Lu-PSMA-617, or combo administered to 3 animal models (CWR, LNCaP, PC3/PSMA)
- Autopsy measurement of cpm/mg tumor assessed at day 3 post-injection
- Radioactivity dose to tumor was greater than additive amount of uptake of 177Lu after combo administration in all 3 models



Alpha/Beta Combination:
- 177Lu-J591, 225Ac-J591, or combo administered
- Most significant reduction in tumor volume with combination of alpha + beta, including pathologic CR's



Intracellular Trafficking of SML +/- mAb:
- 177Lu-PSMA617 administered alone or with mAb J591
- Confocal imaging optical analysis
- Significantly greater cellular retention of SML in the presence of mAb by retaining SML in lysosome

Clinical trial entry criteria summary:
- Progressive mCRPC, ECOG PS 0-1
- Prior exposure to AR pathway inhibitor (e.g. abi/enza) for advanced disease
- Prior chemo (or chemo ineligible/refuse)
- Prior sip-T, Ra223 OK, but not required
- No prior PSMA-targeted therapy (diagnostics OK)
- ANC ≥ 2; Hgb ≥ 9; platelets ≥ 150
- PSMA+ (at least 1 tumor site with PSMA PET SUV > liver)

Phase 1 = dose-escalation (3+3 design, up to 2 dose-levels)
- Fixed dose 177Lu-PSMA I&T (aka PNT2002) at 6.8 GBq
- ^{225}Ac-J591 at 30 or 40 KBq/Kg
- Up to 2 cycles 8 weeks apart

Baseline Demographics (n=9)	
Age, median (range)	68 (55-87)
PSA, median (range)	140 (2.4-9614)
ECOG Performance Status, n (%)	
0	2 (22.2%)
1	4 (44.4%)
2	3 (33.3%)
Bone metastases, n (%)	8 (88.9%)
Lymph node metastases, n (%)	4 (44.4%)
Lung metastases, n (%)	2 (22.2%)
Liver metastases, n (%)	2 (22.2%)
CTC count, median (range)	12 (0-500+)
Detectable, n (%)	7 (77.8%)
Unfavorable, n (%)	6 (66.7%)
≥2 prior ARPI, n (%)	5 (55.6%)
Prior chemo, n (%)	8 (88.9%)
Prior radium-223, n (%)	3 (33.3%)
PSMA PET SUVmax*, median, (range)	32.5 (11.6-69.9)

* Single hottest lesion

Results to date:
- No DLT in 3 subjects Cohort 1 (30 KBq/Kb)
- DLT assessment ongoing in 6 subjects in Cohort 2 (40 KBq/Kg)
  - 1 subject with Gr 3 thrombocytopenia
- Of 8 evaluable to date, 7 with PSA decline (range 8-98%)
- Of 4 evaluable to date, 3 with CTC conversion

Supported by: Weill Cornell Medicine, NIH ULI RR024996

clinicaltrials.gov NCT04886986

stt2007@med.cornell.edu