Dual-Targeting: PSMA

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Weill-Cornell Medicine

Disclosure

- NHB is an Inventor on patents related to this presentation and assigned to Cornell University
- NHB is a paid advisor and shareholder of Convergent Therapeutics, Inc, the company to which this IP has been licensed for further development.

Tumor Therapy with Targeted Atomic Nanogenerators

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A single, high linear energy transfer alpha particle can kill a target cell. We have developed methods to target molecular-sized generators of alpha-emitting isotope cascades to the inside of cancer cells using actinium-225 coupled to internalizing monoclonal antibodies. In vitro, these constructs specifically killed leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels. Injection of single doses of the constructs at kilobecquerel (nanocurie) levels into mice bearing solid prostate carcinoma or disseminated human lymphoma induced tumor regression and prolonged survival, without toxicity, in a substantial fraction of animals. Nanogenerators targeting a wide variety of cancers may be possible.

Alpha particles are high-energy, high linear energy transfer helium nuclei capable of strong, yet selective, cytotoxicity (*1*). A single atom emitting an alpha particle can kill a target cell (*2*). Monoclonal antibodies conjugated to alpha particle–emitting radionuclides (^{213}Bi and ^{211}At) are starting to show promise in radioimmunotherapy (*3, 4*). The conjugates [^{213}Bi]-HuM195 (*2*) and [^{213}Bi]J591 (*5, 6*) have been used in preclinical models of leukemia and prostate cancer, respectively, and in a phase I human clinical trial, [^{213}Bi]HuM195 was active against leukemia, with no significant toxicity (*3*). Astatine-211–labeled antibodies to tenascin (anti-tenascin) have been used clinically to treat malignant gliomas in humans (*4*) in a phase I trial. For clinical use of ^{213}Bi, we developed a therapeutic dose-level ^{225}Ac/^{213}Bi generator device, approximately 1 cm by 6 cm in size,

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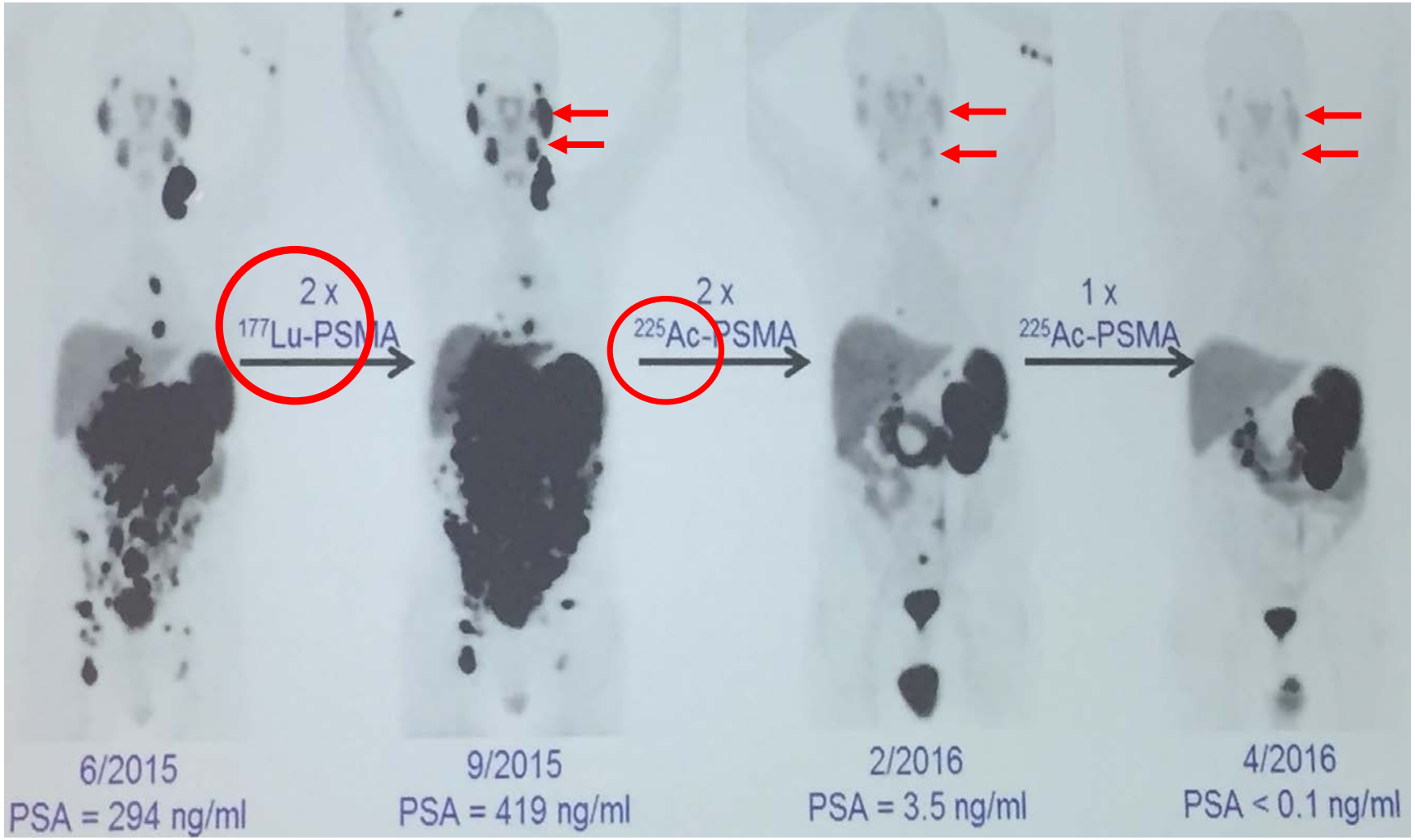
PSMA-617-Ac^{225} exceptional response

Patient-8
radical prostateectomy
radiotherapy of lymphnode metastasis
LHRH (leuprorelin)
LHRH (leuprorelin) + Bicalutamide 150mg/die
Docetaxel (11 cycles)
Cabazitaxel (10 cycles)
Arbiraterone
Enzalutamide - NOT TOLERATED

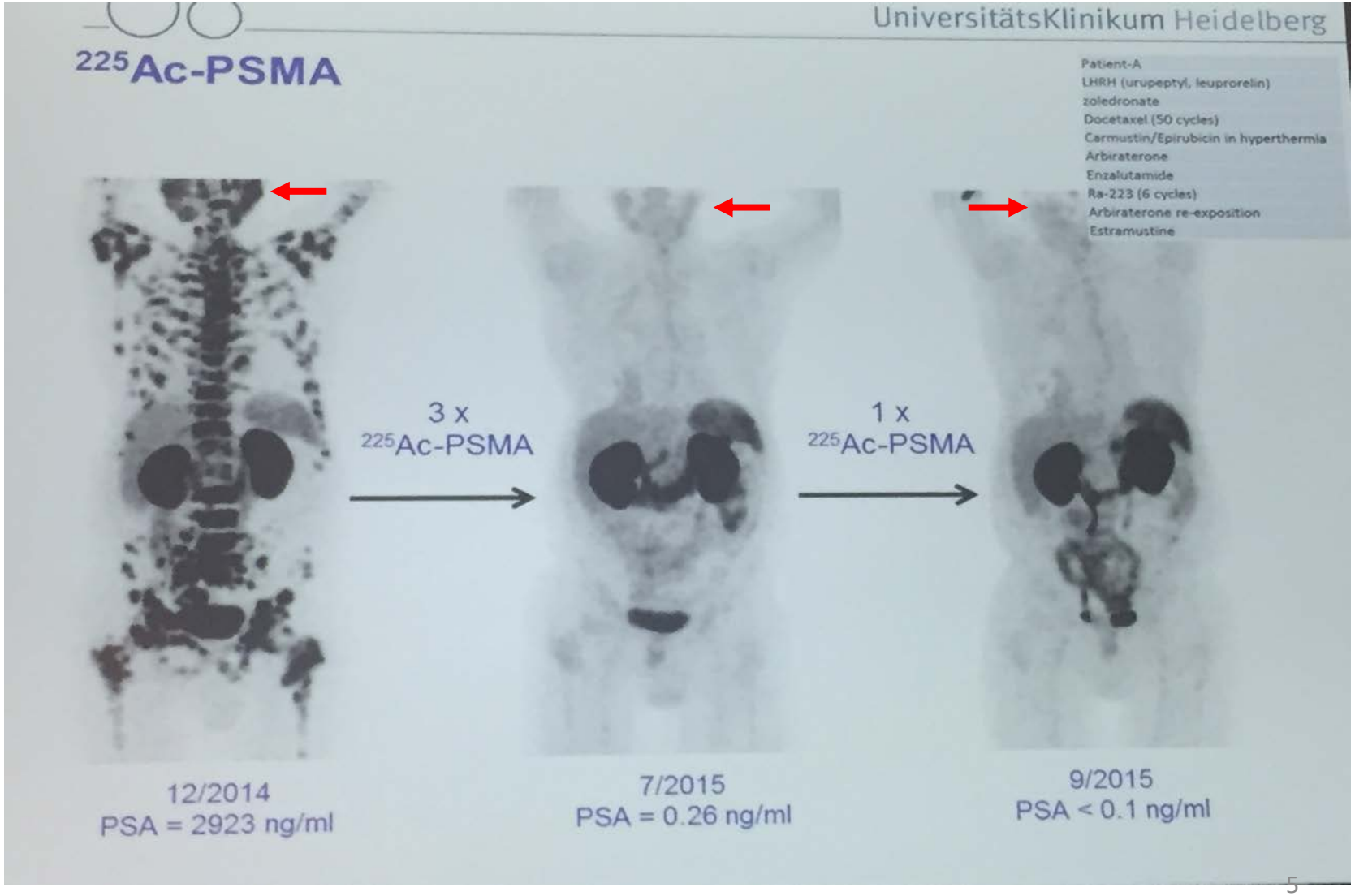


Haberkorn. Heidleberg

PSMA-617-Ac^{225} exceptional response…

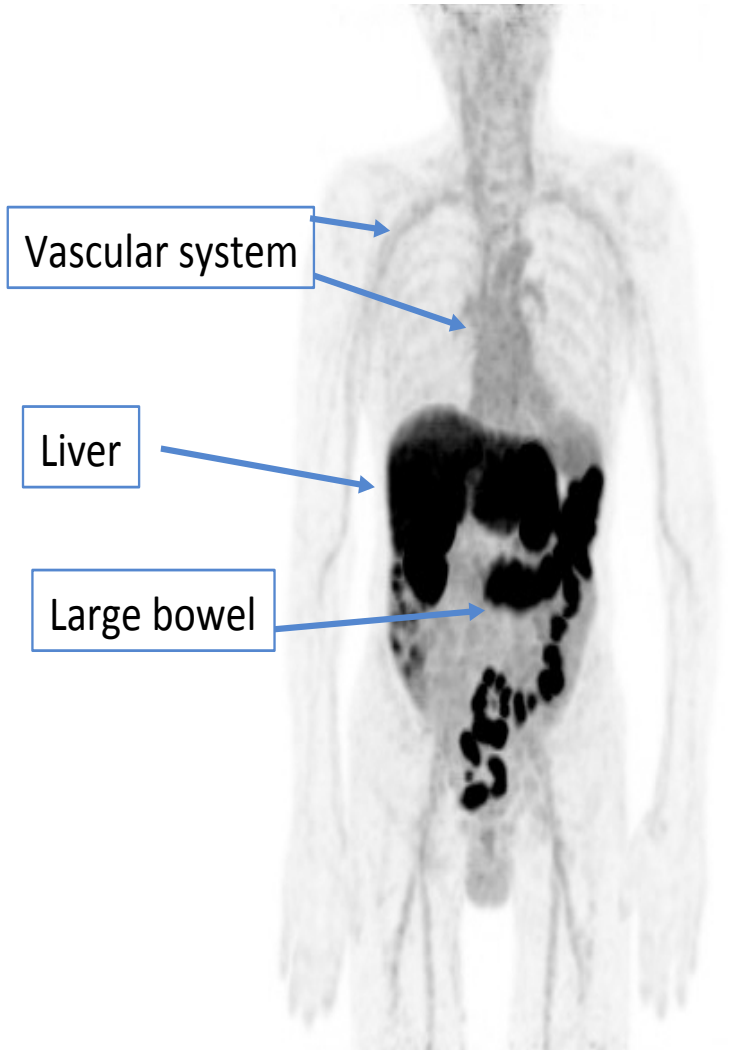
Salivary gland toxicity

High renal exposure



Haberkorn. Heidleberg

PSMA mAb J591 Bio-distribution



J591-Ac^{225} Single Ascending Dose Phase 1

Baseline Demographics (n=32)¥	
Age, median (range)	69.5 (52-89)
PSA, median (range)	149.1 (4.8-7168)
CALGB (Halabi) Prognostic Group, n (%)	
Low	1 (3.1%)
Intermediate	8 (25%)
High	23 (71.9%)
Sites of metastases, n (%)	
Bone	31 (96.9%)
Lymph node	28 (87.5%)
Liver	6 (18.8%)
Lung	5 (15.6%)
Prior therapy, n (%)	
≥ 2 potent AR inhibitors	25 (78.1%)
Chemotherapy	20 (62.5%)
Radium-223	9 (28.1%)
Sipuleucel-T	12 (37.5%)
PSMA-RL-Lu^{177}	14 (43.8%)

¥One pt enrolled in both dose-escalation and expansion

Cohort	Treatment Dose		n
	KBq/Kg	μCi/Kg	
1	13.3	0.36	1
2	26.7	0.72	1
3	40.0	1.08	1
4	53.3	1.44	1
5	66.7	1.80	6*
6	80.0	2.16	6
7	93.3	2.52	16

*Backfilled to gain additional info

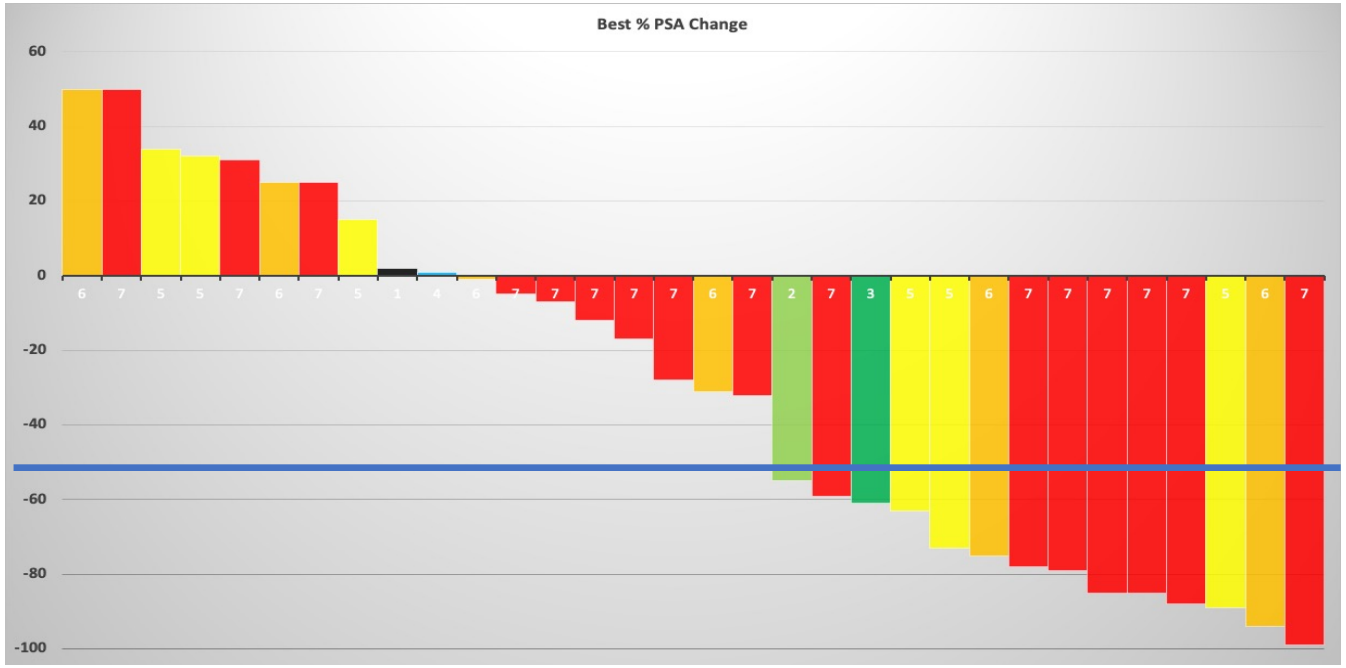
Dose Escalation Results:

- 1 of 6 in Cohort 6 (80 KBq/Kg) had DLT
  (Gr 4 anemia and Gr 4 thrombocytopenia)
- 0 of 6 in Cohort 7 had DLT
- **MTD not reached**
- **RP2D = 93.3 KBq/Kg**

Tagawa et al. ASCO 2021

PSA Response

- 69% experienced any PSA decline
- 44% with >50% PSA decline



Cohort 1 - Black
Cohort 2 - Light Green
Cohort 3 - Green
Cohort 4 - Blue
Cohort 5 - Yellow
Cohort 6 - Dark Yellow
Cohort 7 - Red

Design:

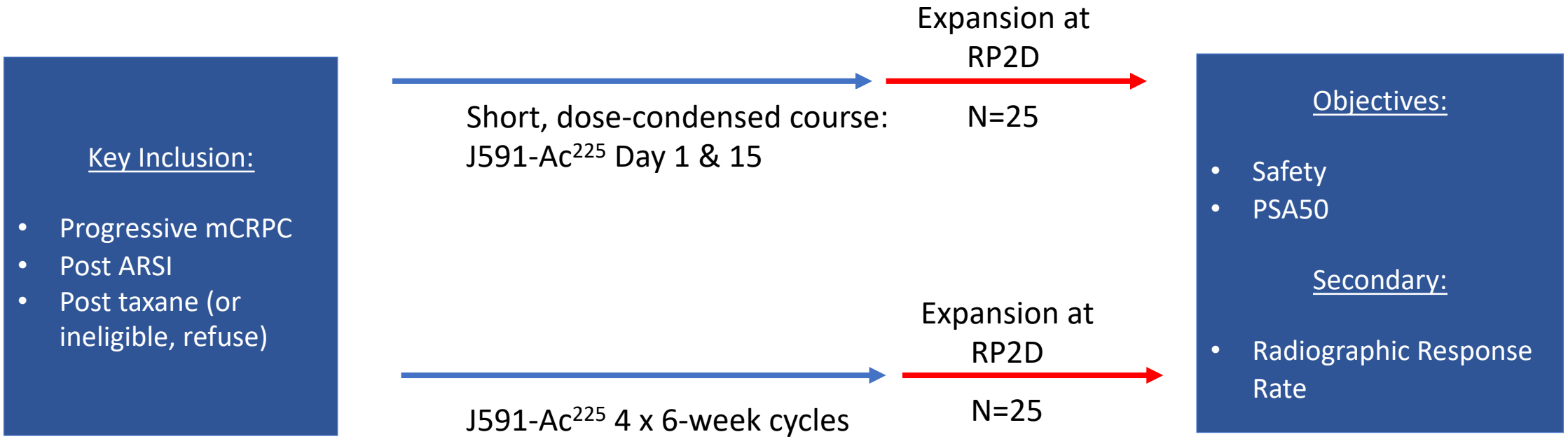
- **32 patients; NO PSMA imaging pre-selection used**
- One dose only; 7 escalating dose levels
- Heavily Pre-treated patients (eg, ARi, chemo)
- **44% relapsed/refractory to prior PSMA-617-Lu^{177}**
- **28% relapsed/refractory to prior Ra^{223}**

Results:

- Well-tolerated
- **PSA_{50} response = 14/32 (44%)**
- 1 DLT (platelets), MTD not reached
- 12 grade 1 xerostomia, 7 had prior 617-Lu^{177}
- Multi-dose trial underway

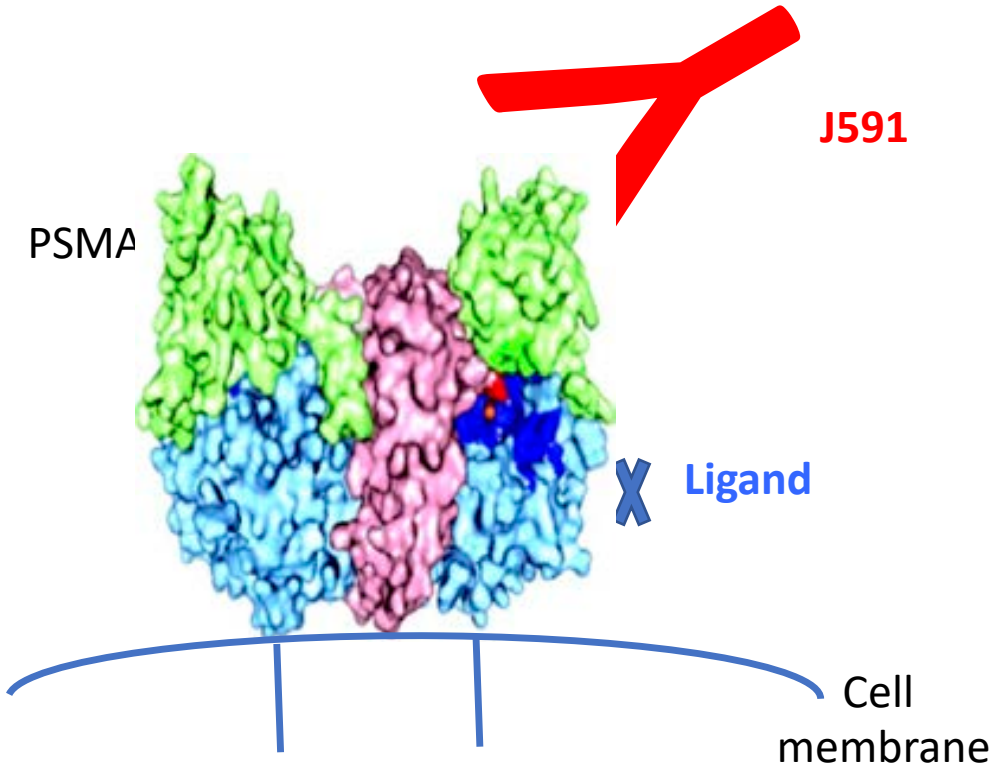
Tagawa et al. ASCO 2021

Multiple ascending dose J591-Ac^{225} Phase 1b / 2a



ClinicalTrials.gov Identifier: NCT04506567

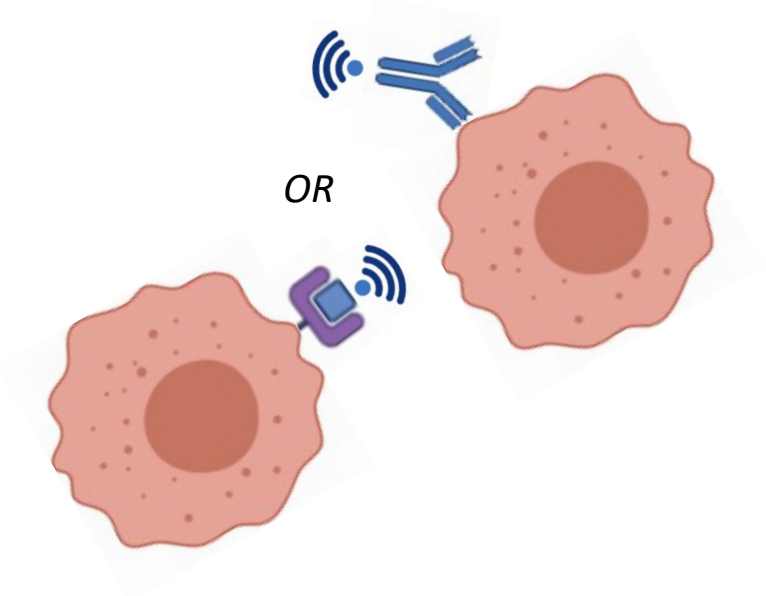
Both PSMA Small Molecule Ligand (SML) and J591 can bind PSMA/tumor simultaneously and additively



PSMA SML and J591 Bio-distributions and AE profiles are non-overlapping

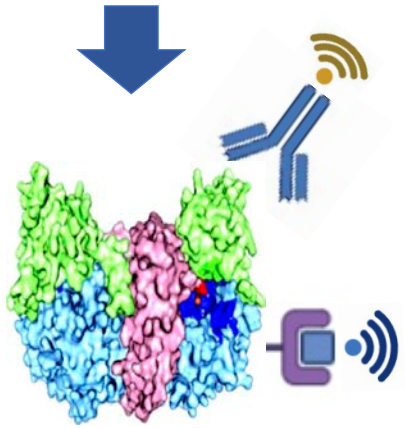
Weill-Cornell's differentiated approach

Others focus on *EITHER* RLs *OR* Abs



WCM recognized potential benefit of dual-targeting with Ab + RL (small molecule ligands)

- *Both* Ab *and* RL converge on the cancer
- No overlapping toxicity on normal tissue
- Each agent can carry a different payload



Substantially better anti-tumor efficacy with *NO* added side effects

PSMA RL plus J591=> SYNERGISTIC uptake

Antibody + RL targeting
Delivers SYNERGISTIC dose to tumor

Animal therapy study:
Synergy of alpha / beta RNT

Weill Cornell Medicine

Three Layers of Benefit from dual-targeted approach

1. Convergent Targeting => ***additive*** *dose to tumor* without increased toxicity

2. Ab **improves uptake and retention of RL** by tumor
   - Resulting dose to tumor is greater than sum of the parts

3. Addition of **α** to **β** radionuclide therapy:
   - Provides the additional potency & precision of **α**
   - Solves the limitations of RL-**β** treatment of small volume lesions

Source: O'Donaghue J et al. Relationships between Tumor Size and Curability for Uniformly Targeted Therapy with Beta-Emitting Radionuclides . *J Nucl Med.* 1995;36:1902-1909

Benefit of Ac^{225} plus Lu^{177} combination
One RNT compensates for the other

Sphere diameter (μm)	Absorbed energy (keV per decay)			
	^{90}Y	^{177}Lu	^{111}In	^{161}Tb
10,000	563	140	33.2	190
5,000	347	135	32.2	183
2,000	152	119	29.6	163
1,000	77.7	96.3	25.7	135
500	39.2	69.2	19.4	104
200	15.8	38.6	11.2	72.3
100	7.93	22.6	8.44	55.9
50	3.92	13.0	7.15	41.8
20	1.56	6.11	5.95	25.4
10	0.77	3.62	4.96	17.7

below PET visibility threshold

- The smaller the lesion, the more poorly it retains SML RNT
- This is exacerbated as Lu^{177} delivers radiation outside the tumor margin of small volume lesions
- Shorter range and more powerful effect of Ac^{225} overcomes this problem

Source: Hindie E. et al. *J Nucl Med.* 2016;57:759–764

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Benefit of adding α to β radionuclide therapy
RL-Lu^{177} undertreats small volume lesions

"The results of multi-modality imaging can be summarised as demonstrating remarkable responses in nodal and visceral disease, but a **pattern of ultimate progression in new sites of osseous disease** or **marrow infiltration**. We postulate that **^{177}Lu is less effective in targeting microscopic deposits of marrow disease**" (pg 832)

Hofman MS* et al. *Lancet Oncol.* 2018 19;825-833

"25% of patients showed **new LM [Lymph Node mets] despite response of existing lesions**."

Taeger P et al. *J Nucl Med* 2018 59;Suppl 1:523

"…three patients had a partial response, whilst four patients exhibited progressive disease due to **new lesions**."

Gafita A et al. *J Nucl Med* 2019 60:644-8

"After an initial response, patients predominantly progressed, with **new** focal or diffuse areas of involvement in the **bone**…"

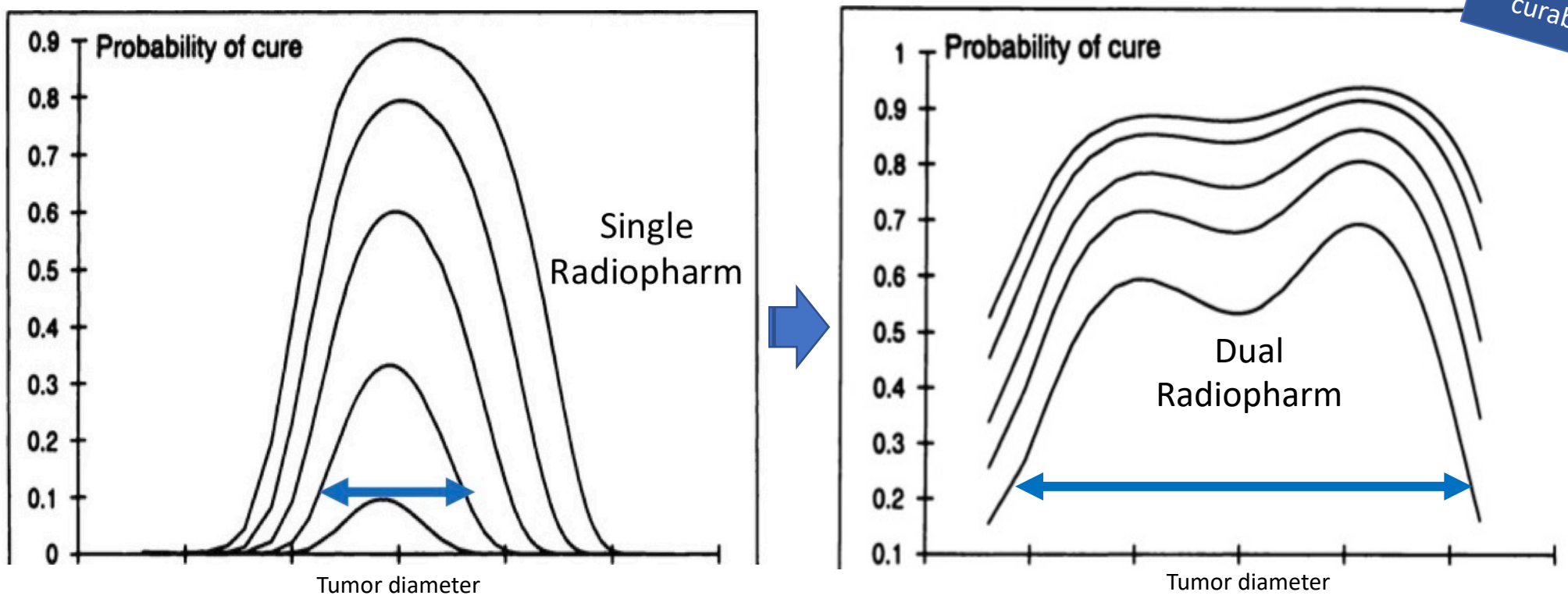
Violet J et al. *J Nucl Med* 2020; 61:857–865

Dual α (Ac^{225}) + β (Lu^{177}) radionuclide therapy

Provides potency & precision of α

Combining α + β particles extends "curability range"

- Any given radiopharm has its own optimal curability range.
- Combining 2 radiopharm agents can **extend** range of curability.



Source: O'Donaghue J et al. Relationships between Tumor Size and Curability for Uniformly Targeted Therapy with Beta-Emitting Radionuclides . *J Nuci Med.* 1995;36:1902-1909

Phase I/II study of ^{225}Ac-J591 plus ^{177}Lu-PSMA-I&T for progressive metastatic Castration-Resistant Prostate Cancer

In progress

ClinicalTrials.gov Identifier: NCT04886986