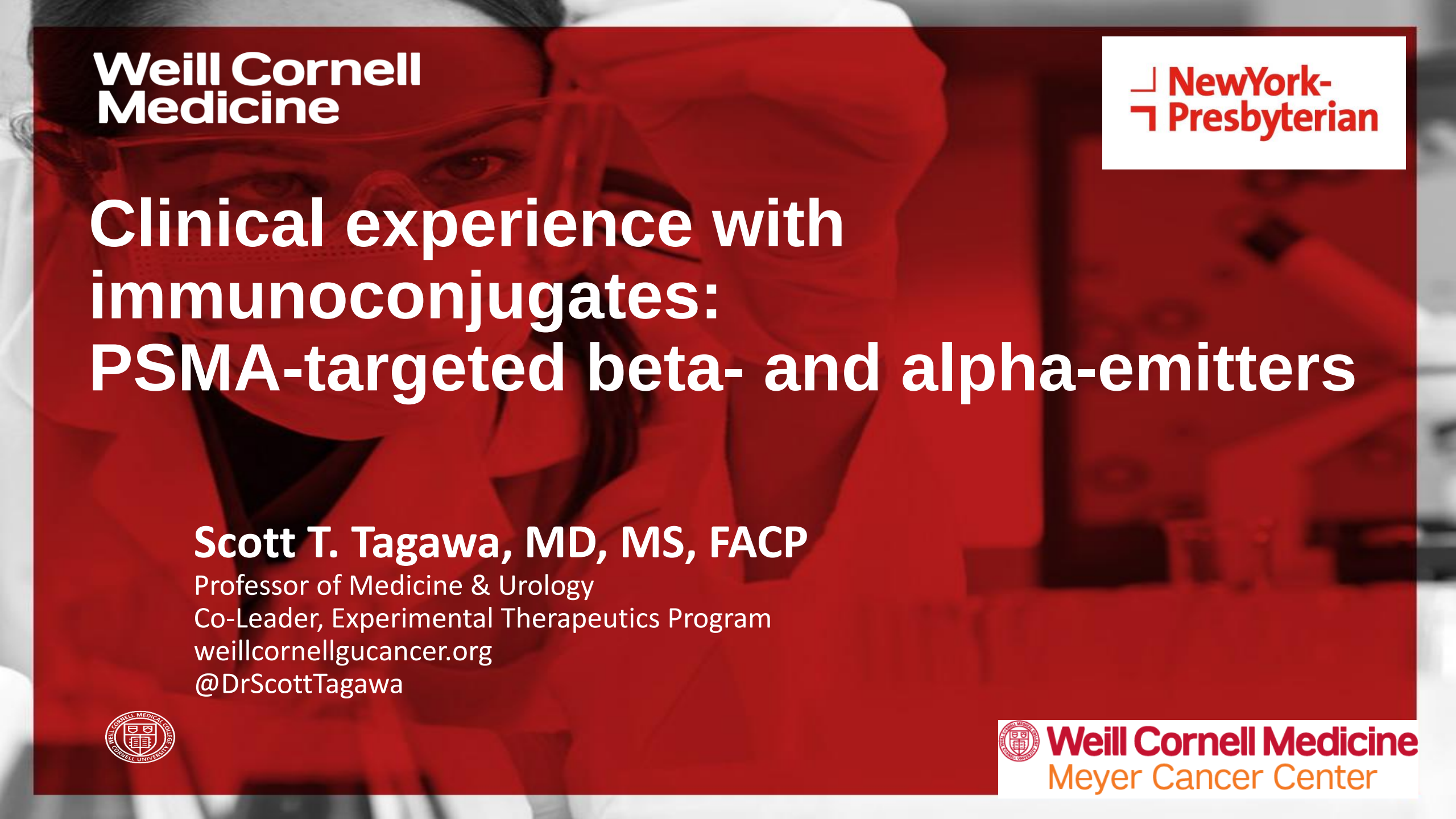

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NewYork-Presbyterian

Clinical experience with immunoconjugates: PSMA-targeted beta- and alpha-emitters

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Co-Leader, Experimental Therapeutics Program

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Weill Cornell Medicine
Meyer Cancer Center

Disclosures

- Research support (to Weill Cornell since 2007):
  - Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics, Dendreon, Lilly, Genentech, Newlink, BMS, Inovio, AstraZeneca, Immunomedics, Aveo, Rexahn, Atlab, Boehringer Ingelheim, Millennium, Bayer, Merck, Abbvie, Karyopharm, Endocyte, Clovis, Seattle Genetics, Novartis, Gilead, POINT Biopharma
- Paid Consultant (since 2007):
  - Sanofi, Medivation/Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm, Abbvie, Tolmar, Seattle Genetics, Amgen, Clovis, QED, Pfizer, AAA/Novartis, Clarity, Genomic Health, POINT Biopharma, Blue Earth, Alkido Pharma, Telix Pharma, Convergent Therapeutics, EMD Serono, Myovant
- Unpaid Consultant:
  - Atlab Pharma, Phosplatin Therapeutics, Amgen, Ambrx
- Patent:
  - Biomarkers for sacituzumab govitecan therapy (Immunomedics / Gilead / Weill Cornell)

Will discuss off-label use of approved drugs and investigational drugs in the context of clinical trials
Non-peer reviewed, unpublished data

Initial Radiolabeled J591 studies

- 2003-5: Initial (1st in human) studies of trace-labeled ^{111}In-DOTA-J591: demonstrated safety and targeting of J591 in men with mCRPC[1-3]
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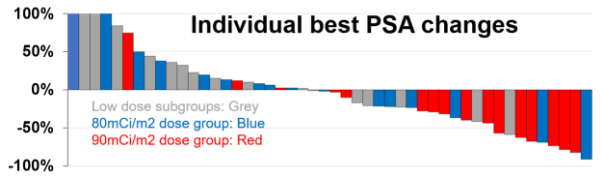
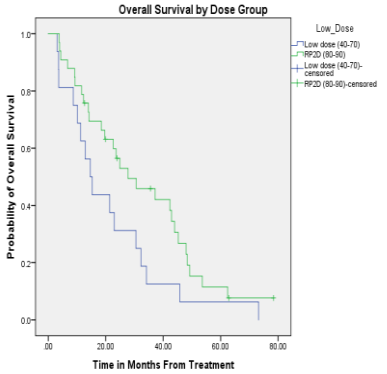
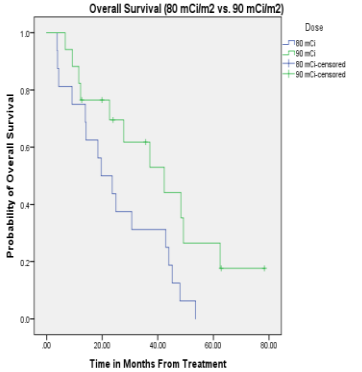
Dose response (and toxicity)

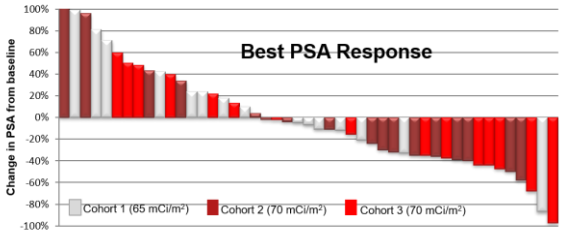
	Single Dose		Fractionated Dose		
Cumulative dose	65 mCi/m2	70 mCi/m2	40-70 mCi/m2	80 mCi/m2	90 mCi/m2
"n"	15	32	16	16	17
Any PSA decline	**46.7%**	**65.6%**	**37.5%**	**50.0%**	**87.5%**
≥30% PSA decline	13.3%	46.9%	12.5%	25.0%	58.8%
>50% PSA decline	6.7%	12.5%	6.3%	12.5%	29.4%
Median survival	**11.9 mo**	**21.8 mo**	**14.6 mo**	**19.6 mo**	**42.3 mo**
Platelets Gr 4	27.0%	56.3%	20.0%	43.8%	58.8%
Platelet transfusion	7.0%	41.0%	0.0%	31.3%	52.9%
Neutropenia Gr 4	0.0%	37.5%	0.0%	31.3%*	29.4%*
Febrile neutropenia	0.0%	2.1%	0.0%	0.0%	5.8%

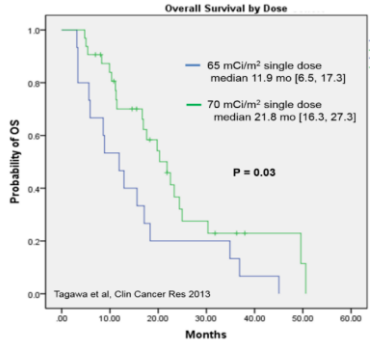
*GCSF allowed











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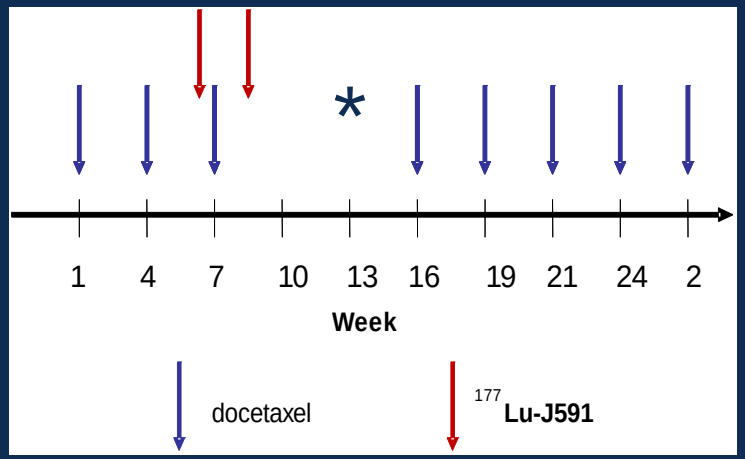
Clin Cancer Res 2013
Cancer 2019

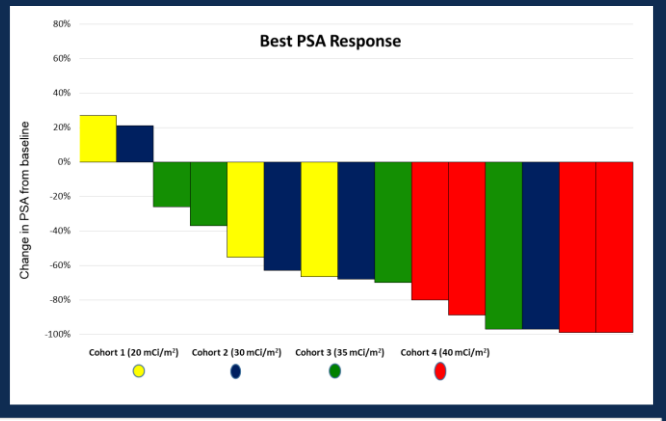
Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody ^{177}Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC)

Weill Cornell Medical College, New York, NY and **University of North Carolina**, Chapel Hill, NC

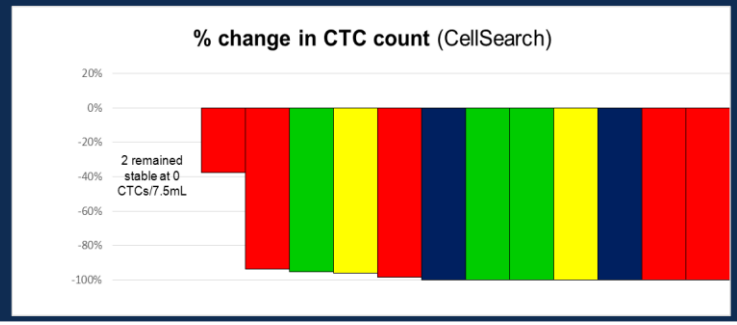
- The combination of fractionated-dose ^{177}Lu-J591 and docetaxel is safe in men with mCRPC
  - Including highest anticipated dose cohort: doce 75 mg/m2 + ^{177}Lu-J591 40 mCi/m^2 x2
- Without pre-selection for PSMA expression, accurate targeting of known sites of disease was observed on ^{177}Lu-J591 imaging



*Docetaxel #4 delivered minimum of 6 wks after docetaxel #3 and upon recovery of ANC>1500 and Plts > 100



73.3% with >50% PSA decline



100% with CTC count decline or persistently favorable CTC counts

Published as Batra et al, Urol Oncol 2020

PRESENTED AT:

ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

Radiolabeled β-DOTA-J591 Summary

- Accurate targeting in 89.1% [unselected population across studies]
- Dose response observed (PSA declines and overall survival)
- Clearance of CTCs (CellSearch) [91% control; 60% decline]
- Dose fractionation allows higher cumulative doses with less myelosuppression
  - Allows concurrent administration of docetaxel
- Predictable, reversible myelosuppression, ability to give subsequent chemo
  - **But most efficacious doses have the highest toxicity**

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8 – Clin Cancer Res 2013
9 – ASCO 2014
10 – Cancer 2019
11 – Frontiers in Oncology 2013

Ongoing ^{177}Lu-J591 studies

- Randomized study of keto/hydrocort + ^{177}Lu vs ^{111}In-J591 for nmCRPC (M0)
- Phase III ProstACT (TLX591)

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All with intermediate (some long)-term follow up
Planar/SPECT pre and/or post-treatment

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NewYork-Presbyterian

Phase I study of ^{225}Ac-J591 for men with metastatic castration-resistant prostate cancer

Scott T. Tagawa, Michael Sun, A. Oliver Sartor, Charlene Thomas, Sharon Singh, Mahelia Bissassar, Escarleth Fernandez, Muhammad J. Niaz, Benedict Ho, Shankar Vallabhajosula, John Babich, Ana M. Molina, Cora N. Sternberg, David M. Nanus, Joseph Osborne, Neil H. Bander

stt2007@med.cornell.edu

clinicaltrials.gov NCT03276572

Weill Cornell Medicine
Meyer Cancer Center

pcdtc The Prostate Cancer Clinical Trials Consortium

Tulane University
TULANE CANCER CENTER

Background

- PSMA is selectively overexpressed in PC with limited expression in other organs
  - Renal tubules, small intestine, salivary/lacrimal glands, neovasculature of solid tumors
- PSMA may be targeted with antibodies or small molecules with significant differences in kinetics and biodistribution
  - mAb = long circulation, non-specific exposure of bone marrow
  - Small molecule = renal, salivary/lacrimal, small bowel uptake
- Alpha emitters more potent with shorter range than beta
- ^{225}Ac-J591 completed radiochemistry and xenograft studies
- Hypothesis
  - mAb J591 will be able to deliver a potent alpha emitter to tumors without dose-limiting toxicity to other organs

Study Design and Procedures

- Entry Criteria Summary:
  - Progressive mCRPC (PCWG)
  - ECOG PS 0-2
  - Adequate organ function (incl neutrophils ≥2, platelets ≥150)
  - At least one prior potent AR pathway inhibitor and prior chemo (or ineligible/refuse)
  - Prior Ra223 and PSMA-TRT allowed
- Baseline CT/MRI, ^{99m}Tc-MDP bone scan, ^{68}Ga-PSMA11 PET/CT

  [eligible for treatment regardless of PSMA imaging results]
- Treatment: Single dose of ^{225}Ac-J591
- Up to 7 planned phase 1 dose-escalation cohorts followed by Simon 2-stage expansion cohort
- Initial single-subject cohorts until attributable Gr >1 AE or Cohort 5 (dose predicted to have moderate toxicity by dosimetry)
- **Definition of dose-limiting toxicity: attributable Gr > 2 non-heme toxicity or any grade > 3 heme toxicity**
- Monitoring: Weekly x2, then q2 wks, then q4 weeks to progression
- Follow up imaging with CT/MRI, bone scan, ^{68}Ga-PSMA11 PET/CT at 12 weeks, then CT/MRI & bone scan q12 wks until progression

Primary Phase 1 Endpoint = define dose-limiting toxicity and maximum tolerated dose

Secondary/Exploratory = CTCAE, PSA, CTC, survival, imaging, PRO, genomic and immune correlates

clinicaltrials.gov NCT03276572

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-TRT	14 (43.8%)

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¥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	6

*Backfilled to gain additional info

Dose Escalation Results:

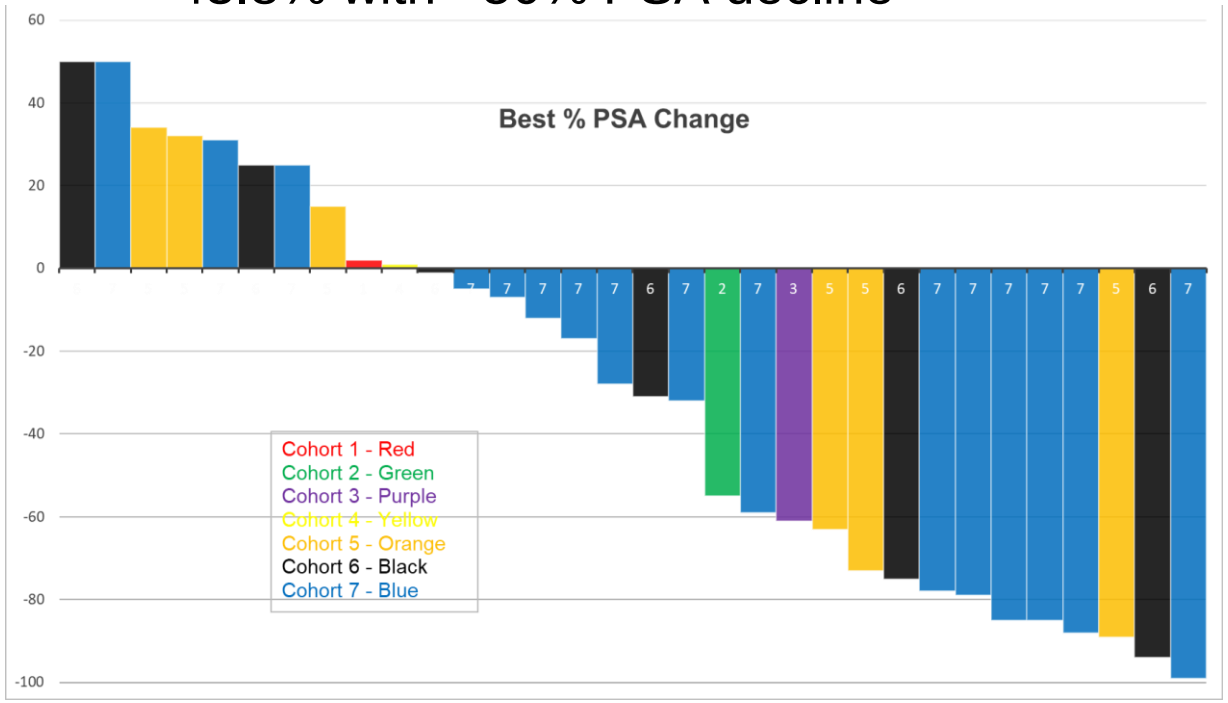
- 1 of 6 in Cohort 6 (80 KBq/Kg) had DLT
  (Gr 4 anemia and Gr 4 thrombocytopenia)
- 0 of 6 in Cohort 7 had DLT
- **No MTD achieved**
- **RP2D = 93.3 KBq/Kg**

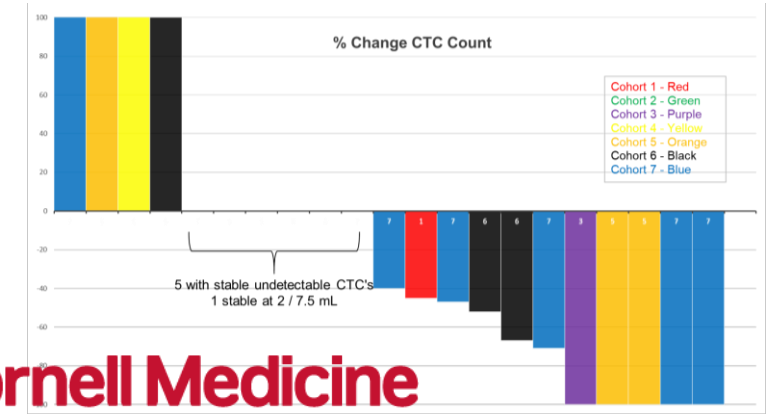
PSMA PET Results (n=28):

- SUVmax (single hottest lesion) 9.6 – 138.5
- 21 (75%) SUVmax > 5x liver SUVmean
- 2 (7.1%) SUVmax 2.5-5x liver SUVmean
- 5 (17.9%) SUVmax 1-2.5x liver SUVmean
- None with SUVmax < liver SUVmean

PSA Response

- 68.8% experienced any PSA decline
- 43.8% with >50% PSA decline





Treatment Emergent Adverse Events (with at least 10% incidence)	Gr 1/2 n (%)	Gr 3 n (%)	Gr 4 n (%)
Fatigue	24 (75%)	4 (12.5%)	0
Thrombocytopenia	20 (62.5%)	2 (3.6%)	3 (9.4%)
Anemia	16 (50%)	3 (9.4%)	1 (3.1%)
Pain	14 (43.8%)	1 (3.1%)	0
Nausea	14 (43.8%)	0	0
Neutropenia	9 (28.1%)	2 (6.3%)	1 (3.1%)
Xerostomia*	12 (37.2%)	0	0
Transaminitis	3 (9.4%)	1 (3.1%)	0

*7 of 12 with xerostomia with prior ^{177}Lu-PSMA

Median PFS 5.1 months [95% CI 4.0 – 9.3]
Median OS 11.1 months [95% CI 7.6 – 27.1]*

*n=31 for OS analysis, censoring for subject enrolled in both dose-escalation and expansion cohorts

CTC count (CellSearch) assessment
n=22 with paired counts baseline – 12 weeks:
- 11 (50%) decreased (40-100% decline)
- 5 (27%) stably undetectable (1 stable at 2)
- 4 (18.2%) increased

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Summary / Conclusions

- PSMA-targeted alpha emitter ^{225}Ac utilizing intact mAb J591 is well tolerated
  - Generally low-grade, temporary toxicity
- Early evidence of clinical activity including PSA and CTC count decline in heavily pre-treated population
  - Without selection by PSMA imaging and 44% with prior PSMA-TRT
  - No difference in PSA response with or without prior ^{177}Lu-PSMA
- Analysis of imaging, genomic, and immune correlates, and patient reported outcomes is ongoing

clinicaltrials.gov NCT03276572

Current ^{225}Ac-J591 studies

- Fractionated / multiple dose ^{225}Ac-J591
  - Fractionated = single cycle administered D1 & D15
    - ^{177}Lu-PSMA exposed and naïve cohorts
  - Multiple dose = infusion q6 weeks up to 4 cycles
- Re-treatment pilot
  - Single dose ^{225}Ac-J591, can be repeated >12 weeks later
- Combo ^{225}Ac-J591 with ^{177}Lu-PSMA I&T
- Randomized pembrolizumab and AR signaling inhibitor with or without single dose of ^{225}Ac-J591

- Planned addition of dosimetry in a subset of above
- Non-prostate solid tumor study in preparation