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NewYork-Presbyterian

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

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pcdtc The Prostate Cancer Clinical Trials Consortium

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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

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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

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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:

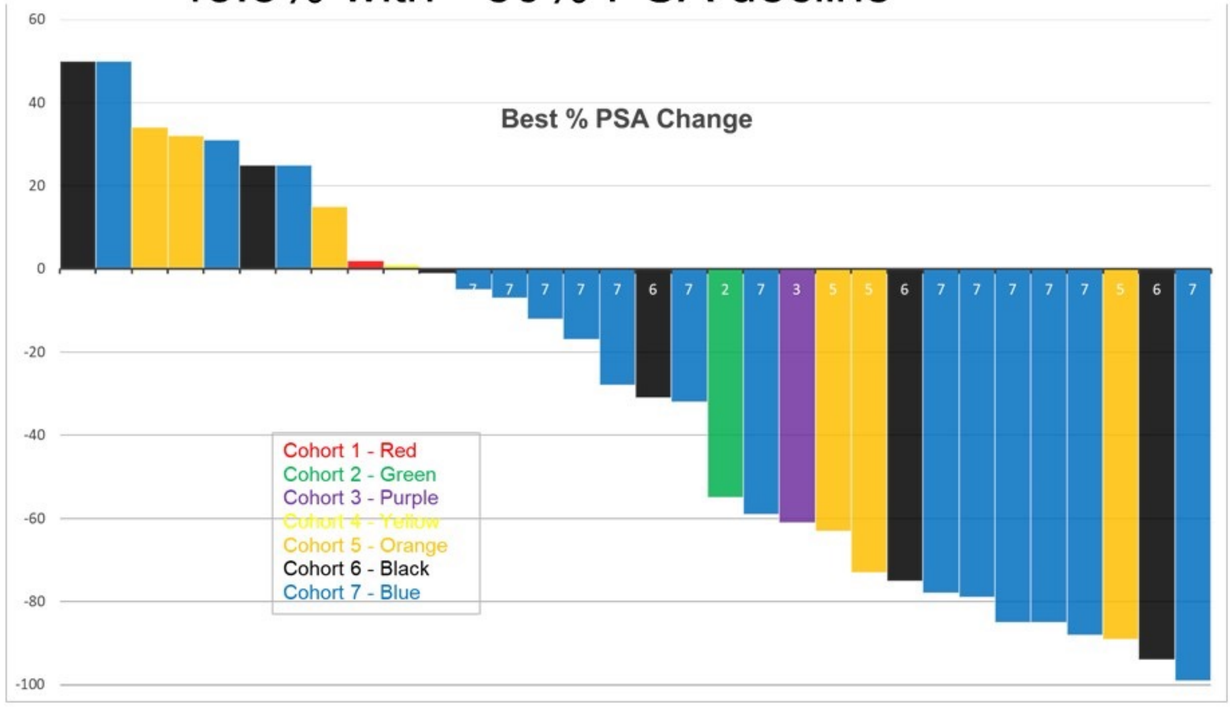
- 1 of 6 in Cohort 6 (80 KBq/Kg) had DLT
  (Gr 4 anemia and Gr 4 thrombocytopenia)
- 0 of 6 in Cohort 7 had DLT
- **No MTD achieved**
- **RP2D = 93.3 KBq/Kg**

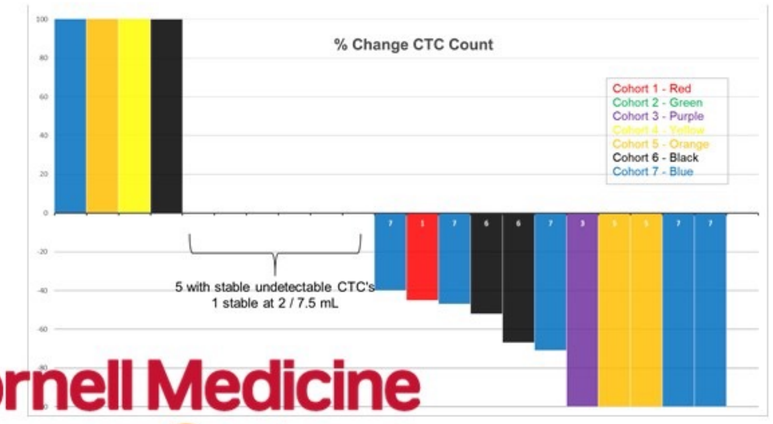
PSMA PET Results (n=28):

- 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
- Analysis of imaging, genomic, and immune correlates, and patient reported outcomes is ongoing
- Additional studies with ^{225}Ac-J591 underway or planned for 2021
  - Fractionated therapy, multiple doses, re-treatment, combo with ^{177}Lu-PSMA I&T, randomized combo with pembrolizumab and AR signaling inhibitor

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