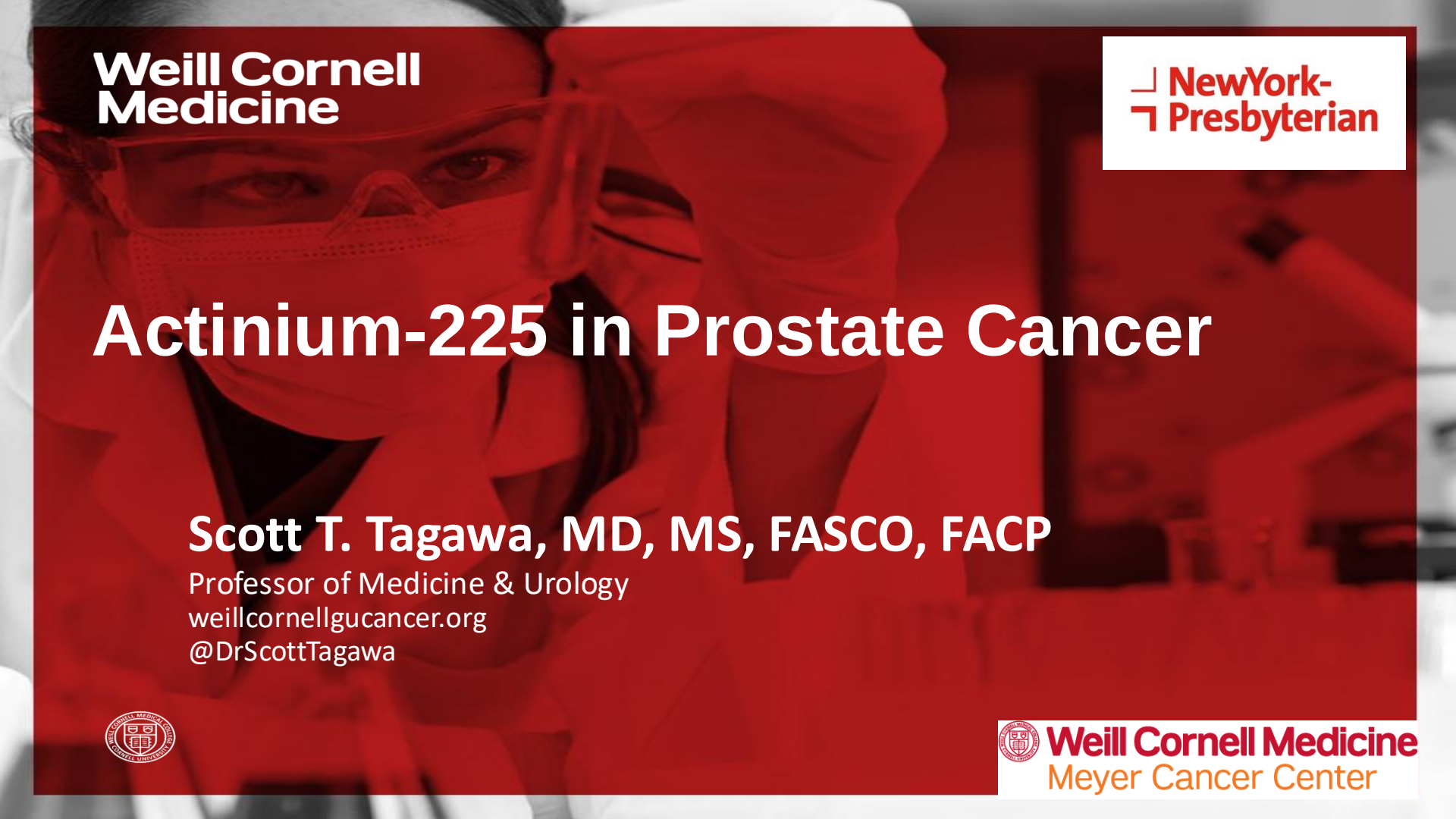

Weill Cornell Medicine

NewYork-Presbyterian

Actinium-225 in Prostate Cancer

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Meyer Cancer Center

Critical Differences in Alpha- and Beta-Particles

Alpha **Beta**

	α	β
Relative particle mass	**7300**	**1**
Initial energy (MeV) per particle	**3-8**	**0.01-2.5**
Range in tissue (μm)	**40-100**	**50-5000**
LET (KeV/μm)	**60-230**	**0.015-0.4**
DNA hits to kill cells	**1-10**	**100-1000**

LET, linear energy transfer.

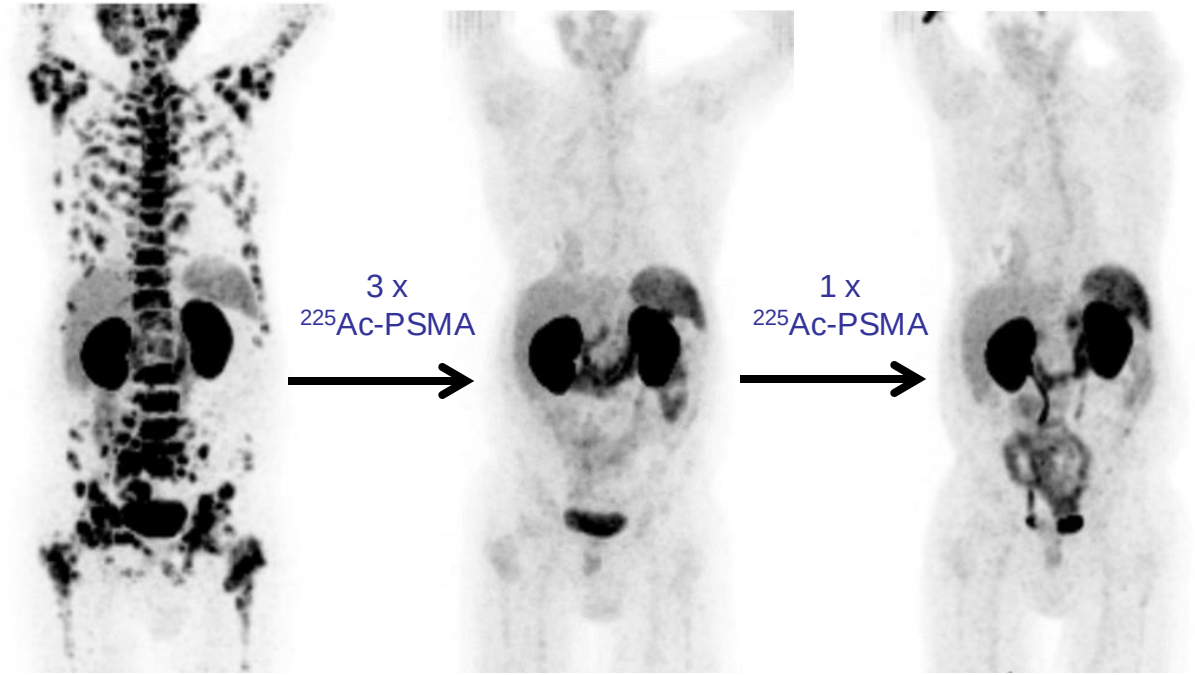
Actinium-225 = 4 alpha emissions (also 2 gamma and beta)

Henriksen G et al. *J Nucl Med*. 2003;44(2):252–259.

Targeted alpha's for PC (partial list)

- **Radium-223 dichloride**
- ^{225}Ac-J591 (aka Conv-01α)
- BAY 2315497 (^{227}Th-pelgifatamab) - dead
- ^{225}Ac-PSMA-617 – early Ph 1 EANM, Ph 3 planned
- ^{225}Ac-PSMA-I&T – TACIST beyond Houston, Ph 3 planned
- ^{25}Ac-PSMA-R2
- ^{225}Ac-pelgifatamab (BAY3546828) – Ph 1 in Europe
- ^{225}Ac-PSMA-trillium (BAY3563254) – AACR 2024, Ph 1 in Europe
- ^{212}Pb-ADVC001 – Ph 1
- JNJ-69086420 (^{225}Ac hK2) – ASCO 2024, redesign

^{225}Ac-PSMA-617 case reports



12/2014
PSA = 2923 ng/ml

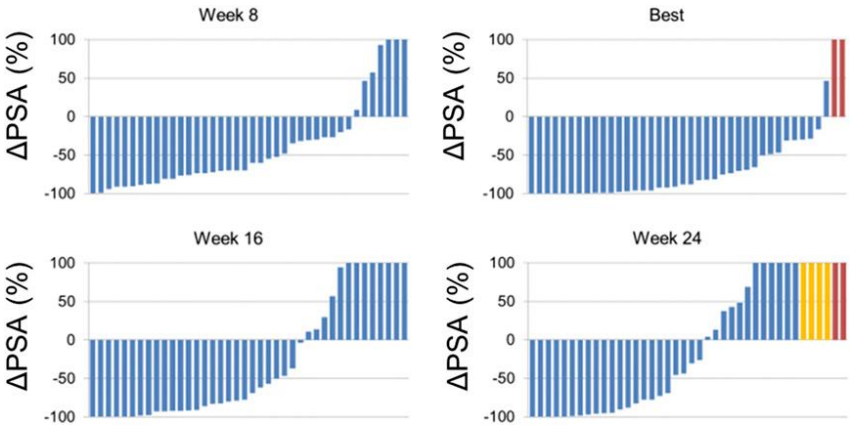
7/2015
PSA = 0.26 ng/ml

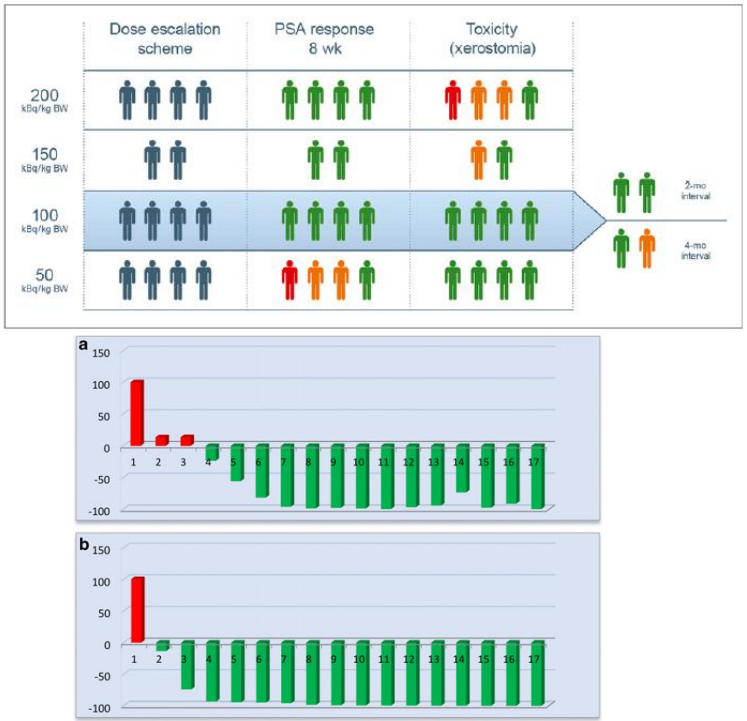
9/2015
PSA < 0.1 ng/ml

Patient-A
LHRH (urupeptyl, leuprorelin)
zoledronate
Docetaxel (50 cycles)
Carmustin/Epirubicin in hyperthermia
Arbiraterone
Enzalutamide
Ra-223 (6 cycles)
Arbiraterone re-exposition
Estramustine

Kratochwil et al J Nuc Med 2016

^{225}Ac-PSMA-617:
Retrospective from Germany and South Africa

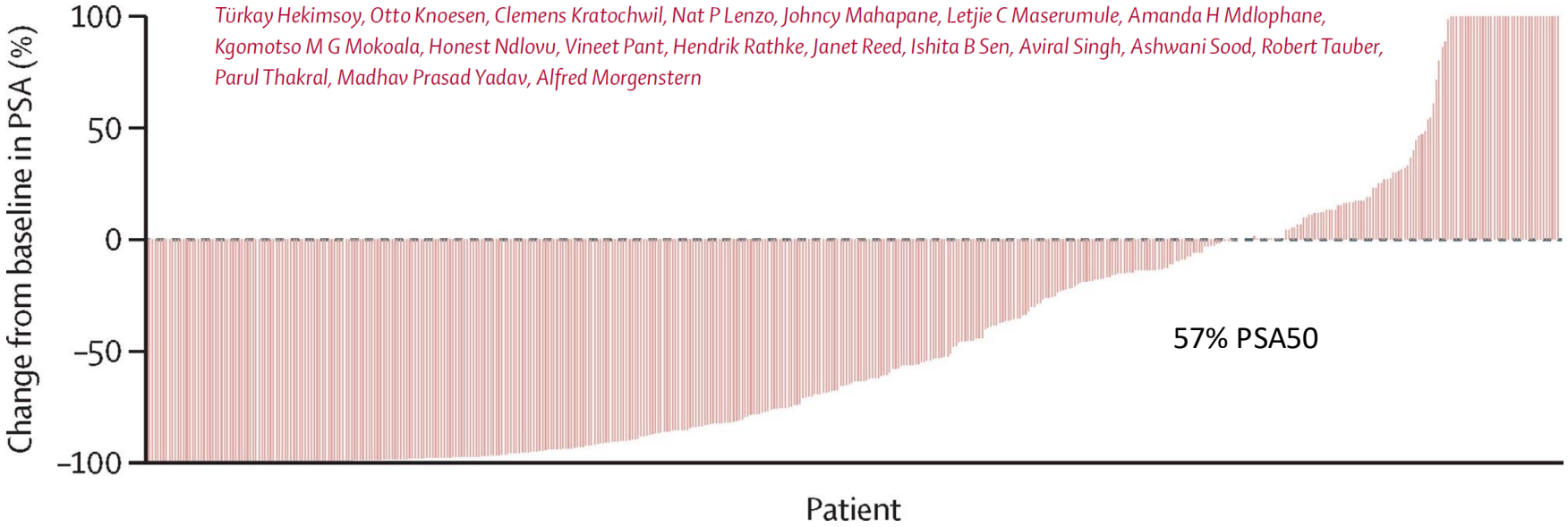




Kratochwil et al J Nuc Med 2017
Kratochwil et al J Nuc Med 2018
Sathekge et al, Eur J Nucl Med Mol Imaging 2018

Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study

Mike M Sathekge, Ismaheel O Lawal, Chandrasekhar Bal, Frank Bruchertseifer, Sajana Ballal, Giuseppe Cardaci, Cindy Davis, Mathias Eiber, Türkay Hekimsoy, Otto Knoesen, Clemens Kratochwil, Nat P Lenzo, Johncy Mahapane, Letjie C Maserumule, Amanda H Mdlophane, Kgomotso M G Mokoala, Honest Ndlovu, Vineet Pant, Hendrik Rathke, Janet Reed, Ishita B Sen, Aviral Singh, Ashwani Sood, Robert Tauber, Parul Thakral, Madhav Prasad Yadav, Alfred Morgenstern

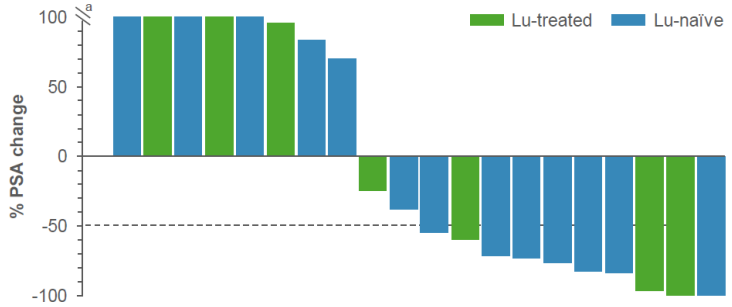


Leukopenia in 18.2% at baseline → 44.5% after treatment
Thrombocytopenia in 30.7% at baseline → 53.4% after treatment
Chart data available in 71% - of those, 68% with xerostomia after cycle 1, 86% after cycle 2, 91% after cycle 3

Sathekge et al, Lancet Oncol 2024

^{225}Ac-PSMA-I&T (FPI-2265) TACIST trial

Figure 4. Maximum percent PSA change from baseline during the treatment period (weeks 0–28) by prior Lu treatment



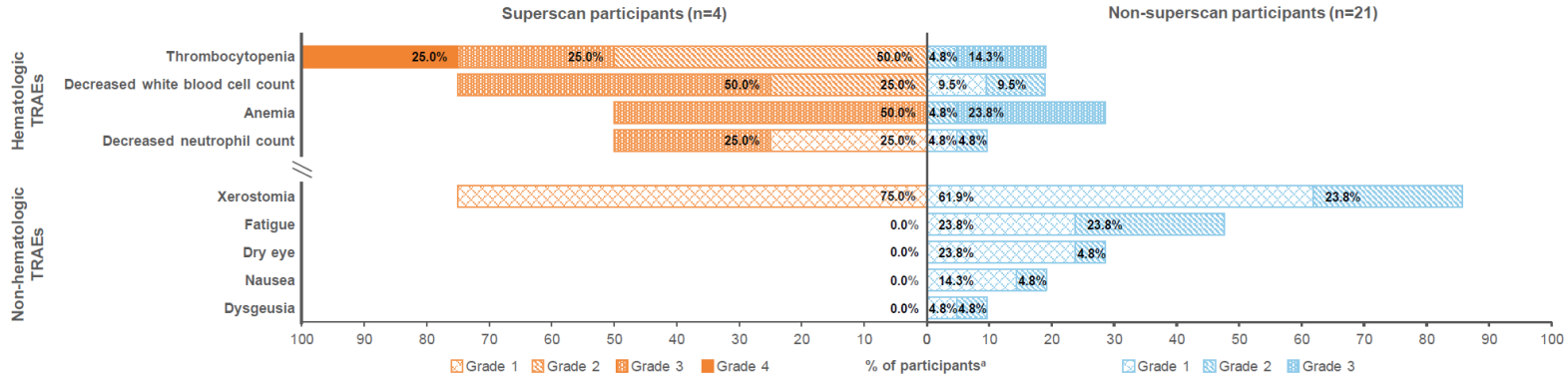
[a]% maximum PSA increase shown to 100%.

Table 4. Independent reviewer response by RECIST v1.1 criteria

Best Response by RECIST v1.1	Participants Evaluable by RECIST 1.1 (n=9)
PR, n (%)	3 (33)
SD, n (%)	4 (44)
PD, n (%)	2 (22)

PD, progressive disease; SD, stable disease.

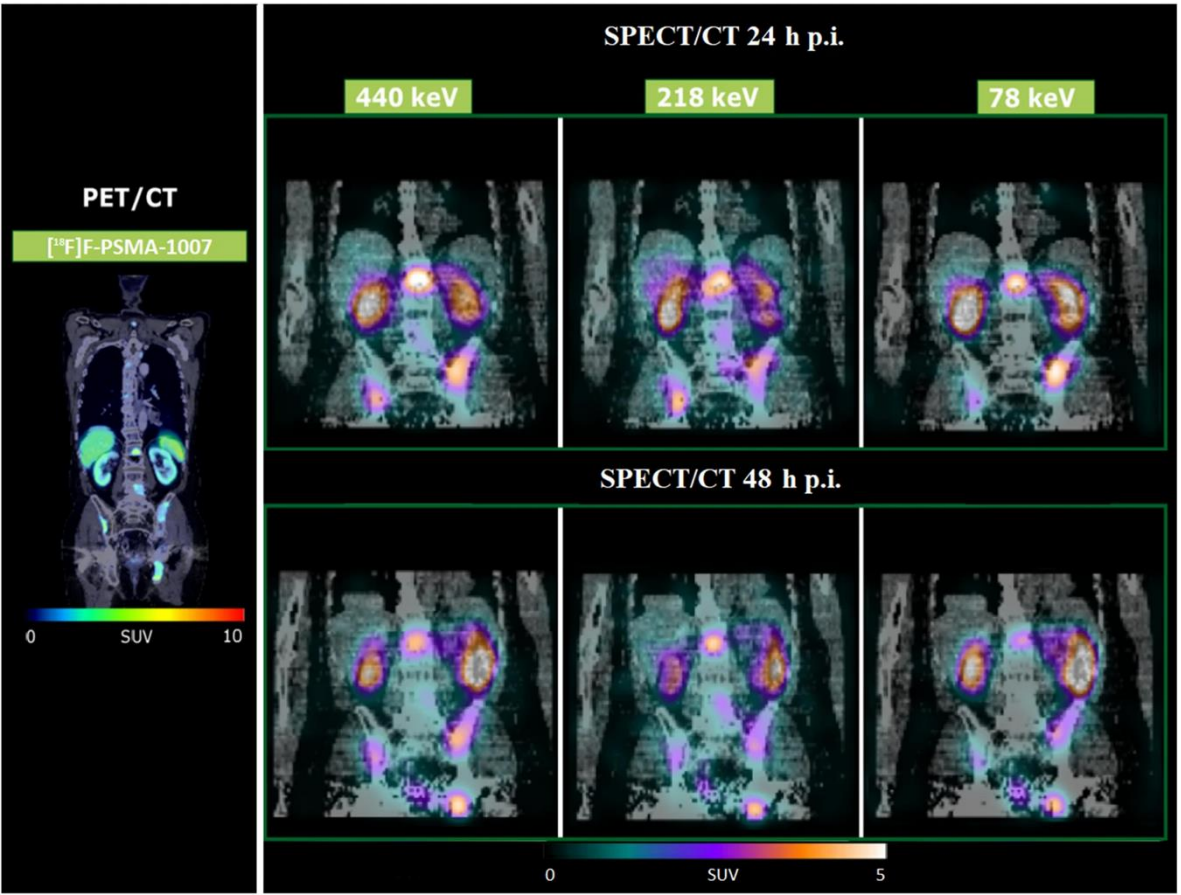
Figure 6. TRAEs occurring in >10% of participants (safety population)

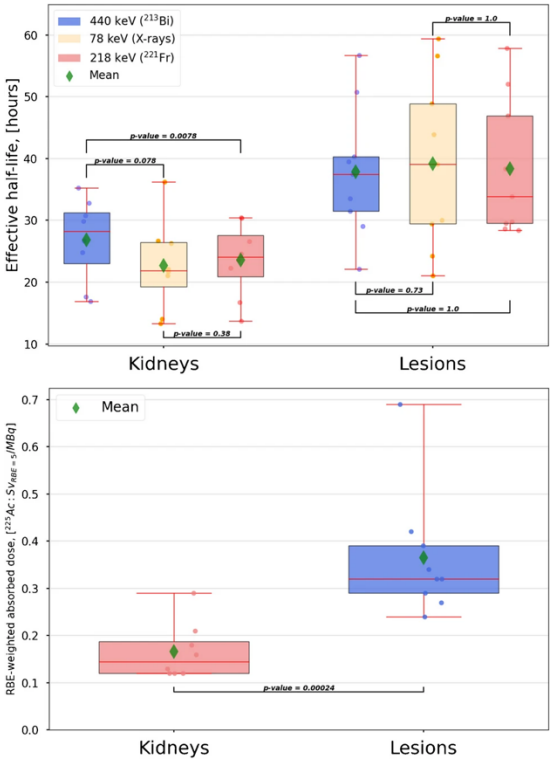


[a]Participants were counted once in a preferred term category for the worst severity if >1 event occurred in that category.

Delpassand et al, AACR 2024

Image-based dosimetry for 225Ac-PSMA-I&T and the effect of daughter-specific pharmacokinetics





Liubchenko et al, EJNMMI 2024

AcTION: A phase 1 study of 225Ac-PSMA-617 for PSMA-positive mCRPC with or without prior 177Lu-PSMA-617

Approximately 60 patients

Key inclusion criteria
- Confirmed diagnosis of mCRPC with disease progression on prior treatment
- ECOG performance status 0–2
- PSMA-positive by ^{68}Ga-PSMA-11[a] PET/CT scan (within 28 days of study entry)
  - PSMA-positive soft tissue or visceral disease

Key exclusion criteria
- PSMA-negative disease at baseline in any of the following regions:
  - One or more PSMA-negative lymph nodes > 2.5 cm
  - Bone metastasis with a PSMA-negative soft tissue component > 1 cm
  - PSMA-negative solid organ metastases ≥ 1 cm
- Previous treatment with bone-targeting radiopharmaceuticals

Group A (n = ~20)
- Prior chemotherapy and a novel ARPI
- No prior ^{177}Lu-PSMA radioligand therapy

Group B (n = ~20)
- No prior chemotherapy or novel ARPI
- No prior ^{177}Lu-PSMA radioligand therapy

Group C (n = ~20)
- Prior ^{177}Lu-PSMA radioligand therapy
- Prior chemotherapy and/or ARPI not required

Primary endpoint
- Recommended phase 2 dose and schedule of administration

Secondary endpoints
- Safety and tolerability
- Anti-tumour activity
  - RECIST 1.1 response rate (ORR, DOR, DCR)
  - PFS (radiographic, clinical, PSA)
  - Biochemical response (PSA, ALP, LDH)
- Health-related quality of life (FACT-P, BPI-SF, EQ-5D-5L and XeQOLS)

Exploratory endpoint
- Correlation between repeat ^{68}Ga-PSMA-11 PET/CT scans and ^{225}Ac-PSMA-617 anti-tumour activity

[a][^{68}Ga]Ga-PSMA-11.

ALP, alkaline phosphatase; ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory – Short Form; CT, computed tomography; DCR, disease control rate; DOR, duration of response ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; FACT-P, Functional Assessment of Cancer Therapy – Prostate; LDH, lactate dehydrogenase; ORR, objective response rate; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; XeQOLS, Xerostomia Quality of Life Scale.

Sathekge et al

Group A
- Prior chemotherapy and a novel ARPI
- No prior ^{177}Lu-PSMA radioligand therapy

	4 MBq[a] (n = 3)		6 to 4 Mbq[a,b] (n = 3)		6 MBq[a] (n = 1)		8 MBq[c] (n = 4)		10 MBq[c] (n = 3)		Total (n = 14)
	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades
Any AE, n (%)	3 (100.0)	0 (0)	3 (100.0)	1 (33.3)	1 (100.0)	0 (0)	4 (100)	0 (0)	2 (66.7)	0 (0)	13 (92.9)
Dry mouth, n (%)	1 (33.3)	0 (0)	2 (66.7)	0 (0.0)	1 (100.0)	0 (0)	3 (75.0)	0 (0)	2 (66.7)	0 (0)	9 (64.3)
Fatigue	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)	1 (33.3)	0 (0)	7 (50.0)
Nausea, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (50.0)	0 (0)	0 (0)	0 (0)	2 (14.3)

Group B
- No prior chemotherapy or novel ARPI
- No prior ^{177}Lu-PSMA radioligand therapy

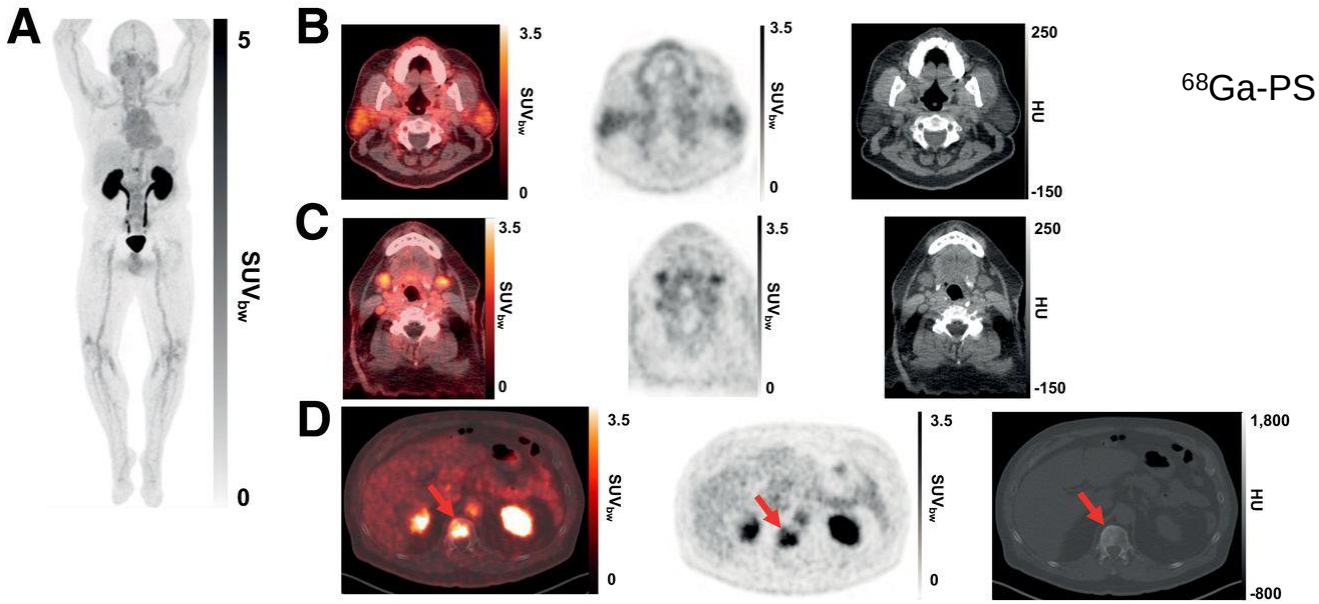
	4 MBq[a] (n = 3)		6 to 4 Mbq[a,b] (n = 3)		8 MBq[c] (n = 3)		Total (n = 9)
	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades
Any AE, n (%)	3 (100.0)	0 (0)	3 (100.0)	0 (0)	3 (100.0)	0 (0)	9 (100.0)
Dry mouth, n (%)	3 (100.0)	0 (0)	3 (100.0)	0 (0)	3 (100.0)	0 (0)	9 (100.0)
Urinary tract infection, n (%)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22.2)

Group C
- Previous ^{177}Lu-PSMA radioligand therapy
- Prior chemotherapy and/or ARPI not required

	4 MBq (n = 3)		8 MBq[a] (n = 6)		10 MBq (n = 6)		Total (n = 15)
	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades	Grades ≥ 3	All grades
Any AE, n (%)	3 (100.0)	1 (33.3)	6 (100.0)	1 (16.7)	6 (100.0)	1 (16.7)	15 (100.0)
Dry mouth, n (%)	3 (100.0)	0 (0.0)	5 (83.3)	0 (0.0)	5 (83.3)	0 (0.0)	13 (86.7)
Nausea, n (%)	2 (66.7)	0 (0.0)	3 (50.0)	0 (0.0)	3 (50.0)	0 (0.0)	8 (53.3)
Fatigue, n (%)	0 (0.0)	0 (0.0)	5 (83.3)	0 (0.0)	3 (50.0)	0 (0.0)	8 (53.3)
Decrease appetite, n (%)	1 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	4 (26.7)
Anaemia, n (%)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	3 (20.0)
Diarrhoea, n (%)	1 (33.3)	1 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Neutropenia, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	2 (13.3)

Trial
[a]Part
AE, a

Sathekge et al

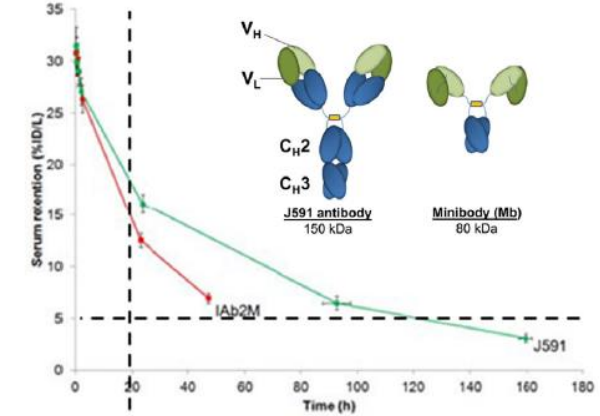


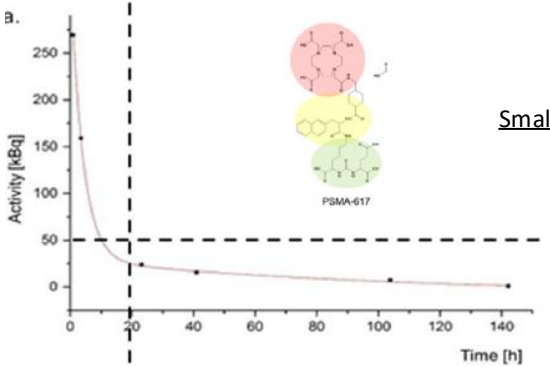
^{68}Ga-PSMA-R2

- SatisfACtion: Phase I/II, Open-label, Multi-center Study of [225Ac]Ac-PSMA-R2 in Men With mHSPC and Heavily Pre-treated PSMA-positive mCRPC, With/Without Prior 177Lu-labelled PSMA-targeted Radioligand Therapy
- ClinicalTrials.gov Identifier: NCT05983198
- Novartis Reference Number: CAAA802A1210

Lindenberg et al, J Nuc Med 2025

Antibody vs Small Molecule

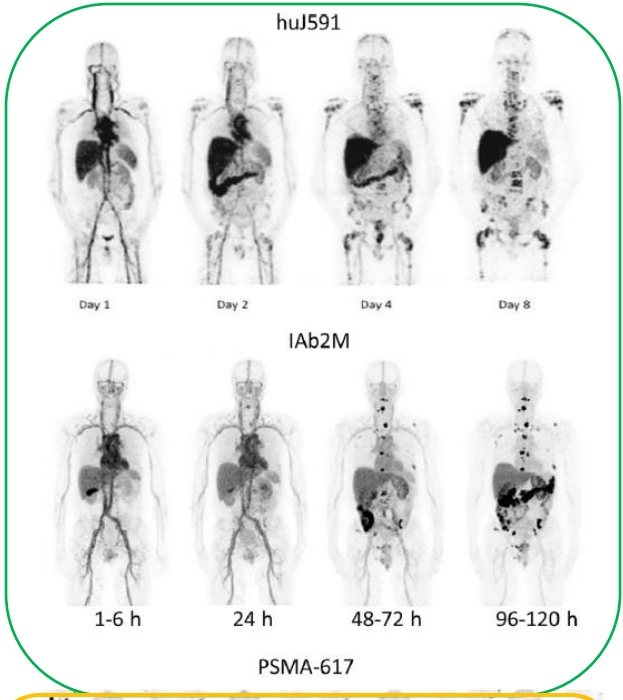


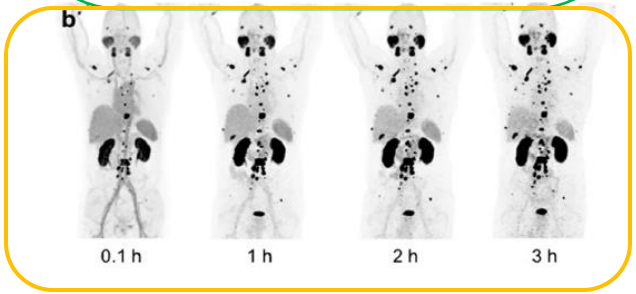


Small molecule
1 kDa

- Large size → in blood for **days**
  - *Optimal imaging days later*
- Target via blood vessels
- Exposure / Predicted side effects:
  - Infusion reaction
  - Off tumor exposure
    - **Bone marrow** (myelosuppression)
    - **Liver**

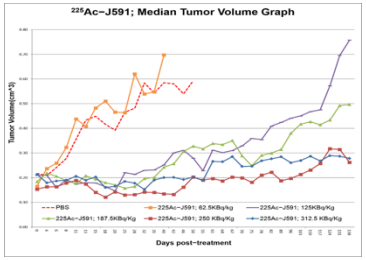
- Small size → in blood for **hours**
  - *Optimal imaging within hours*
- Rapidly penetrate tissues
- Exposure / Predicted side effects:
  - Non-tumor PSMA uptake:
    - **Kidney**
    - **Salivary glands** (dry mouth, altered tase)
    - **Lacrimal glands** (dry eye)
    - **Small intestine** (nausea)





Kratochwil C et al. *Sem Nuc Med.* 2019;49(4):313-325.

Phase I ^{225}Ac-J591



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%)

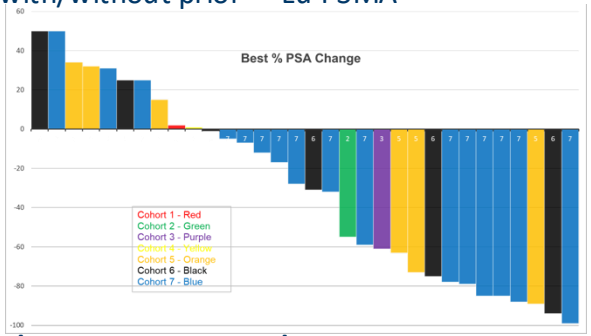
¥One pt enrolled in both dose-escalation and expansion

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**

PSA Response

- 68.8% experienced any PSA decline
- 46.9% with >50% PSA decline at any time
  - Similar with/without prior ^{177}Lu-PSMA



Additional ongoing studies

- Fractionated & multiple dose; re-treatment
- Pembro/ARSI +/- ^{225}Ac-J591

J Clin Oncol 2023

Ph 1 Fractionated/Multiple Cycle Rationale and Study Design

Fractionated Dose (single cycle)
Principle: Maximize dose intensity, limit resistance (repopulation)
Successful with ^{177}Lu-J591[1] (now Ph 3 NCT04876651) and ^{177}Lu-PSMA-617[2] (now Ph 3 NCT06320067)
Regimen = single fractionated cycle administered on D1 and D15[3]

Dose Level	KBq/kg	# of Patients
1	45	3
2	55	7
3	65	6
2.5	60	7
*Post 177Lu**	*50*	*4*

Multiple Cycles
Typical empiric dosing of radionuclides
Potential for combination (scientific rationale for combining α + β and mAb + SML
Regimen = 6 week intervals (up to 4)

Dose Level	KBq/kg	# of Patients
1	65	6
-1	55	6
-2	45	6

- Definition of Dose-Limiting Toxicity
  - Grade 4 neutropenia or any febrile neutropenia
  - Grade 4 thrombocytopenia or Gr 3 thrombocytopenia with major bleeding
  - Grade >2 non-heme toxicity at least possibly related to ^{225}Ac-J591
  - Any grade attributable toxicity that delays subsequent treatment
    - Fractionated cohort: delay in D15 treatment by more than 2 weeks
    - Multiple cycle cohort: delay in cycle 2 or cycle 3 by more than 3 weeks
  - DLT assessment period
    - Fractionated = 8 weeks; multiple = minimum of 6 weeks after cycle 2

1 - *Cancer* 2019; 125: 2561-2569
2 - ESMO 2022 / ASCO 2024
3 – Nauseef et al, AACR 2023

Dose-Limiting Toxicity / RP2D

Fractionated Dose
Dose-Limiting Toxicity

Cohort	KBq/kg	DLT
3	65	G4 TCP
3	65	G2 TCP delaying D15 >2 weeks
2.5	60	G4 TCP

Recommended phase II dose:
60 KBq/kg on D1 and D15
(total 120 KBq/kg)

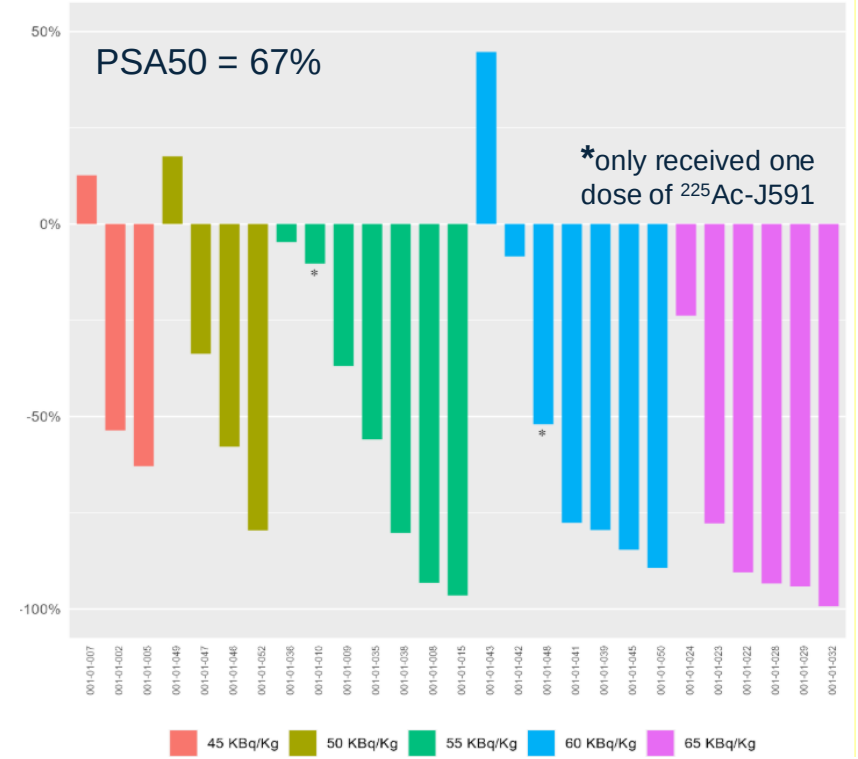
Multiple Cycle
Dose-Limiting Toxicity

Cohort	KBq/kg	DLT
1	65	G3 TCP delaying C3 >2 weeks
1	65	G1 TCP delaying C3 >2 weeks
-1	55	G4 TCP
-1	55	G4 TCP
-1	55	G3 TCP delaying C2 >2 weeks
-2	45	G2 TCP delaying C3 >2 weeks
-2	45	G1 TCP delaying C3 >2 weeks

RP2D: q6 wk schedule not recommended

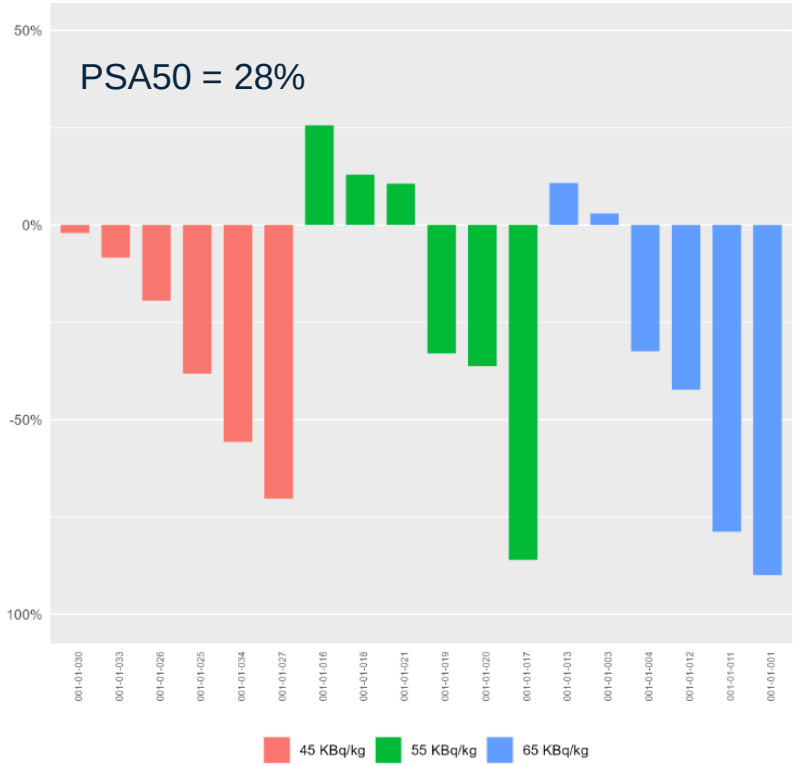
Best % change in PSA

Fractionated Dose



Post-^{177}Lu

Multiple Cycles



Combo ^{225}Ac-J591 with ^{177}Lu-PSMA I&T

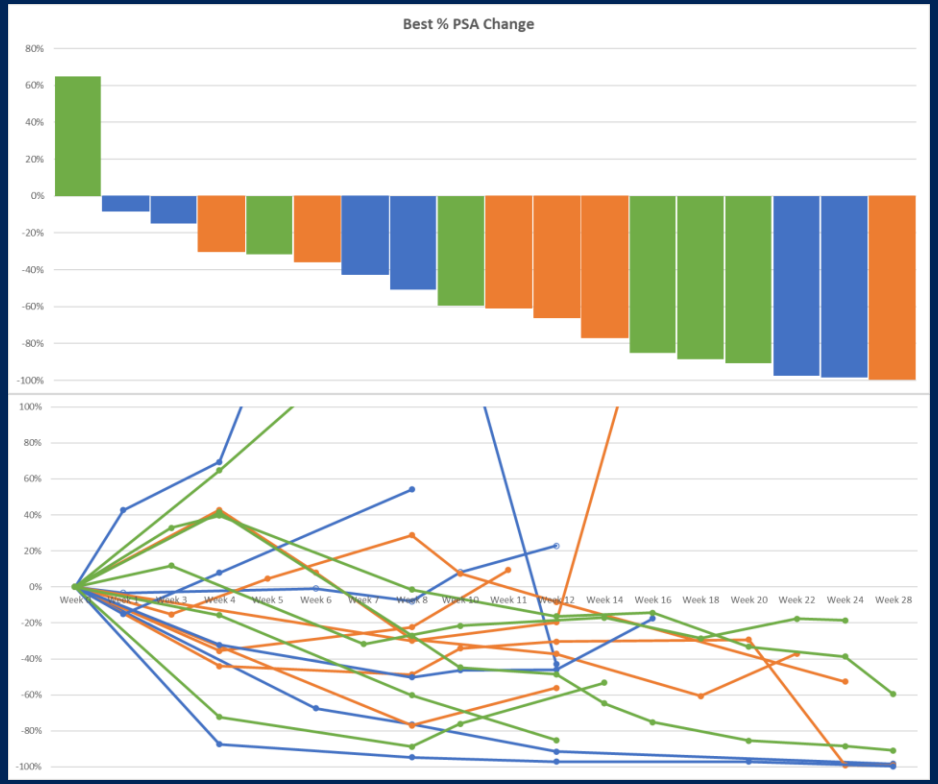
Patient Characteristics	N = 18
Median PSA (ng/mL)	54.4 (range 2.43 – 9614)
Median Age at Treatment	70 (range 55 – 87)
CALGB (Halabi) Risk Category	
Low	1 (5%)
Intermediate	7 (39%)
High	10 (56%)
Prior Therapies	
Sipuleucel-T	5 (28%)
>1 ARPI	12 (67%)
Radium-223	3 (17%)
Chemotherapy	12 (67%)
Lymph Node Metastasis	9 (50%)
Lung Metastasis	2 (11%)
Bone Metastasis	13 (72%)
Liver Metastasis	2 (11%)
SUV_{max} (single lesion)	31.4 (range 11 – 108.9)
$SUV_{maxmean}$ (5 lesions)*	19.6 (range 6.7 – 39.8)
Baseline CTC (CellSearch)	
0/undetectable	3 (17%)
1-4	4 (22%)
5 or greater	11 (61%)

2 DLT's at 40 KBq/Kg: 1 Gr 2 and 1 Gr 3 platelets that delayed cycle 2 > 3 wks

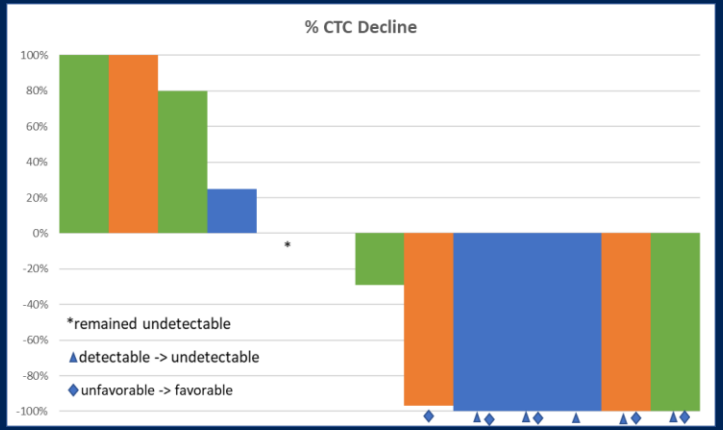
Adverse Event	Total	Gr 1	Gr 2	Gr 3	Gr 4
Neutropenia	3 (17%)	3 (17%)	0 (0%)	0 (0%)	0 (0%)
Platelets	12 (67%)	9 (50%)	1 (5%)	2 (11%)	0 (0%)
Anemia	9 (50%)	4 (22%)	2 (11%)	3 (17%)	0 (0%)
Pain	11 (61%)	9 (50%)	1 (5%)	1 (5%)	0 (0%)
Xerostomia	12 (67%)	11 (61%)	1 (5%)	0 (0%)	0 (0%)
Fatigue	8 (44%)	8 (44%)	0 (0%)	0 (0%)	0 (0%)
Nausea	10 (56%)	10 (56%)	0 (0%)	0 (0%)	0 (0%)

Results (efficacy)

2025 update (Raab/Okobi et al, ASCO GU 2025):
3/6 at RP2D progression free > 1 year (13, 17, 18 mo)
mOS = 29.8 mo [95% CI 7.4 – NR]

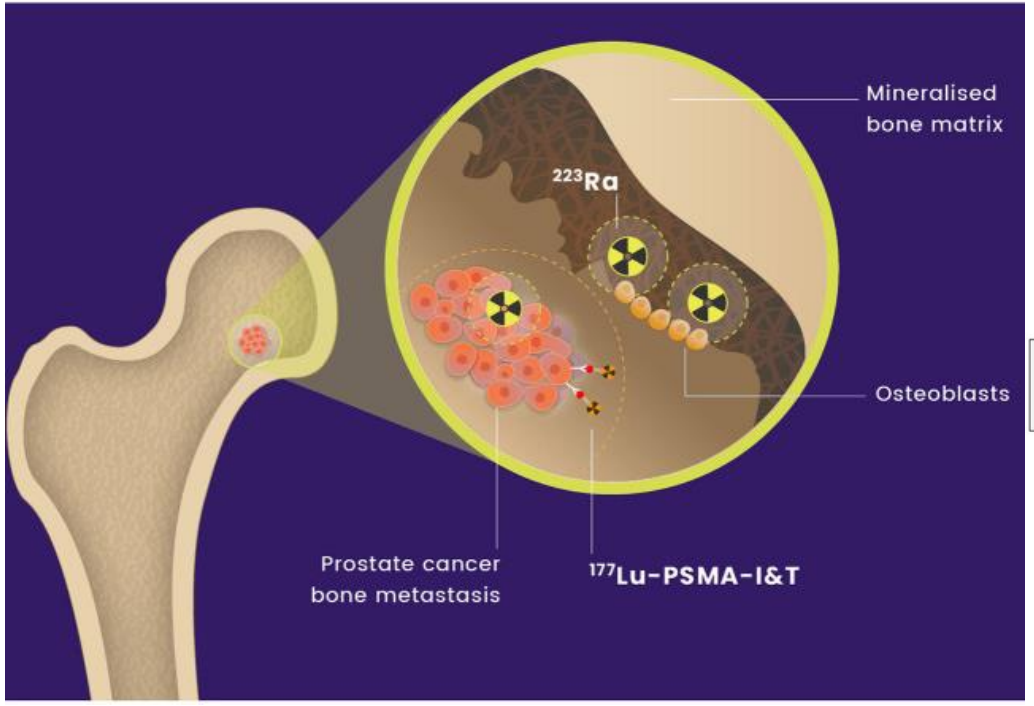


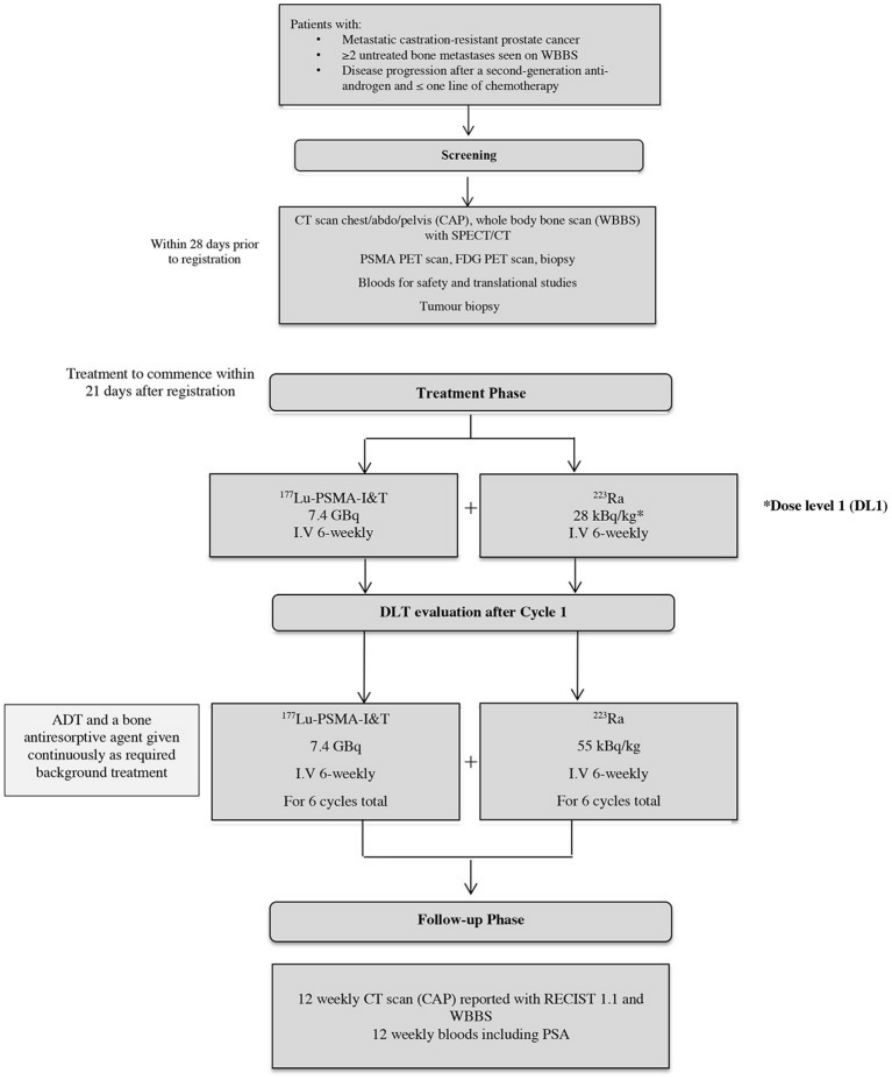
- 17 (94%) experienced PSA decline
- 11 (61%) with PSA50
- 5 of 7 (71%) with paired CTCs converted from unfavorable to favorable at 12 weeks
- 5 of 11 (45%) converted from detectable to undetectable



PRESENTED BY: Scott T. Tagawa, MD, MS, FASCO, FACP

TRT + TRT combo AlphaBet





Will α-PSMA-TRT improve efficacy of immune checkpoint inhibition?

RATIONALE

- RT → improves response to immune checkpoint inhibition (at least in mice)
  - PSMA-TRT allows most sites to receive RT
  - Alpha = dsDNA breaks
- AR pathway inhibition → increased PSMA
- AR pathway inhibition → radiosensitization
- Enza resistance → increased PD-L1

Trial Population
- Progressive mCRPC after at least 1 AR pathway inhibitor
- Chemo-naïve for CRPC

Ph 1 dose finding
ARSI + pembro + ^{225}Ac-J591
2 dose levels:
65 KBq/Kg or 80 KBq/Kg

Pick the winner

Ph 2
R
1:1

N = 64

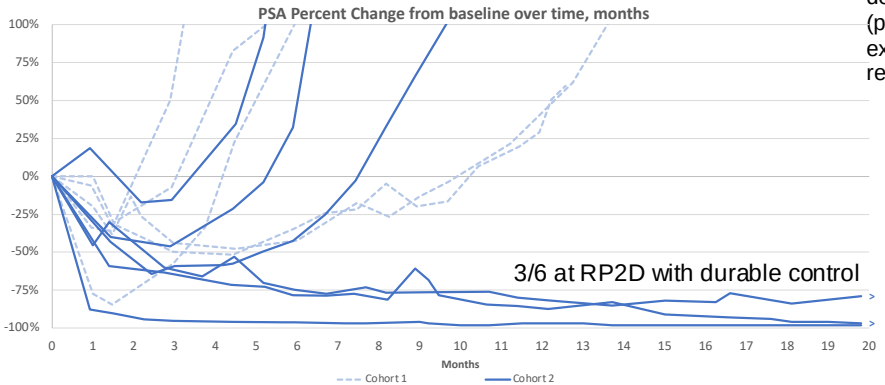
Pembrolizumab 400 mg q6 wks
AR signaling inhibitor
^{225}Ac-J591 x1

Pembrolizumab 400 mg q6 wks
AR signaling inhibitor

Strat factors:
Prior ARSI
Visceral mets
PSMA imaging

A sample of 64 randomized patients will have 90% power with a 0.10 one-sided significance level to detect the difference between the control group (pembro + ARSI) response rate of 20% and the experimental group (pembro+ ARSI + ^{225}Ac-J591) response rate of 50%, using a chi-square test.

Ph 1 = Sun et al, 2022 ASCO GU



Weill Cornell Medicine
Meyer Cancer Center

NCT04946370
Supported by DOD CTA and DOD PCCTC

^{225}Ac-J591 → CONV01-α

CONVERGE-01 Phase II trial

Key eligibility

- Progressive CRPC
- ≥1 PSMA PET (+) metastatic lesion and no PSMA PET (-) lesions
- Post ≥1 ARSI
- No prior PARPi, Ra-223, or platinum chemotherapy

For Part 2

- Conventional imaging (-) [M0] or conventional imaging (+) [M1]
- No prior Lu-177-PSMA-RL or other radiopharmaceutical therapy
- No prior chemotherapy for CRPC

For Part 3

- Conventional imaging (+) [M1]
- Post Lu-177-PSMA-RL (up to 6 doses of Pluvicto or 4 doses of Lu-177-PSMA-I&T)
- 1 prior taxane chemotherapy mandated

Biodistribution Lead-in (Part 1)

In-111 rosopatamab tetraxetan 148 ± 37 MBq on Day 1
(N = 5)

Pre-RL Dose Optimization [Part 2]

Ac-225 rosopatamab tetraxetan 60 kBq/kg on Days 1 and 15
(N = 12)

Randomization 1:1

Stratification factor: Conventional imaging findings (M0 vs M1)

Ac-225 rosopatamab tetraxetan 45 kBq/kg on Days 1 and 15
(N = 6-12)

Post-RL Dose Escalation and Expansion [Part 3]

Ac-225 rosopatamab tetraxetan on Days 1 and 15

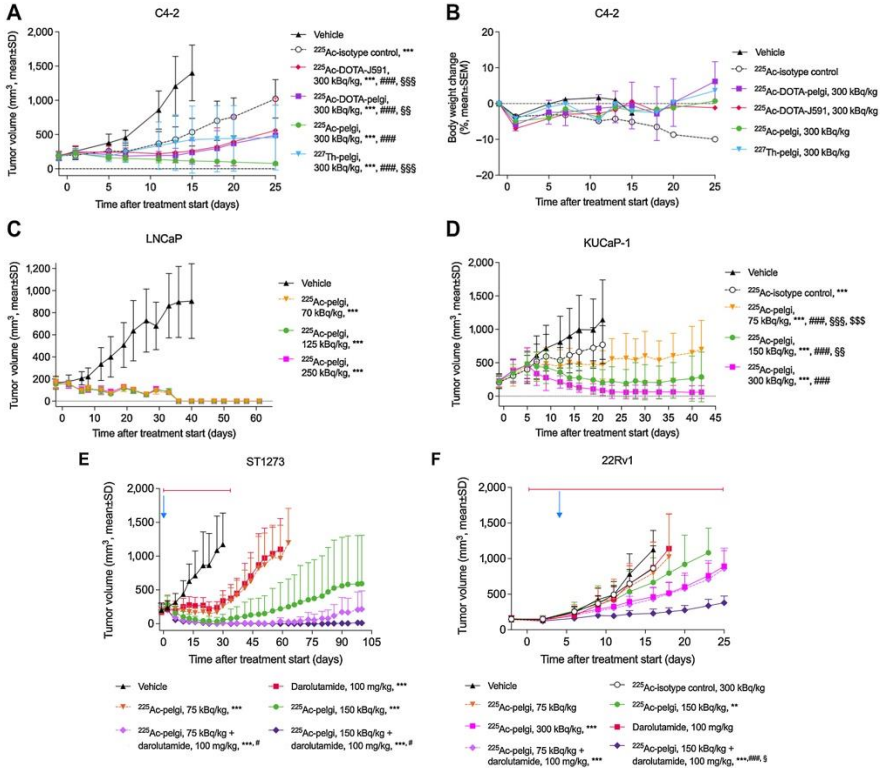
(BOIN design, N = up to 36)

BOIN = Bayesian optimal interval, PARPi = PARP inhibitor, RL = radioligand

https://clinicaltrials.gov/study/NCT06549465

^{225}Ac-pelgifatamab (BAY3546828)

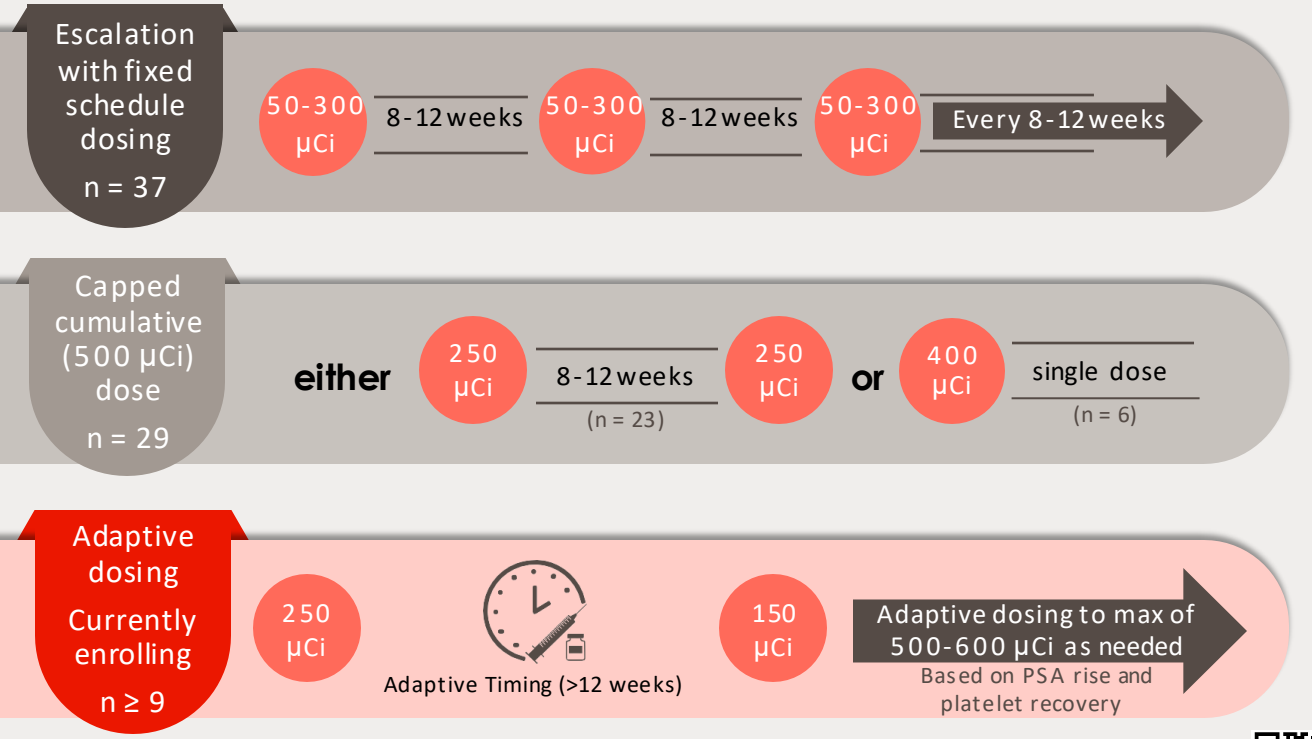
- Pelgifatamab = anti-PSMA mAb used in prior human studies
  ["PSMA-ADC"]
- Used with 227Th (BAY2315497)
  - Ph 1 results pending
- Now conjugated via Macropa with 225Ac
- Ph 1 trial started in Finland, now expanding to other sites [NCT06052306]



Schatz et al, Clin Cancer Res 2024

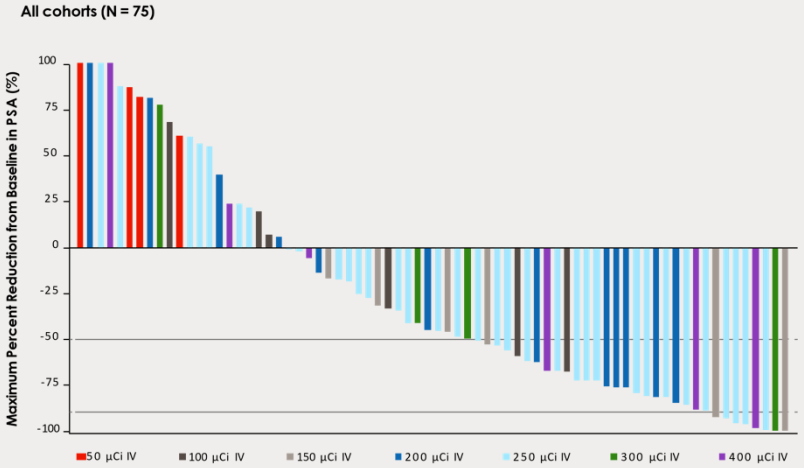
JNJ-69086420 is an hK2-Targeted, Humanized mAb Conjugated to ^{225}Ac. Study Design:

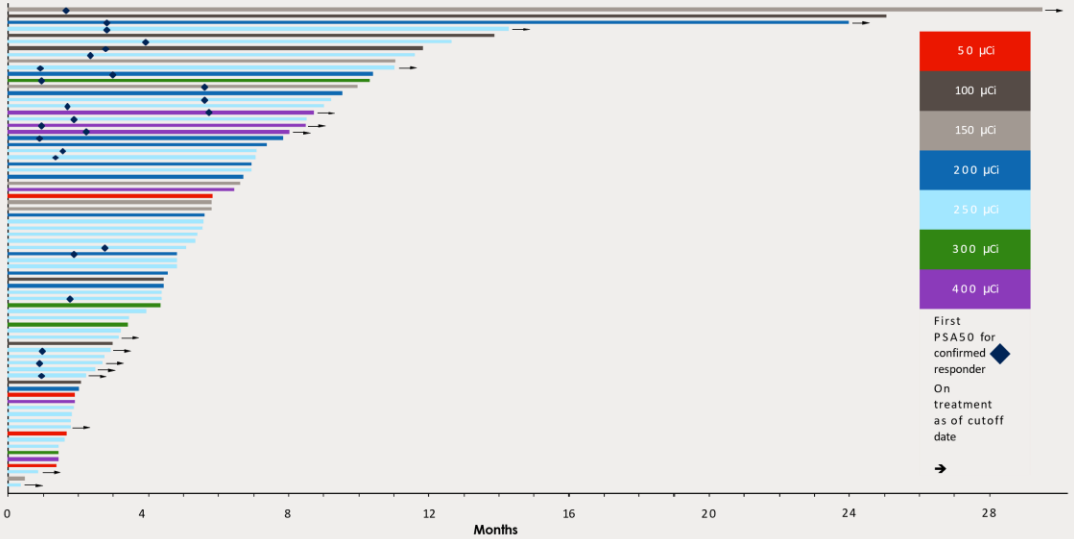
- NCT04644770: phase 1 first-in-human trial of JNJ-69086420 in mCRPC
- Key eligibility criteria
  - ≥1 prior ARPI
  - Prior chemotherapy allowed
  - No prior radiopharmaceutical therapy
  - No superscans
- Primary objectives
  - RP2D and safety



Data cut off date: April 22, 2024.

JNJ-69086420 Induces Deep and Durable PSA Responses





[a]Confirmed by another reduction 3 weeks or later. N = 32 subjects who were on treatment for ≥12 weeks or discontinued treatment or achieved any PSA50. [b]N = 17 with measurable disease at baseline and at least 1 post-baseline assessment or off study. Confirmed ORR based on RECIST, without evidence of bone progression based on PCWG3.

Data cutoff date: April 22, 2024.

Safety |TEAEs of Interest

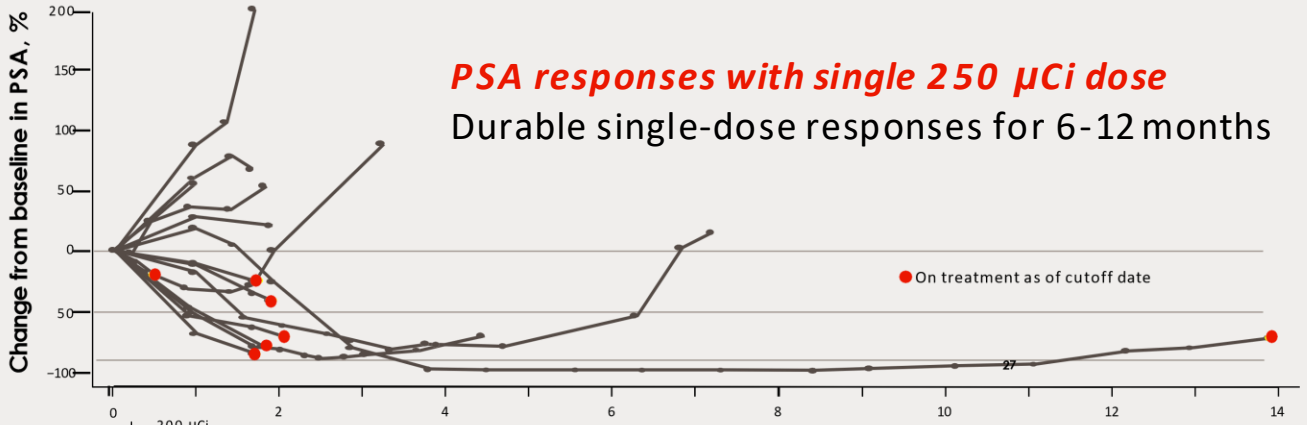
Adverse Events	All participants N=75	
	Any grade (%)	Grade ≥3 (%)
Any TEAE (in ≥20%)	96.0	61.3
Thrombocytopenia	58.7	17.3
Fatigue	53.3	1.3
Anemia	48.0	25.3
Decreased appetite	41.3	4.0
Nausea	40.0	2.7
Leukopenia	29.3	8.0
Vomiting	29.3	2.7
Cough	24.0	1.3
Dyspnea	24.0	0
Diarrhea	22.7	1.3
Hypertension	20.0	9.3
Dry mouth	20.0	0
Back pain	20.0	2.7
ILD[a]	6.7	5.3
Serious TEAE/TRAE (%)	32.0/16.0	
TEAE/TRAE leading to discontinuation (%)	14.7/12.0	
TEAE/TRAE leading to death[b] (%)	6.7/5.3	

[a]ILD includes reports of pneumonitis, ground glass opacities, and acute hypoxic respiratory failure.
[b]ILD (n=2), respiratory failure (COVID-19, n=1), decreased appetite/hypotension (n=1).
Data cutoff date: April 22, 2024.

- Persistent G3/G4 thrombocytopenia on fixed dosing schedule at cumulative doses ≥500 µCi
- Only 1/26 (3.8%) G3 thrombocytopenia without recovery following a single 250-400 µCi dose

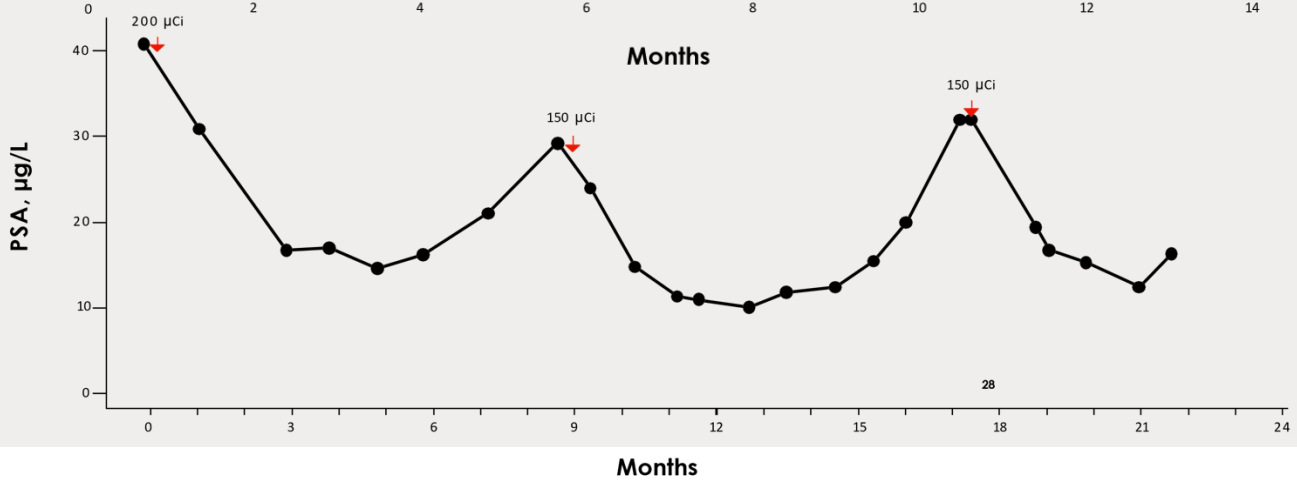
- Overall, 6.7% of patients had ILD, including 2 fatal cases
  - All ILD associated with cumulative doses ≥600 µCi
  - No ILD associated with cumulative dose cohorts ≤500 µCi

Adaptive Dosing is Supported by Single-Dose Data



PSA responses with single 250 µCi dose

Durable single-dose responses for 6-12 months



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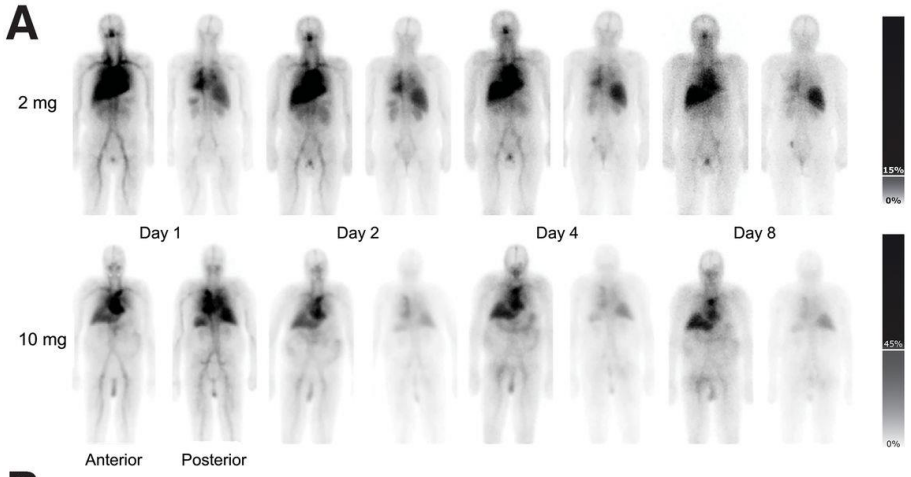

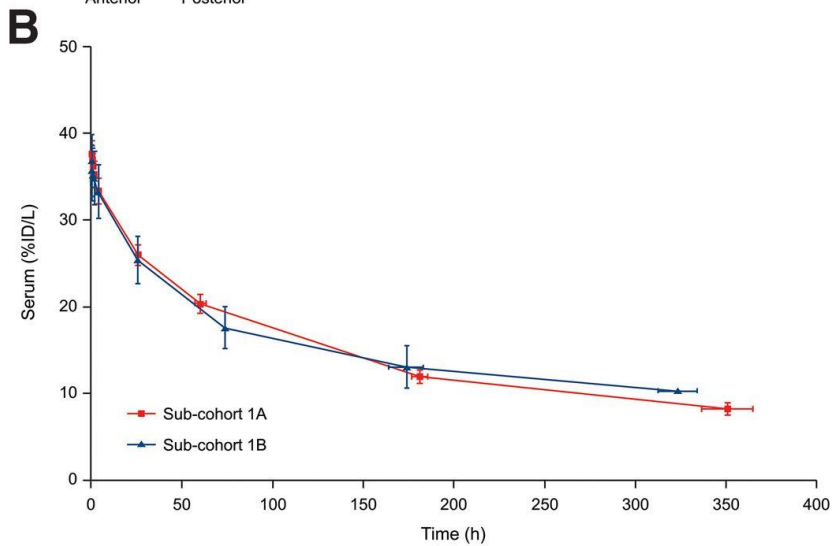

	[^{111}In] absorbed dose (mGy/MBq)	
	1A (2 mg)	1B (10 mg)
	n = 15	*n* = 6
Organ of interest	**Mean (SE)**	**Mean (SE)**
Adrenals	0.19 (0.01)	0.19 (0.01)
Brain	0.08 (0.003)	0.08 (0.01)
Breasts	0.09 (0.002)	0.09 (0.01)
Gallbladder wall	0.22 (0.01)	0.23 (0.01)
LLI wall	0.12 (0.004)	0.12 (0.01)
Small intestine	0.13 (0.004)	0.14 (0.01)
Stomach wall	0.14 (0.003)	0.14 (0.01)
ULI wall	0.14 (0.004)	0.14 (0.01)
Heart wall	0.54 (0.02)	0.49 (0.04)
Kidneys	0.23 (0.01)	0.22 (0.02)
Liver	0.45 (0.02)	0.46 (0.05)
Lungs	0.15 (0.004)	0.15 (0.01)
Muscle	0.10 (0.003)	0.11 (0.01)
Pancreas	0.19 (0.004)	0.19 (0.01)
Red marrow	0.17 (0.01)	0.17 (0.01)
Osteogenic cells	0.19 (0.01)	0.19 (0.01)
Skin	0.07 (0.002)	0.07 (0.003)
Spleen	0.24 (0.01)	0.24 (0.01)
Testes	0.08 (0.003)	0.09 (0.01)
Thymus	0.16 (0.004)	0.16 (0.01)
Thyroid	0.10 (0.003)	0.10 (0.01)
Urinary bladder wall	0.11 (0.004)	0.12 (0.01)
Total body	0.12 (0.003)	0.12 (0.01)

Pandit-Taskar N, et al. J Nucl Med. 2024

Threshold for tolerance to ^{225}Ac-mAb?

- ^{225}Ac-J591 single-dose phase 1 (JCO 2023)
  - RP2D = 93 KBq/Kg (2.52 µCi/Kg) → 176 µCi for 70 Kg (Max actual = 324 µCi following prior ^{177}Lu-PSMA-617)

Fractionated Dose (single cycle)

Dose Level	KBq/kg	# of Patients
1	45	3
2	55	7
3	65	6
2.5	60	7
*Post 177Lu**	*50*	*4*

Multiple Cycles

Dose Level	KBq/kg	# of Patients
1	65	6
-1	55	6
-2	45	6

- ^{225}Ac-J591 fractionated dose
  - RP2D = 60 KBq/Kg (1.62 µCi/Kg) → 227 µCi for 70 Kg
- ^{225}Ac-J591 multiple cycles q6 wks
  - Highest dose level = 65 KBq/Kg (1.76 µCi/Kg) → 443 µCi for 70 Kg (4 cycles) (Max actual = 589 µCi)

^{225}Ac-lintuzumab 1.5 µCi/Kg up to 4 cycles → 420 µCi for 70 Kg 4 cycles NCT03867682

J Clin Oncol 2024
Sun et al, AUA 2024

^{225}Ac-TRT for prostate cancer summary

- Alpha emitters have higher LET over a shorter range than betas
- Several cell-surface targets, including PSMA, have relative selectivity and are attractive for ^{225}Ac-TRT
- Both antibodies and small molecules accurately target PSMA+ cells, can be radiolabeled, and have different kinetics and biodistribution
  - Initial start with mAbs
- Theranostics paradigm may hold for alphas like betas, but not yet proven
- We can exploit the selectivity of targets to deliver high doses of radioactive particles (or drugs) to tumors with relative sparing of normal organs
  - Can we get a high enough dose to all tumors for cure? [heterogeneity noted]
  - Many potential combinations (AR, taxane, immune checkpoint inhibitors, PARP, etc.)
  - Can we pre-select the optimal pt population (imaging, genomics, etc)?