A phase 1 study of JNJ-69086420, an ^{225}Ac-labeled antibody targeting human kallikrein 2 to treat metastatic castration-resistant prostate cancer

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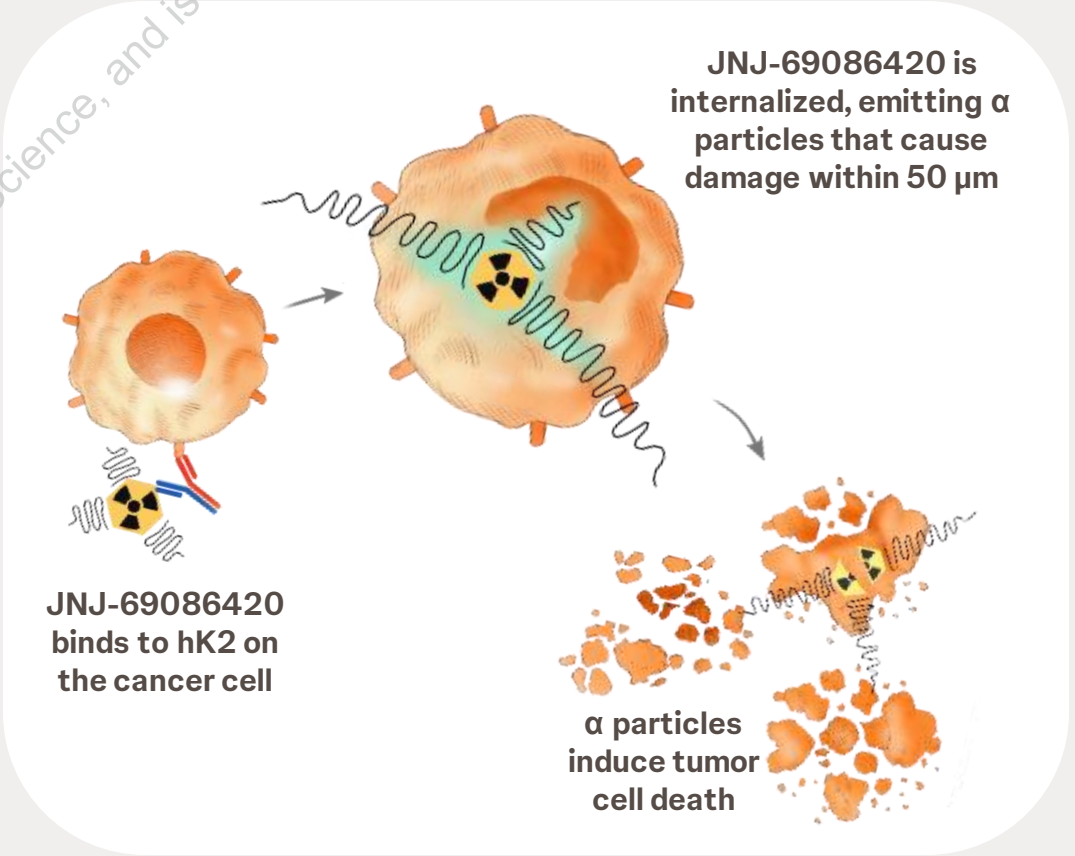
Conclusions

- Human kallikrein 2 (hK2/KLK2) is a cell surface antigen highly and specifically expressed on prostate cells and across the spectrum of prostate cancer[1]
- JNJ-69086420 is an actinium-225–labeled radioligand therapy that is the first to target hK2/KLK2
- Thrombocytopenia and pulmonary toxicity were dose limiting using a fixed dosing schedule. These risks are mitigated using a dose cap and adaptive dosing schedule
- In this first-in-human study, 1-2 doses of JNJ-69086420 elicited deep and durable responses in advanced mCRPC

1. Pandit-Taskar N, et al. *J Nucl Med.* 2024; 10.2967/jnumed.124.267416.

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

- hK2 is regulated by androgen receptor signaling, similar to PSA[1-3]
- hK2, encoded by *KLK2*, has high membranous expression in prostate cancer[4-7]
- hK2 exists in both a secreted and membrane-associated form
- JNJ-69086420 preferentially binds to the membrane-associated form of hK2[4,5]
- JNJ-69086420 delivers α-particle radiation to prostate tumor cells[2]



1. Saedi MS, et al. *Int J Cancer*. 2001;94:558-563. 2. McDevitt MR, et al. *Nat Commun*. 2018;9(1):1629. 3. Lövgren J, et al. *Eur J Biochem*. 1999;262:781-789. 4. Thorek DL, et al. *Sci Transl Med*. 2016;8(367):367. 5. Morris MJ, et al. *J Clin Oncol*. 2022;40(6 suppl):TPS206. 6. Darson MF, et al. *Urology*. 1997;49:857-862. 7. Darson MF, et al. *Urology*. 1999;53(5):939-944.

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.

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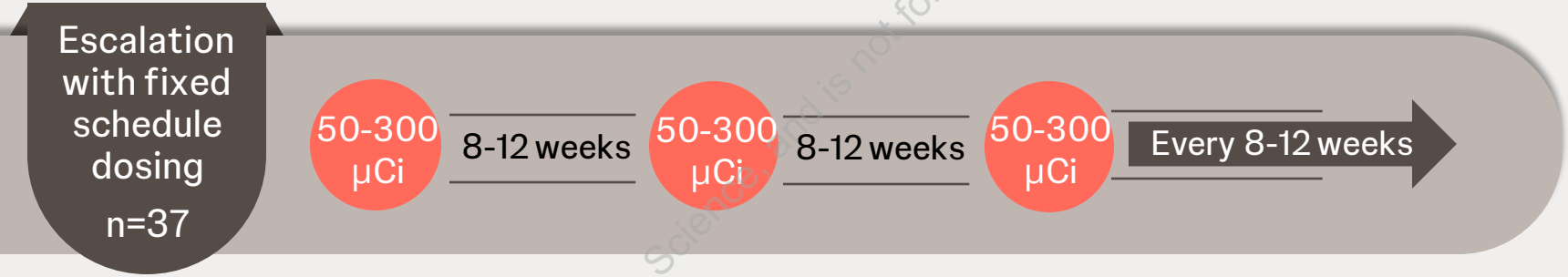

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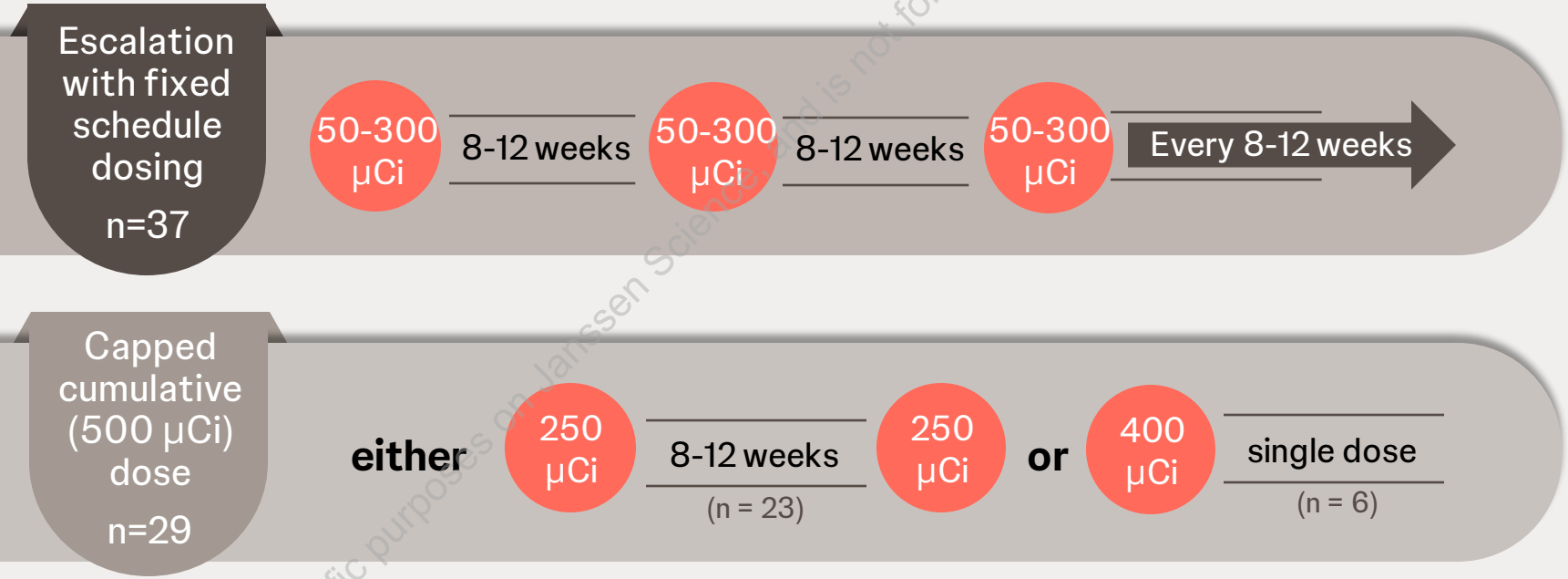

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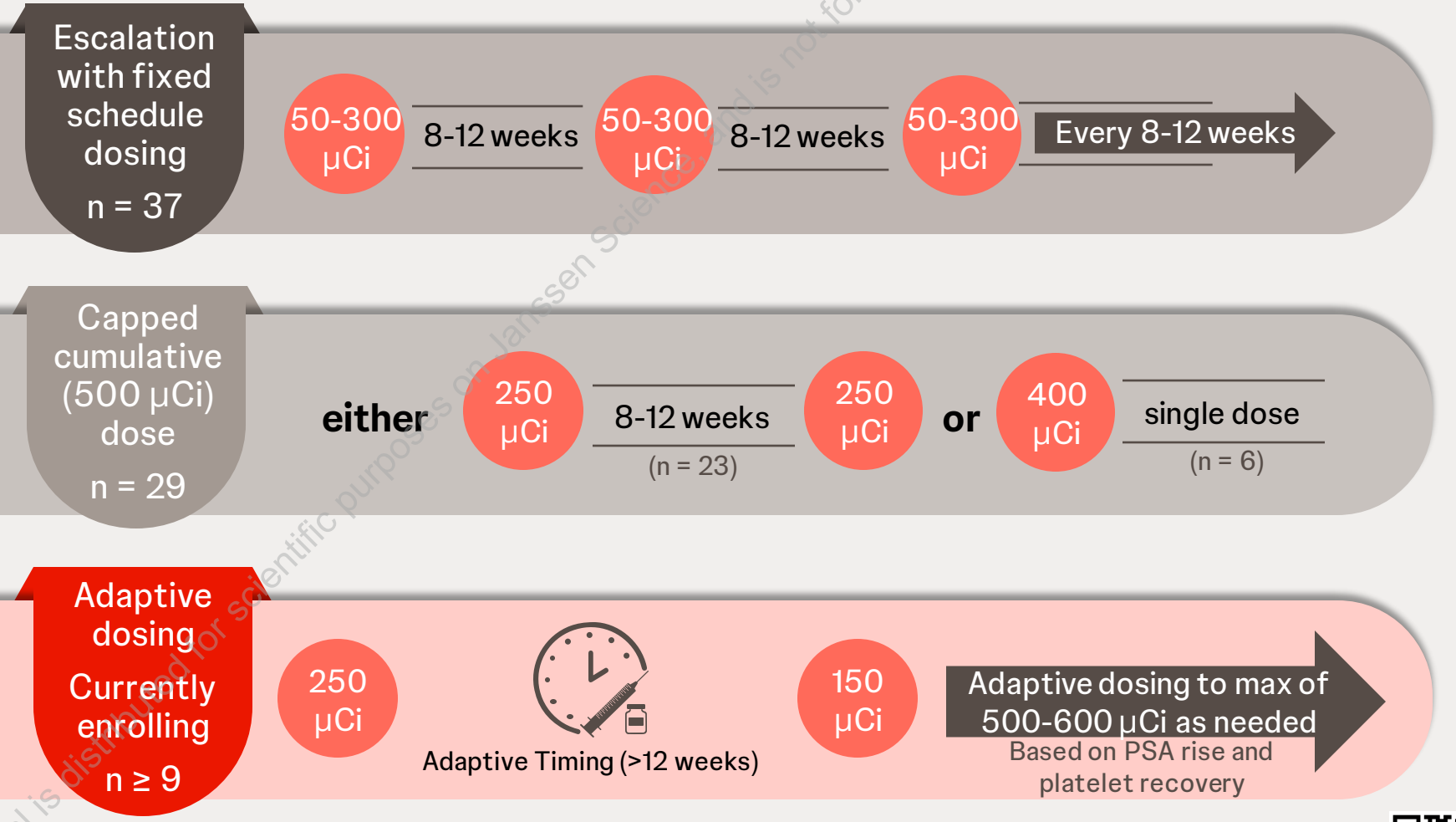

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Baseline Characteristics

Characteristic	All participants N = 75
Age, median (range), years	68 (46-84)
Prior cancer-related therapies	
Lines of prior therapy, median (range)	4 (0-12)
ARPI, n (%)	75 (100%)
≥2 ARPI, n (%)	40 (53%)
Any taxane-based chemotherapy, n (%)	49 (65%)
1 taxane-based chemotherapy, n (%)	28 (37%)
≥2 taxane-based chemotherapy, n (%)	21 (28%)
Primary RT, n (%)	17 (23%)
Palliative RT, n (%)	23 (31%)
No. courses RT, median (range)	1 (1-5)

Characteristic	All participants N = 75
PSA, median (range), µg/L	68.6 (0.4-2767.9)
Platelets, median (range), 10^9/L	222 (112-620)
Hemoglobin, median (range), g/dL	11.6 (7.7-15.7)
Extent of disease, n (%)	
Bone	66 (88%)
Soft tissue	36 (48%)
Visceral[a]	14 (19%)
Liver metastases	4 (5%)
Lymph node[b]	31 (41%)
Other	10 (13%)

[a]Includes lung, liver, adrenal, and central nervous system. [b]Includes pelvic and extra-pelvic.
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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).
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- 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

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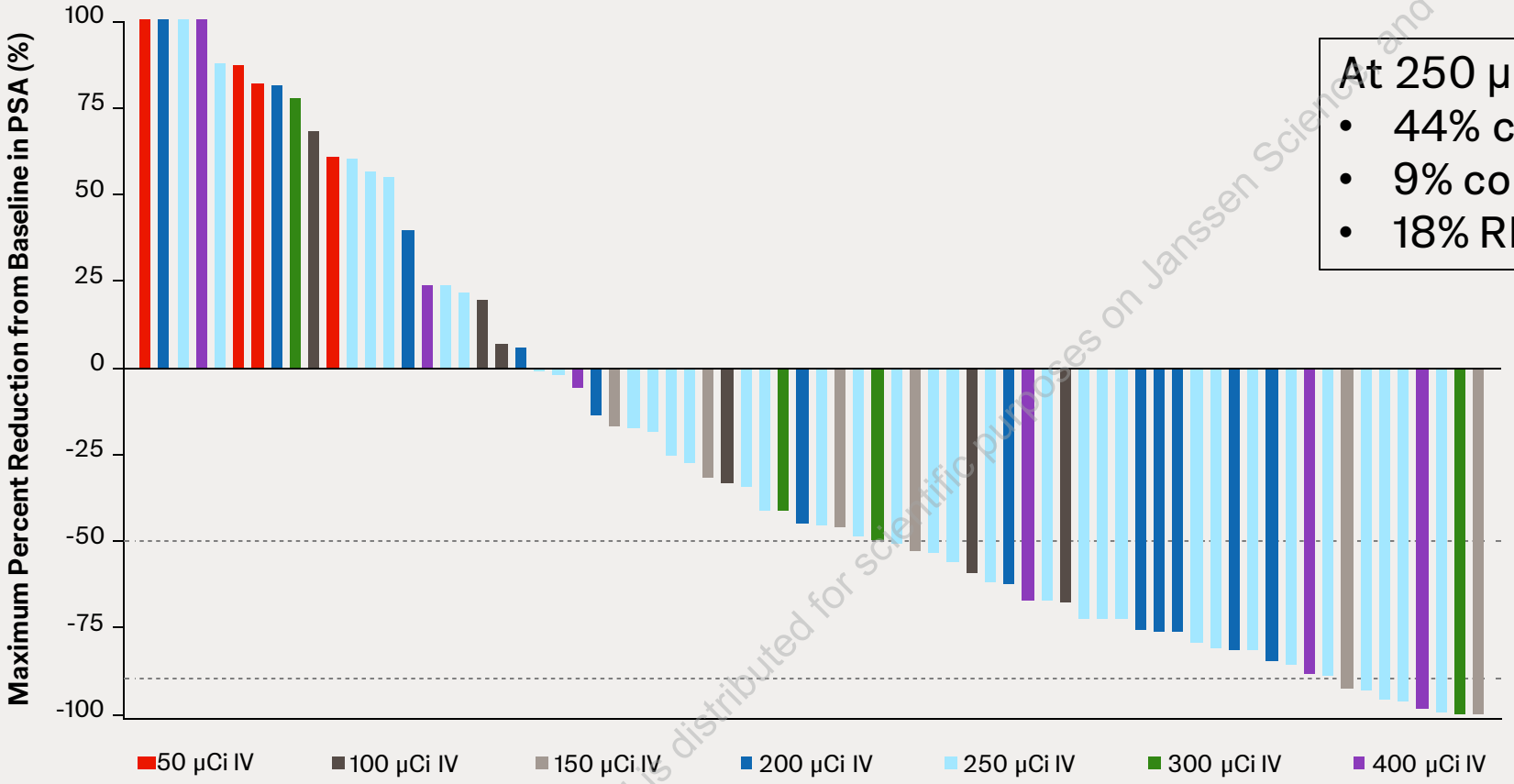
- Only 1/26 (3.8%) G3 thrombocytopenia without recovery following a single 250-400 µCi dose

- 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

JNJ-69086420 Induces Deep and Durable PSA Responses

All cohorts (N = 75)



At 250 µCi dose level (n = 36)

- 44% confirmed PSA50[a]
- 9% confirmed PSA90
- 18% RECIST ORR (1 CR, 2 PR; n/N=3/17)[b]

[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.

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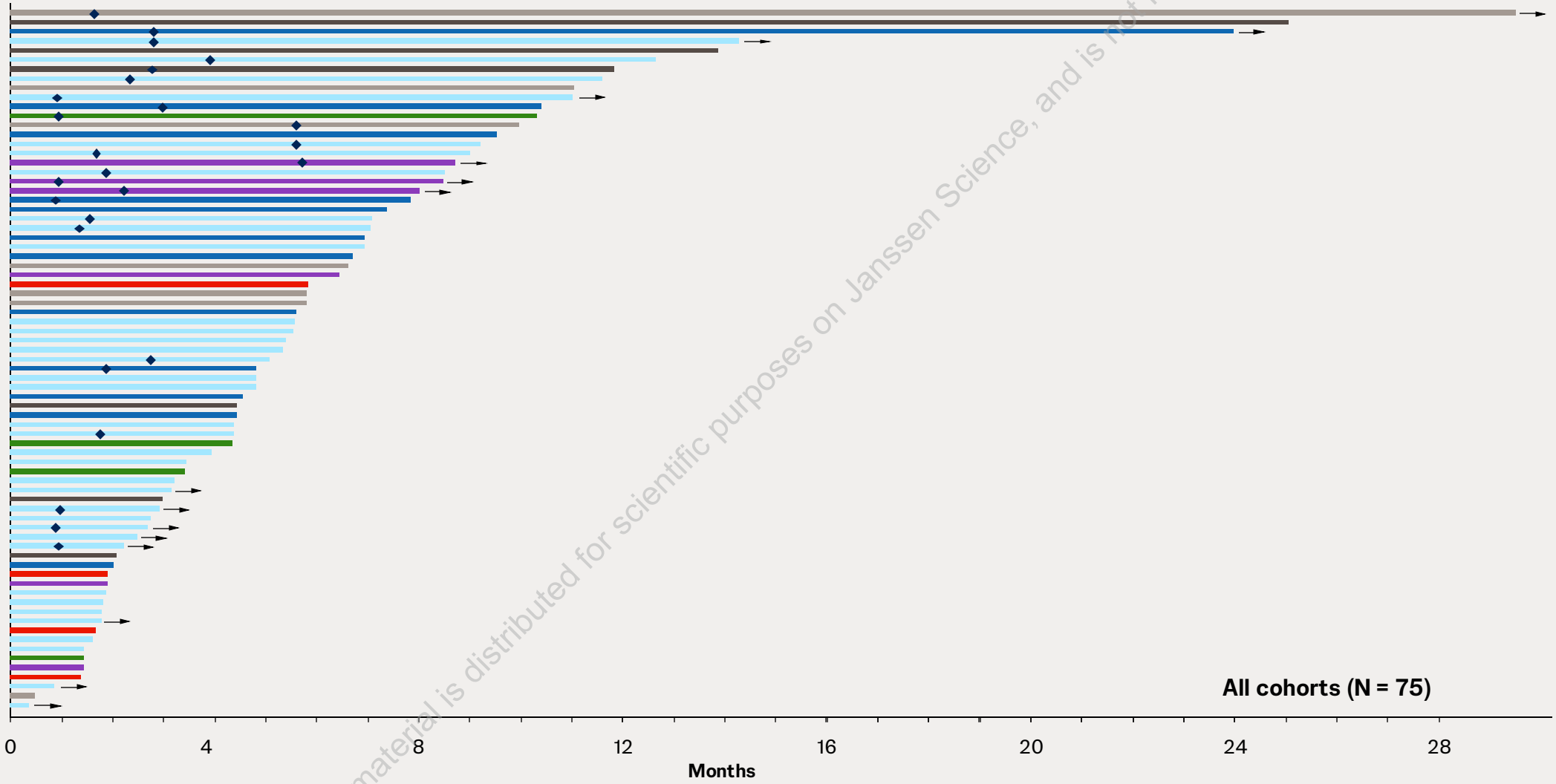


50 µCi
100 µCi
150 µCi
200 µCi
250 µCi
300 µCi
400 µCi

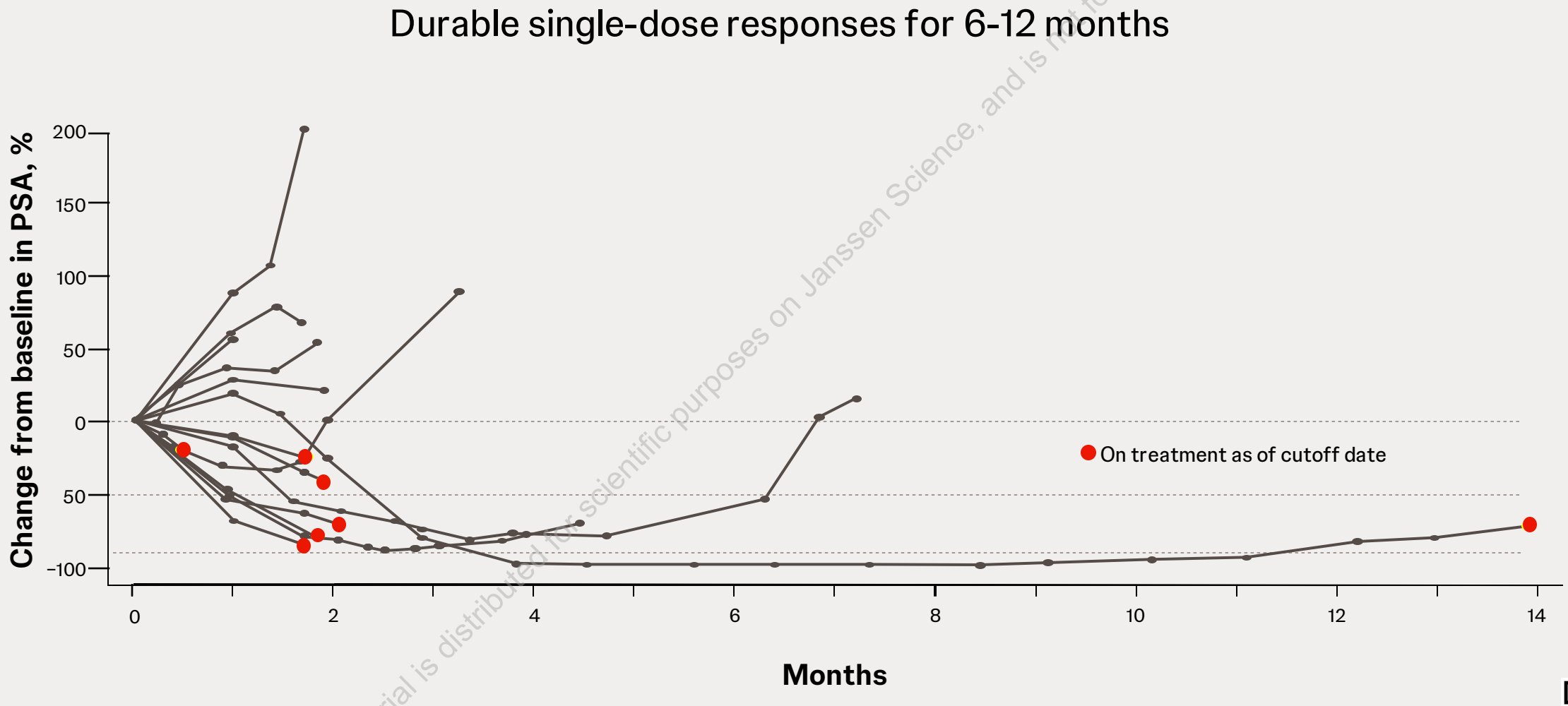
First PSA50 for confirmed responder ◆

On treatment as of cutoff date →

Data cutoff date: April 22, 2024.

Adaptive Dosing is Supported by Single-Dose Data

PSA responses with single 250 µCi dose



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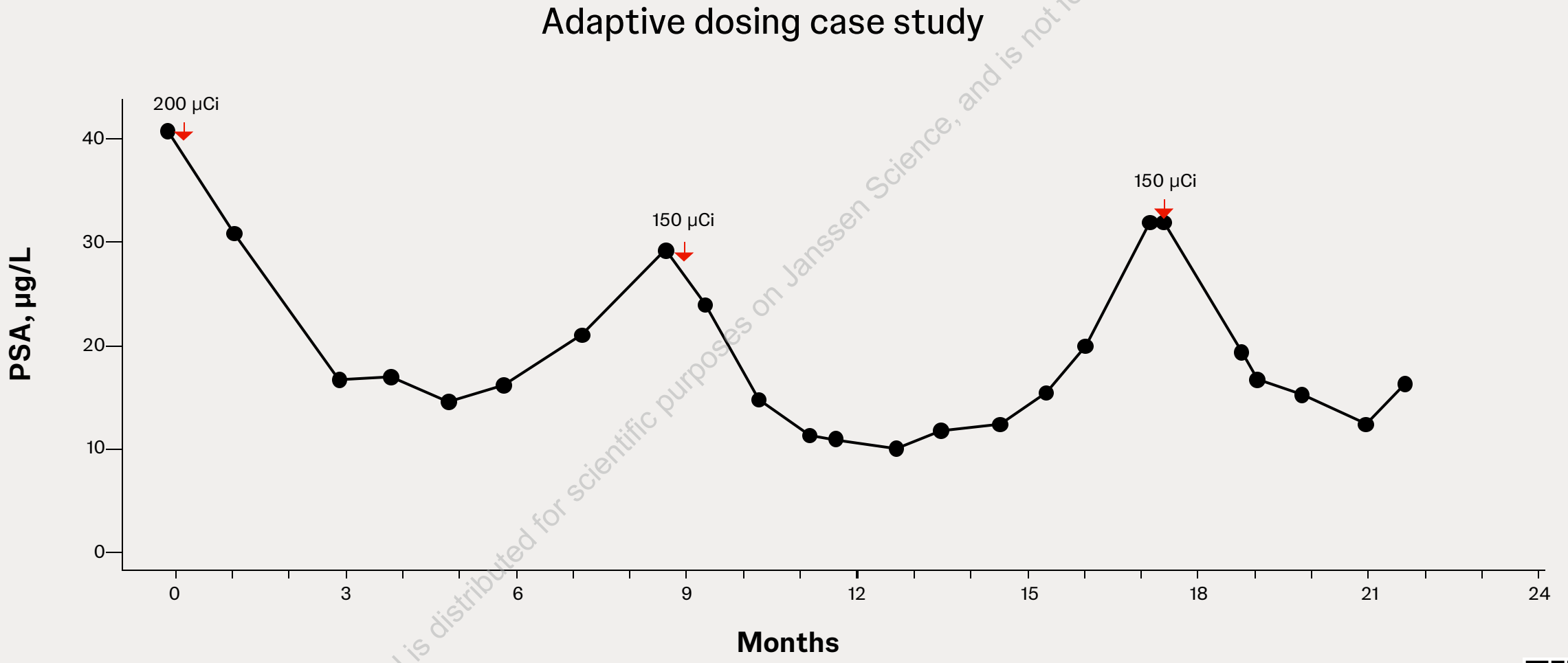
Adaptive Dosing is Supported by Single-Dose Data

PSA responses with extended interval retreatment



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Future Directions

- JNJ-69086420, an α-emitting radioligand therapy that is the first to target hK2, elicited deep and durable biochemical responses in patients with mCRPC
- ILD and thrombocytopenia were dose limiting; these risks are mitigated with a cumulative dose cap and an adaptive dosing schedule
- Assessment in patients with prior radioligand therapy is ongoing as evaluation of the RP2D and adaptive dosing regimen continues

https://www.congresshub.com/Oncology/AM2024/ProstateEarlyAssets/Morris

We are grateful to the patients, their families/caregivers, and the clinical trial team for their contribution to this study

This study is continuing to enroll: NCT04644770

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