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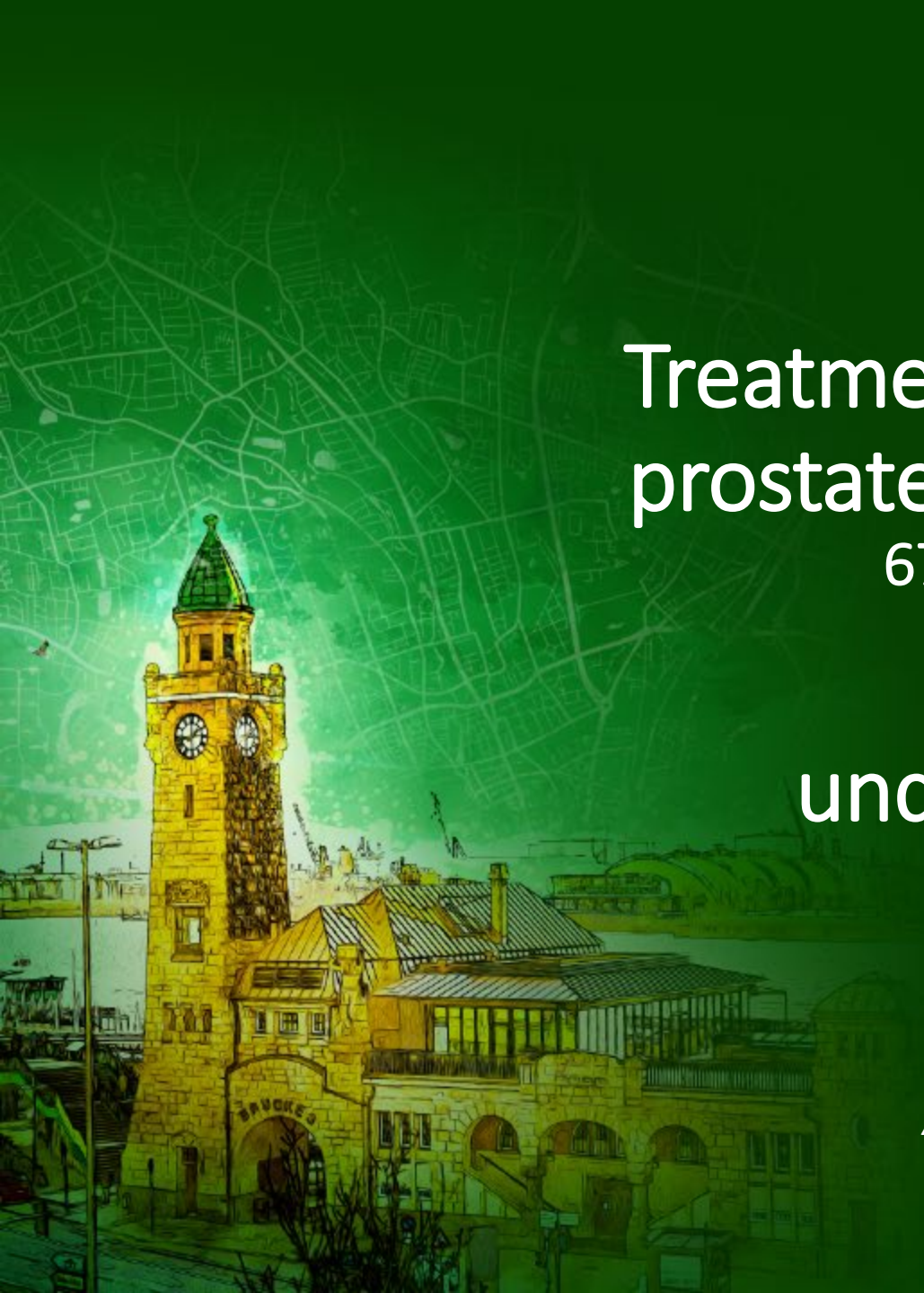

Treatment of metastatic castrate-resistant prostate cancer patient with two cycles of ^{67}Cu-SAR-bisPSMA (8 GBq) leads to complete response (RECIST) and undetectable PSA level: A case report

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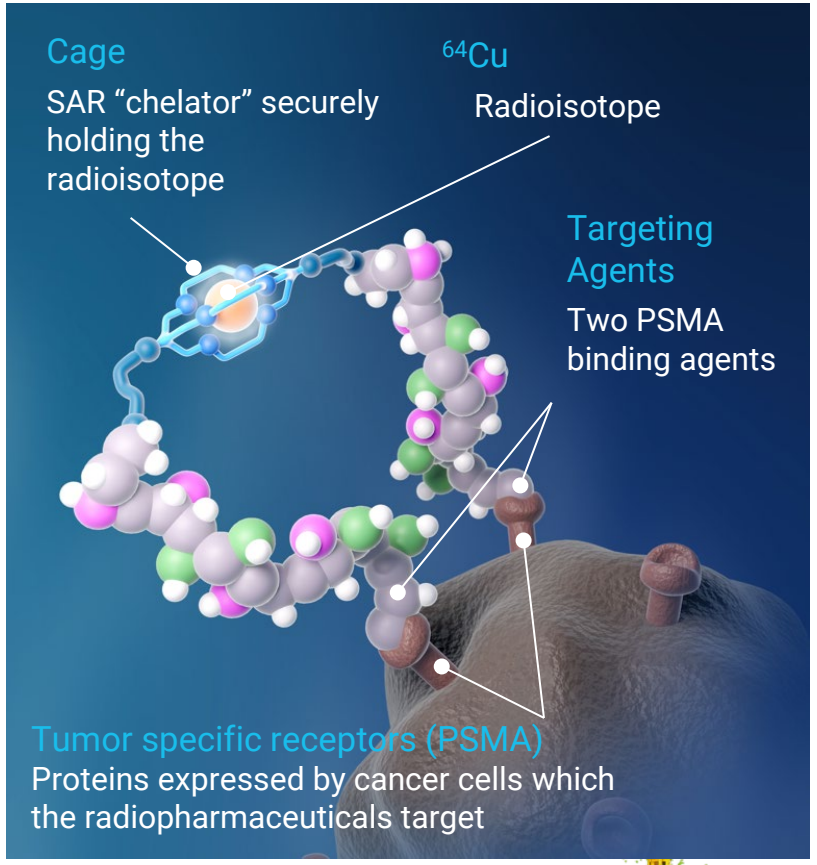
EANM Disclosure of Interest Statement

1. Othon Gervasio: employee of Clarity Pharmaceuticals Ltd.

Background

- Despite recent advances in treatment options for prostate cancer (PC), patients with metastatic disease continue to face poor outcomes, highlighting the need for new and more effective therapies in this setting.
- Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein and is expressed in normal and benign tissue but overexpressed in malignant prostate tissues[1].
- Characteristics of ^{67}Cu-SAR-bisPSMA, including its double PSMA binding moiety (bisPSMA) and half-life of ^{67}Cu (2.6 days) may offer advantages compared to currently used single-target PSMA agents.



	Copper-67[2,3]	Lutetium-177[4]
Half-life	2.6 days	6.7 days
Decay mode	Beta emitter	Beta emitter
Range in tissue	~0.2 mm	~0.7 mm
Production mode	Electron accelerators	Nuclear reactors

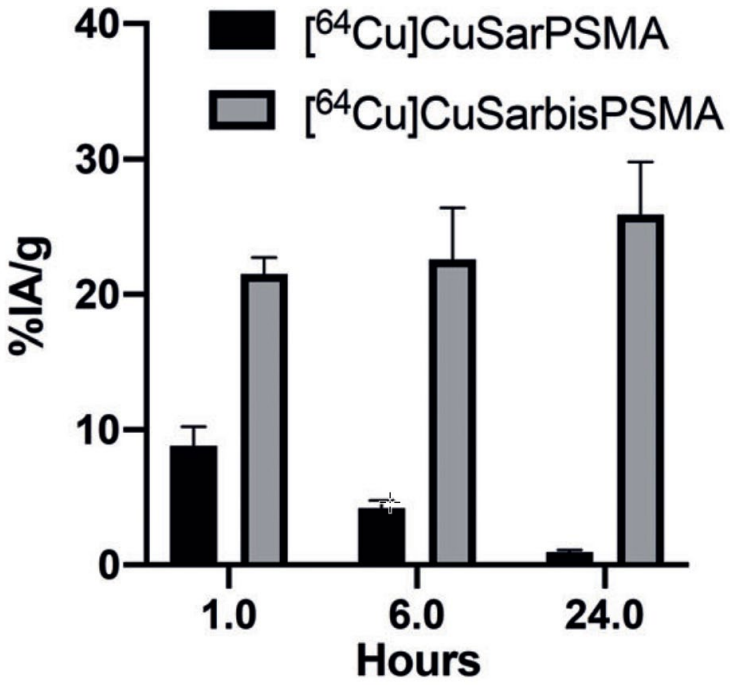
1. Silver et al. Clin Cancer Res. 1997. 2. Cullinane et al. JNM, 2020. 3. Kazakov et al. J Radioanal Nucl Chem, 2021. 4. Dash et al. Nucl Med Mol Imaging, 2015.

Theranostic pair $^{64/67}$Cu-SAR-bisPSMA

Higher uptake and prolonged retention in lesions (^{64}Cu, imaging)

Increased survival (^{67}Cu, therapy – translational)

1



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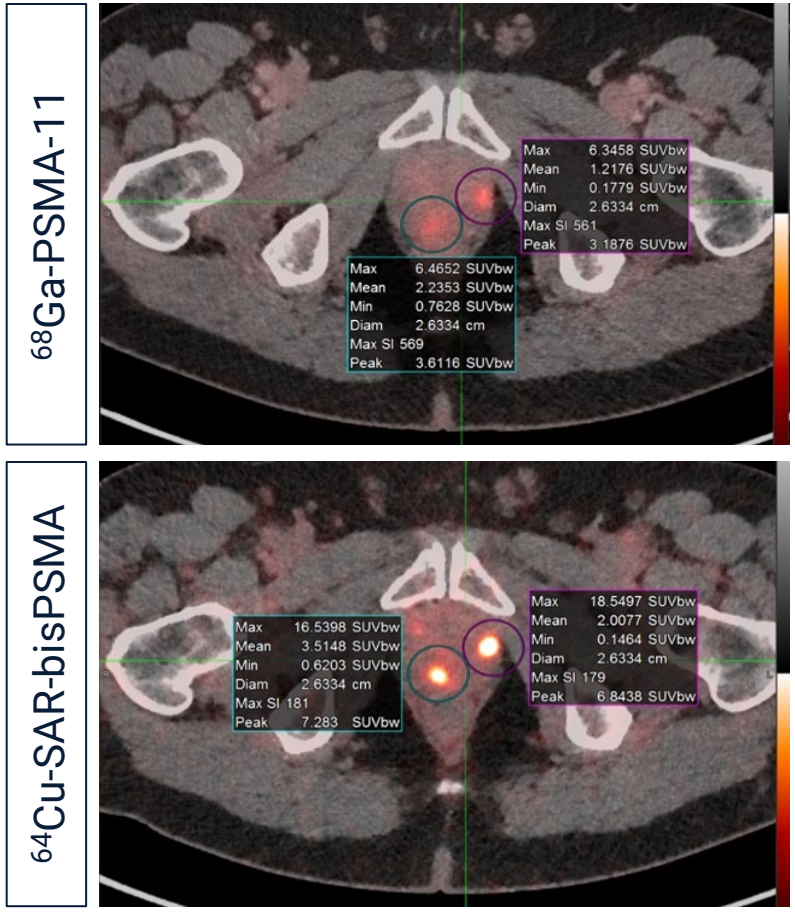

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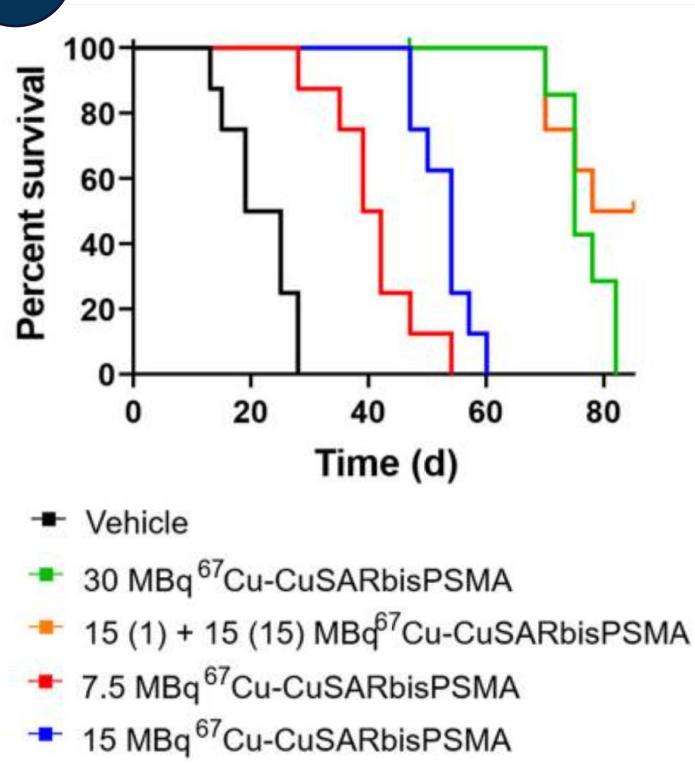


1. Ex vivo tumor uptake expressed as percent injected activity per gram tissue (%IAg^{-1}) (mean±SEM, n=3/group) in LNCap-tumor-bearing NSG mice following injection of either [64Cu]CuSarPSMA (2 MBq, 0.9 nmol of peptide) or [64Cu]CuSarbisPSMA (2 MBq, 0.2 nmol of peptide). Zia et al. Angew. Chem. Int. Ed. 2019. **2.** Concordant lesions on ^{64}Cu-SAR-bisPSMA (200 MBq) and ^{68}Ga-PSMA-11 PET/CT consistently showed higher SUVmax, SUVmean and TBR with ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11 (statistically significant values for all parameters, p<0.001). Interval between scans: 8 days. Lengyelova & Emmett et al. ASCO, 2023. **3.** (A) Antitumor efficacy of ^{67}Cu-SAR-bisPSMA against LNCaP tumor xenografts. Kaplan–Meier curve of percentage survival data; endpoint represents day on which tumor size was at least 1,200 mm^3 or censoring occurred (day 85). McInnes et al. JNM, 2021.

Case report

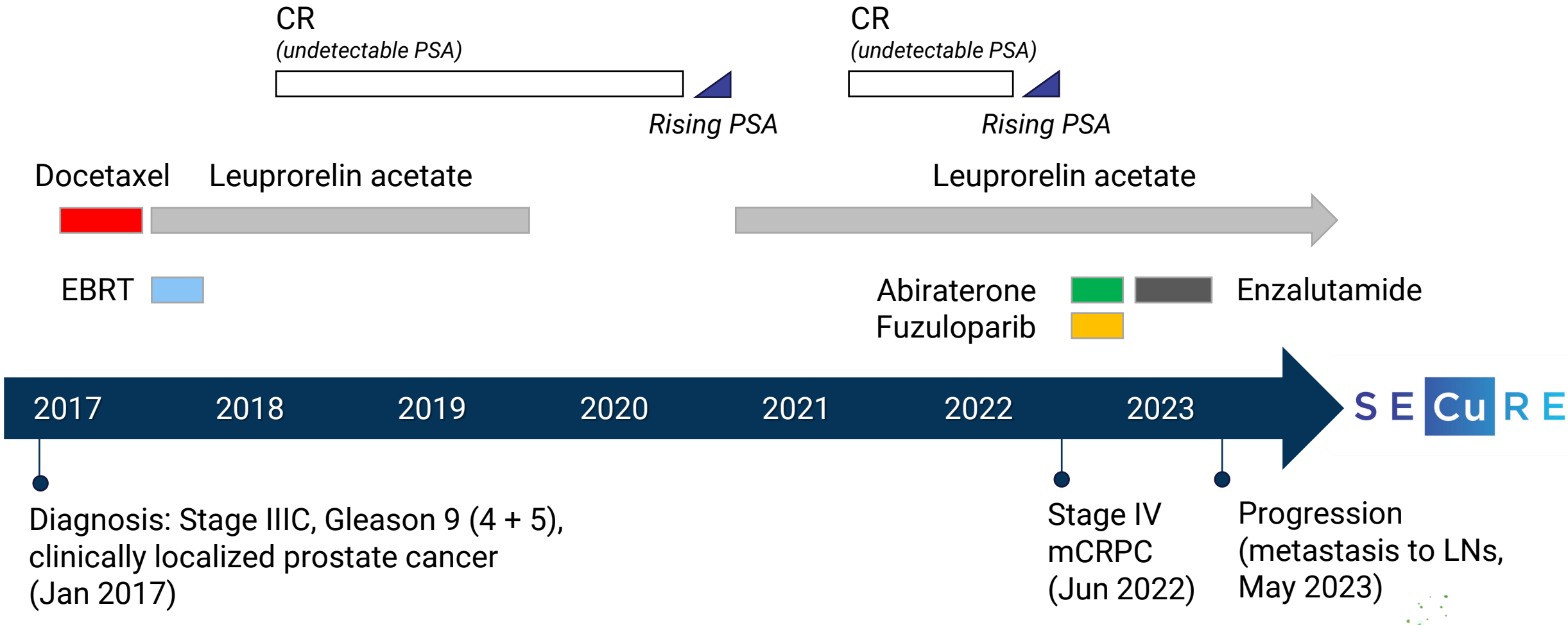
Diagnosis

- 68-year-old male
- Prostate cancer diagnosis in 2017 (core biopsy, clinically localized)
- Gleason score 9 (4+5), stage IIIC
- Prostate-specific antigen (PSA) 20.5 ng/mL

Treatment

- Neo-adjuvant chemotherapy
- Definitive therapy (radiation)
- Androgen deprivation therapy (ADT)
- Poly(ADP-ribose) polymerase inhibitor (PARPi)
- Androgen receptor pathway inhibitors (ARPI)

Clinical Timeline



Clinical timeline. Diagnosis: Jan 2017. Treatment: Mar-Jul 2017 chemotherapy (docetaxel, 6 cycles) [red], Jul-Sep 2017 external beam radiation therapy (EBRT, total dose of 81 Gy) [light blue], Jul 2017-Jul 2019 ADT (leuprorelin acetate) [grey]. Patient had a CR (undetectable PSA). Rising PSA led to re-initiation of leuprorelin acetate in Nov-2020 (ongoing) [grey]. PSA undetectable in 2021, but increased again in 2022. Aug-Oct 2022 ARPI (abiraterone) [green] and PARPi (fuzuloparib) [orange]. Treatment stopped in Oct-2022 due to progression. Nov 2022-May 2023 ARPI (enzalutamide) [dark grey]. Treatment was stopped in May 2023 due to progression. LNs: lymph nodes.

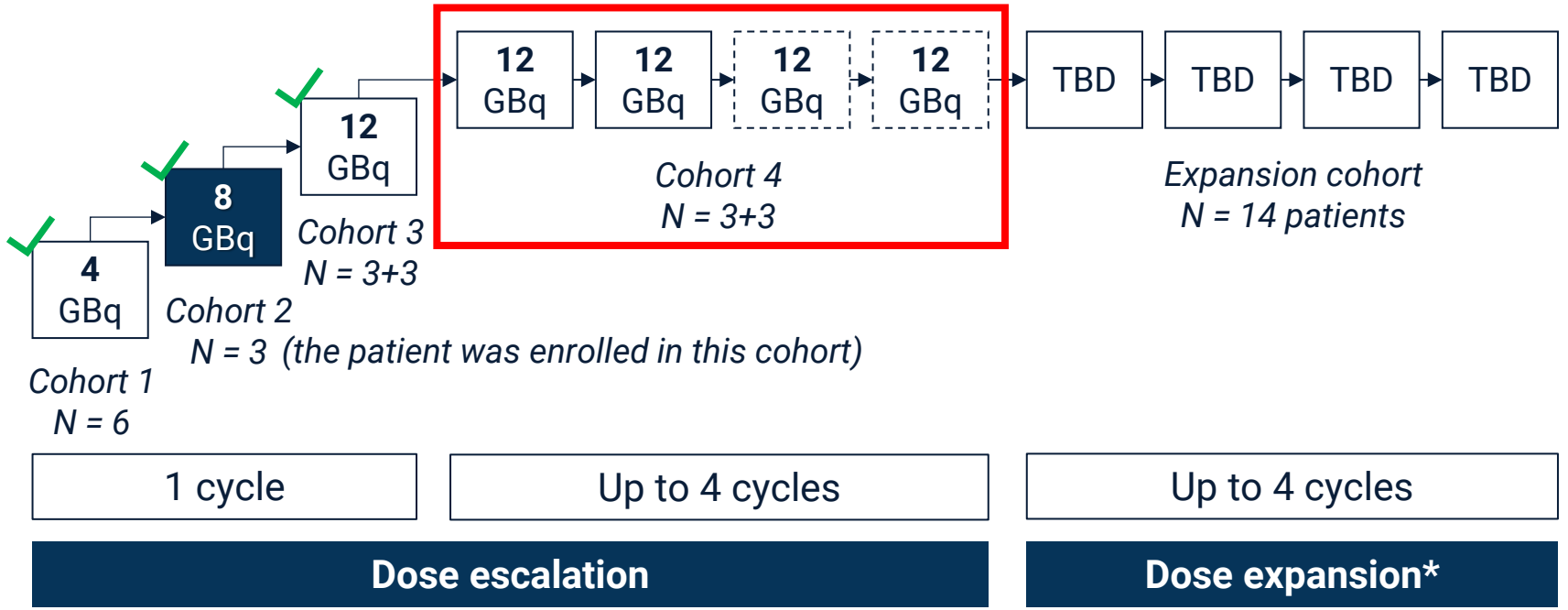
SECuRE Study Design

Patient population

- Progressive mCRPC, prior ADT and at least one ARPI (pre- or post-chemotherapy)[1]
- Positive ^{64}Cu-SAR-bisPSMA PET/CT scan
- ≥1 metastatic lesion on CT, MRI or bone scan

Maximum dose being investigated

- 12 GBq (>50% higher than the approved dose of Pluvicto®)[2]



Primary objectives include:

- To investigate the safety and tolerability of ^{64}Cu/Cu^{67}-SAR-bisPSMA
- To investigate the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA (PSA and radiographic response)

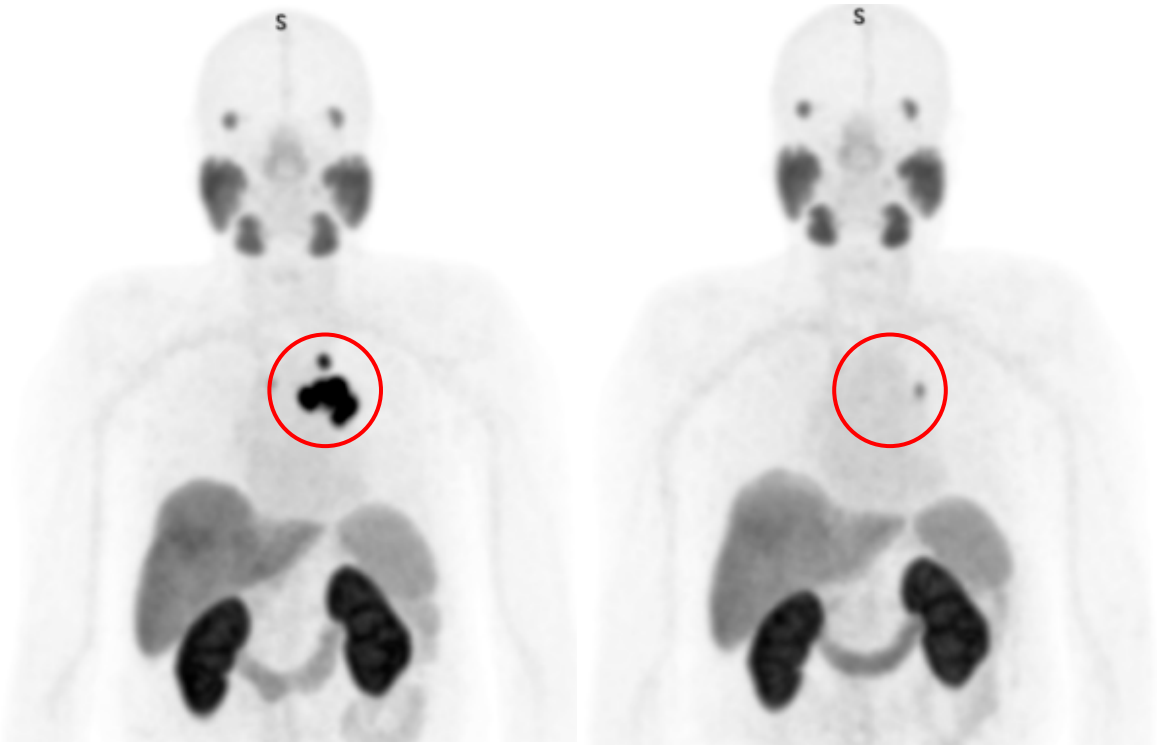
At the time of this presentation, no dose limiting toxicities have been observed in cohorts 1, 2, 3 and 4. In the United States, 5 sites are active. Additional sites in the United States and Australia are currently in start-up.

Dosimetry Phase not shown. Cohorts 1, 2 and 3 completed. Cohort 4 is currently recruiting (red box). Patients in cohort 4 may receive up to 4 doses of ^{67}Cu-SAR-bisPSMA (12 GBq). Doses for each cohort: cohort 1, 4 GBq (single dose); cohort 2, 8 GBq (single dose); cohort 3, 12 GBq (single dose); cohort 4, 12 GBq (multi-dose). *Dose level of the expansion cohort will be determined based on safety review from Cohort 4 (TBD: to be determined). 1. Additional eligibility criteria apply NCT04868604. 2. Pluvicto FDA Approved Product Information, accessed 7 Oct 2024.

Reduction in PSA (94%) following one cycle of ^{67}Cu-SAR-bisPSMA (8 GBq)

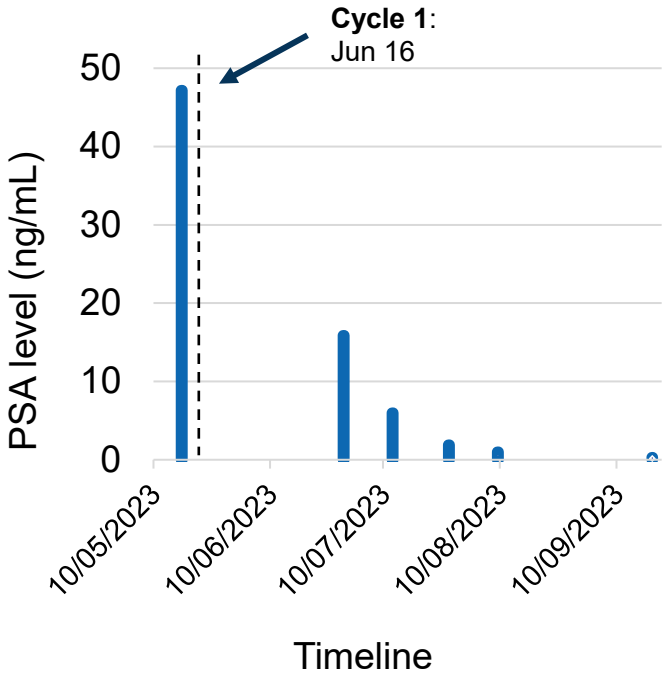
Partial response (RECIST)

Pre-^{67}Cu-SAR-bisPSMA (Baseline)	Post-^{67}Cu-SAR-bisPSMA (One cycle, 8 GBq)



24 May 2023 | 10 Aug 2023

PSA reduction following one cycle of ^{67}Cu-SAR-bisPSMA



Reductions in:

PSA

94%

Tumor volume

99%

Safety: xerostomia (Grade 1), dysgeusia (Grade 1), both improved; fatigue (Grade 2), resolved.

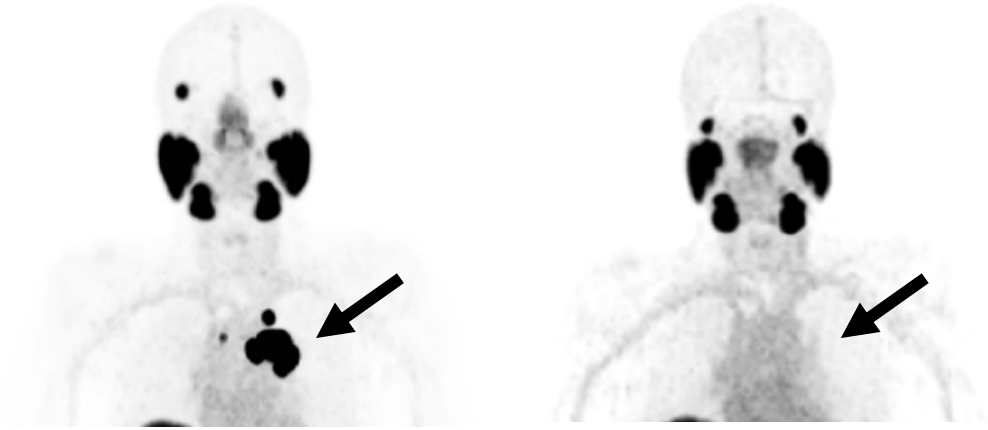
PET images show reduction in lesion uptake of ^{64}Cu-SAR-bisPSMA after one cycle of ^{67}Cu-SAR-bisPSMA (8 GBq). PSA reduced 99.4% (from 47.2 to 0.3 ng/mL; limit of detection 0.05 ng/mL). SUVmax reduced from 140.1 to 14.1 (-89.96%). SUVmean reduced from 34.2 to 8.4 (-75.39%). Tumor volume reduced from 51.7 to 0.5 (-98.97%). Partial response (RECIST v1.1). No adverse events (AEs) related to ^{64}Cu-SAR-bisPSMA. AEs related to ^{67}Cu-SAR-bisPSMA described above. Data cut off 24 Aug 2023. Images: maximum intensity projection.

Second cycle of ^{67}Cu-SAR-bisPSMA (8 GBq) leads to complete response

Multi-dose of ^{67}Cu-SAR-bisPSMA under EAP

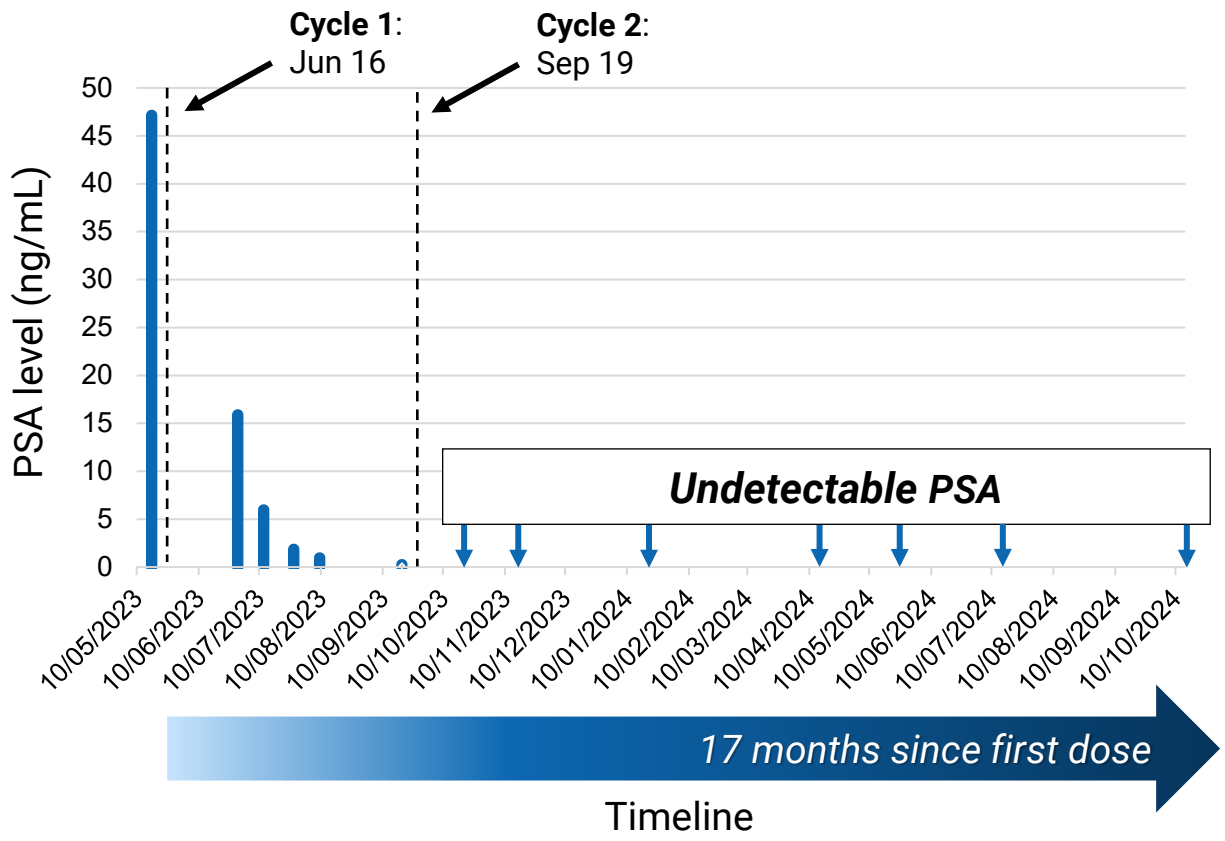
- Complete **anatomical** response (CT; RECIST v1.1)
- Complete **molecular** response (PET)
- Complete **biochemical** response (undetectable PSA)

Pre-^{67}Cu-SAR-bisPSMA (Baseline)	Post-^{67}Cu-SAR-bisPSMA (Two cycles, 8 GBq each)



Safety: thrombocytopenia (Grade 1), anaemia (Grade 3, improved to Grade 2).

PSA reduction following 2 doses of ^{67}Cu-SAR-bisPSMA



Images: PET scan showed no uptake of ^{64}Cu-SAR-bisPSMA above the background level following 2 doses of ^{67}Cu-SAR-bisPSMA, demonstrating a complete molecular response. Dash lines in graph: administration of ^{67}Cu-SAR-bisPSMA. EAP: Expanded Access Program. Data cut off 14 Oct 2024. PSA limit of detection: 0.05 ng/ml. Images: maximum intensity projection.

Conclusions

1. A single cycle of ^{67}Cu-SAR-bisPSMA led to a partial response (RECIST) and a reduction in PSA of 94% in a heavily pre-treated patient with mCRPC.

2. Two doses of ^{67}Cu-SAR-bisPSMA (8 GBq) led a complete response (assessed by CT [RECIST], PET [^{64}Cu-SAR-bisPSMA] and PSA).

3. The safety profile ^{67}Cu-SAR-bisPSMA was favourable: most AEs related to ^{67}Cu-SAR-bisPSMA were mild to moderate, which either improved or resolved over time.

4. The patient remains in follow-up with undetectable PSA for almost 13 months.

5. ^{67}Cu-SAR-bisPSMA may represent an effective option for the treatment of patients with mCRPC.