(316b) SECuRE: A dose escalation/expansion study to assess the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castration-resistant prostate cancer

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Background

Prostate cancer (PC) is common and despite recent advances in treatment options, patients with metastatic disease still have poor outcomes, warranting the development of new 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 SAR-bisPSMA, including the double PSMA binding moiety in ^{64}Cu-SAR-bisPSMA (imaging) and ^{67}Cu-SAR-bisPSMA (therapy), may offer advantages compared to currently used single-target PSMA agents (Tables 1 and 2, Figure 1).

Figure 1. SAR-bisPSMA Stylized Structure

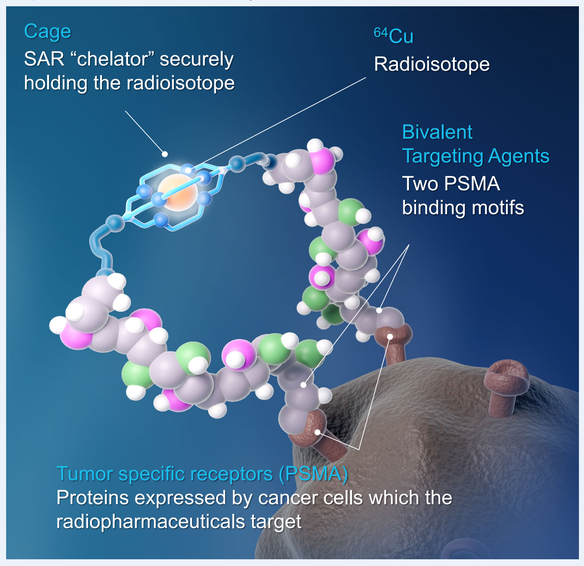


Table 1. Cu-64 Characteristics Compared to Ga-68 and F-18[2,3]

	Copper-64	Gallium-68	Fluorine-18
Half-life	12.7 hours	1.1 hours	1.8 hours
Typical product shelf-life	Up to 48 hours	Up to 4 hours	Up to 10 hours
Imaging window	1 to 30 hours*	50-100 mins	60-90 mins

*Up to 72 h for dosimetry

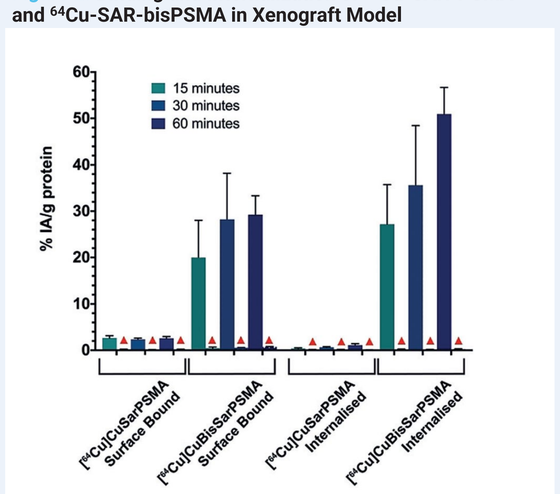
Table 2. Cu-67 Characteristics compared to Lu-177[4]

	Copper-67	Lutetium-177
Half-life	2.6 days	6.7 days
Decay mode	Beta emitter	Beta emitter
Range in tissue	~0.7 mm	~0.7 mm
Production mode	Electron accelerators	Nuclear reactors

Pre-clinical Rationale for Development of $^{64/67}$Cu-SAR-bisPSMA

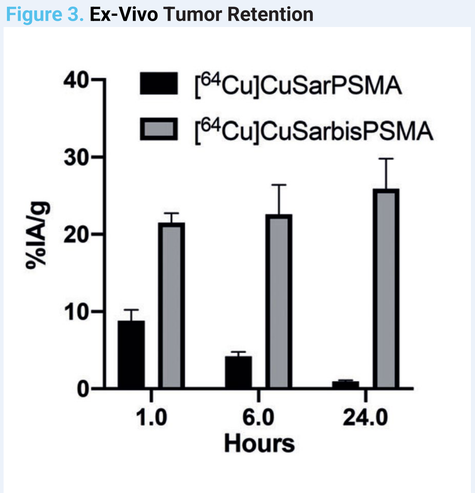
Preclinical models using PSMA-positive LNCaP cells demonstrate that bivalent ^{64}Cu-SAR-bisPSMA displays higher cell surface binding and internalization, low background uptake, and prolonged retention even at 24 hours post-injection compared to monovalent ^{64}Cu-SAR-PSMA (Figure 2, Figure 3).[5] Efficacy data in a prostate cancer xenograft study showed statistically significant ($p<0.001$) and dose-dependent tumor growth inhibition and increased survival in mice treated with ^{67}Cu-SAR-bisPSMA compared to the control group (Figure 4).[6]

Figure 2. Binding and Internalization of ^{64}Cu-SAR-PSMA and ^{64}Cu-SAR-bisPSMA in Xenograft Model



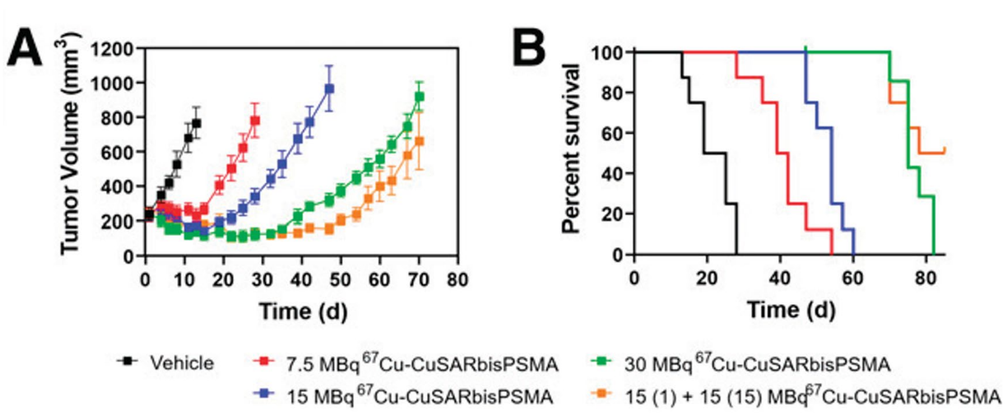
Binding to the cell surface and internalization of ^{64}Cu-SAR-PSMA and ^{64}Cu-SAR-bisPSMA in PSMA-positive LNCaP cells, expressed as % injected activity per mg of protein (%IA mg^{-1} ± SEM). Red triangles highlight the extent of cell binding and internalization under the same conditions except in the presence of a 100-fold excess of non-radioactive, SAR-PSMA or SAR-bisPSMA.

Figure 3. Ex-Vivo Tumor Retention



Ex vivo tumor uptake expressed as percent injected activity per gram tissue (%IA g^{-1}) (mean ± SEM, n = 3/group) in LNCap-tumor-bearing NSG mice following injection of either ^{64}Cu-SAR-PSMA (2 MBq, 0.9 nmol of peptide) or ^{64}Cu-SAR-bisPSMA (2 MBq, 0.2 nmol of peptide).

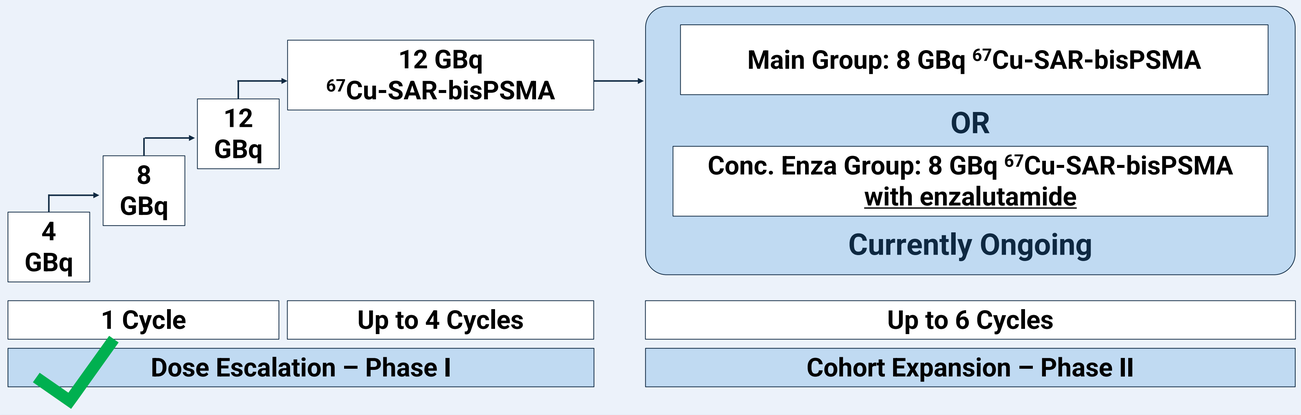
Figure 4. Anti-Tumor Effect of ^{67}Cu-SAR-bisPSMA in Xenograft Model



(A) Antitumor efficacy of ^{67}Cu-SAR-bisPSMA against LNCaP tumor xenografts, expressed as average tumor size (± SEM) (n = 8 per group).
(B) 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).

Study Design

SECuRE is a multi-center, open-label, non-randomized, dose-escalation, dose-finding, cohort expansion study of ^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA administered to participants with metastatic castration-resistant prostate cancer (mCRPC). This study consists of 3 phases: a ^{64}Cu-SAR-bisPSMA Dosimetry Phase, a Dose Escalation Phase (with ^{67}Cu-SAR-bisPSMA dosimetry) and a Cohort Expansion Phase. Dose Escalation has been completed, and the Safety Review Committee has recommended to proceed to Cohort Expansion Phase with 8 GBq of ^{67}Cu-SAR-bisPSMA, with an increase in the number of therapy cycles. The recently amended study protocol will focus on the evaluation of mCRPC participants in the pre-chemotherapy setting and include a subset of patients who may also receive ^{67}Cu-SAR-bisPSMA with enzalutamide.



Key Eligibility Criteria

1. Life expectancy > 6 months
2. Histological, pathological, and/or cytological confirmation of PC
3. Positive ^{64}Cu-SAR-bisPSMA PET/CT scan, where ^{64}Cu-SAR-bisPSMA uptake (SUVmax) of at least 1 known lesion is higher than that of the liver on the 1 hour PET/CT scan
4. ≥ 1 metastatic lesion that is present at screening CT, MRI, or bone scan imaging obtained ≤ 28 days prior to enrollment
5. Participants must have progressive mCRPC despite prior ADT and:
   - Cohort Expansion Main Group: Participant has progressed once or twice on ARPI. No concomitant ARPI on study allowed.
   - Cohort Expansion Concomitant Enzalutamide Group: Participant has progressed only once on prior ARPI.
6. Castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L)
7. Participants must have adequate organ function and ECOG 0-2
8. Prohibited previous systemic treatments in Cohort Expansion:
   - Previous treatment with a systemic radionuclide.
   - Prior treatment with cytotoxic chemotherapy for CRPC; prior treatment with PARP inhibitors.

Primary Objectives

^{64}Cu-SAR-bisPSMA Dosimetry Phase
- To determine the biodistribution and dosimetry of ^{64}Cu-SAR-bisPSMA and estimate the dosimetry of ^{67}Cu-SAR-bisPSMA

Dose Escalation Phase
- To determine the MTD or MFD of a single dose of ^{67}Cu-SAR-bisPSMA
- To determine the recommended dose of two doses of ^{67}Cu-SAR-bisPSMA

Cohort Expansion Phase
- To investigate the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in terms of PSA and radiographic response

Dose Escalation and Cohort Expansion Phase
- To determine the safety and tolerability of ^{67}Cu-SAR-bisPSMA

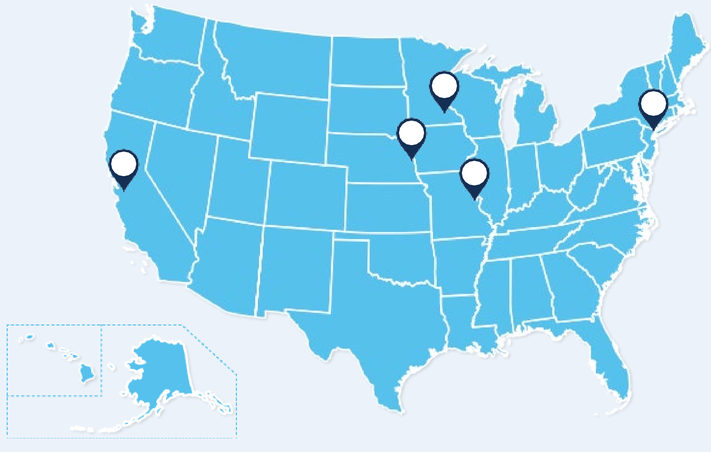
^{64}Cu-SAR-bisPSMA Dosimetry, Dose Escalation, and Cohort Expansion Phase
- To determine the safety and tolerability of ^{64}Cu-SAR-bisPSMA

Selected Secondary Objectives

Dose Escalation and Cohort Expansion Phase
- To investigate tumor response following treatment with ^{67}Cu-SAR-bisPSMA based on RECIST Version 1.1 and PCWG3
- To investigate rPFS following treatment with ^{67}Cu-SAR-bisPSMA based on PCWG3

Current Status & Locations

Enrollment of participants to the Cohort Expansion Phase is ongoing at the time of this presentation. Five sites in the United States are currently enrolling participants to the Cohort Expansion Phase of SECuRE (NCT04868604).



SECuRE

For more information on active sites, please visit: https://clinicaltrials.gov/study/NCT04868604

ClinicalTrials.gov Identifier: NCT04868604. This study is sponsored by Clarity Pharmaceuticals Ltd.
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Abstract Number: TPS5125

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