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

Geoffrey Johnson[1], Eva Lengyelova[2], Luke T. Nordquist[3], Vikas Prasad[4], Monique Anderson[2], Othon Gervasio[2], Michelle Parker[2], Robert M. Miller[2], Oliver Sartor[1], Scott T. Tagawa[5]

[1]Mayo Clinic, Rochester, MN; [2]Clarity Pharmaceuticals, Sydney, Australia; [3]XCancer, Omaha, NE; [4]Washington University in St. Louis, MO; [1]Mayo Clinic, Rochester, MN; [5]Weill Cornell Medical College of Cornell University, New York, NY

2024 SNMMI Poster Award Candidate

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).

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

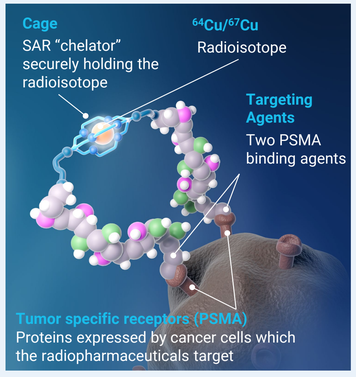
	Copper-64	Gallium-68	Fluorine-18
Half-life	12.7 hours	1.1 hours	1.83 hours
Typical product shelf-life	Up to 48 hours	Up to 4 hours	Up to 10 hours
Imaging window	1 to 30 hours*	50-100 mins	60-90 mins

*up to 72 h for dosimetry

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

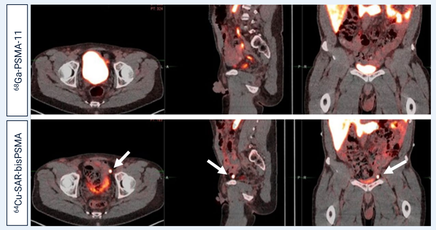
	Copper-67	Lutetium-177
Half-life	2.6 days	6.7 days
Decay mode	Beta emitter	Beta emitter
Range in tissue	~0.7 mm	~0.7 mm
Production mode	Electron accelerators	Nuclear reactors

Figure 1. SAR-bisPSMA stylized structure



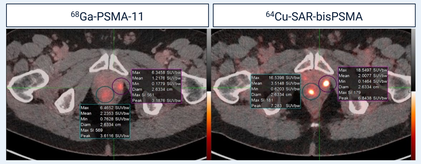
In the Phase I PROPELLER study in with PC scheduled for radical prostatectomy, ^{64}Cu-SAR-bisPSMA demonstrated 2-3 times higher tumor uptake and detection of additional PC lesions compared to ^{68}Ga-PSMA-11 PET (Figures 2 and 3)[5].

Figure 2. ^{64}Cu-SAR-bisPSMA detects lymph node not identified on ^{68}Ga-PSMA-11 PET



In the PROPELLER study, readers did not detect uptake in pelvic lymph nodes on the ^{68}Ga-PSMA-11 PET/CT (Top). PET/CT demonstrated uptake of ^{64}Cu-SAR-bisPSMA (200 MBq, Bottom, arrows) in a left pelvic lymph node according to both readers. PC was confirmed via histopathology. Interval between serial imaging: 7 days.

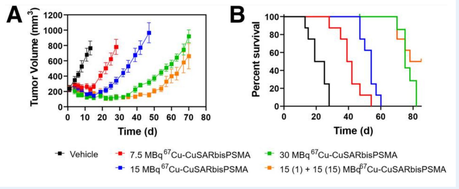
Figure 3. ^{64}Cu-SAR-bisPSMA demonstrated higher tumour uptake than ^{68}Ga-PSMA-11



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

Efficacy data in a PC 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 4. Anti-tumour 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).

Efficacy and safety results from two doses of ^{67}Cu-SAR-bisPSMA (8 GBq) administered to a metastatic castrate-resistant PC (mCRPC) patient have been recently reported. Prior to ^{67}Cu-SAR-bisPSMA, the patient had received several lines of therapy (androgen deprivation therapy [ADT], chemotherapy, abiraterone, enzalutamide and a clinical trial [PARP inhibitor]). The prostate-specific antigen (PSA) level (47.2 ng/mL at baseline) became undetectable following the treatment with ^{67}Cu-SAR-bisPSMA (limit of detection: 0.05 ng/mL; Figure 5). Molecular and anatomical complete responses have been confirmed (no uptake of ^{64}Cu-SAR-bisPSMA using PET [Figure 6], anatomical assessment using RECIST v1.1, respectively). Adverse events related to ^{67}Cu-SAR-bisPSMA were dry mouth, altered taste and thrombocytopenia (all Grade 1, improved), fatigue (Grade 2, resolved), anaemia (Grade 3, improved to Grade 2)[7].

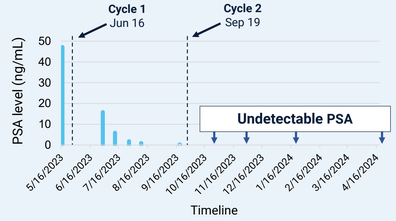


Figure 5. Undetectable PSA following 2 doses of ^{67}Cu-SAR-bisPSMA

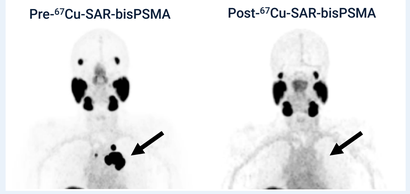


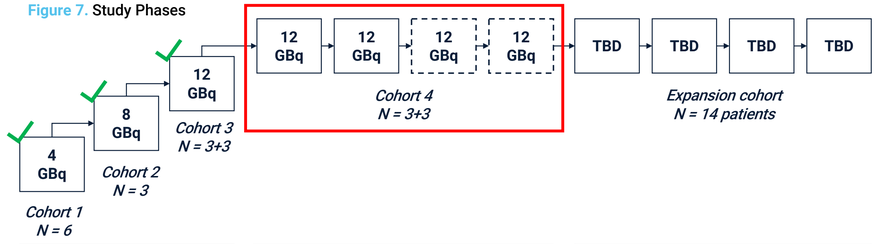
Figure 6. Uptake of ^{64}Cu-SAR-bisPSMA shown in lymph nodes before the treatment with ^{67}Cu-SAR-bisPSMA (left). No uptake was observed following 2 doses of ^{67}Cu-SAR-bisPSMA (right).

METHODS

Study Design

SECuRE is a Phase I/IIa multi-center, open-label, non-randomized, dose-escalation and cohort expansion study of ^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA. mCRPC patients with progression, prior exposure to at least one androgen receptor pathway inhibitor (ARPI), and positive ^{64}Cu-SAR-bisPSMA PET may be treated with ^{67}Cu-SAR-bisPSMA. The primary and key secondary objectives include assessment of ^{64}Cu- and ^{67}Cu-SAR-bisPSMA safety and dosimetry, determining the maximum tolerated dose (MTD) or maximum feasible dose (MFD) and anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA. Radiological response will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and Prostate Cancer Clinical Trials Working Group 3 (PCWG3). This study is being conducted in 3 phases: a ^{64}Cu-SAR-bisPSMA Dosimetry Phase (n=6), a ^{67}Cu-SAR-bisPSMA Dose Escalation Phase (n=up to 24), and a ^{67}Cu-SAR-bisPSMA Cohort Expansion Phase (n=14) (Dose Escalation and Expansion Phases depicted in Figure 7).

Figure 7. Study Phases



Cohorts 1, 2 and 3 completed. Cohort 4 is currently recruiting (red box). Patients in cohort 4 will receive 2 doses of ^{67}Cu-SAR-bisPSMA (12 GBq) according to the current study protocol. A protocol amendment is underway to allow 2 additional doses of ^{67}Cu-SAR-bisPSMA in cohort 4. A Safety Review Committee meeting will take place after 3 and 6 participants receive the first 2 doses in this cohort (minimum period of 6 weeks for safety follow-up). Doses for each cohort: cohort 1, 4 GBq (108 mCi, single dose); cohort 2, 8 GBq (216 mCi, single dose); cohort 3, 12 GBq (324 mCi, single dose); cohort 4, 12 GBq (324 mCi, multi-dose). *Dose expansion cohort. TBD: to be determined, dose based on the MTD or MFD, pending safety assessment of cohort 4.

METHODS

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. Castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L)
5. ≥1 metastatic lesion that is present at screening CT, MRI, or bone scan imaging obtained ≤28 days prior to enrolment
6. Participants must have adequate organ function and ECOG 0-2
7. Participants must have progressive mCRPC despite prior ADT and at least one ARPI
8. Previous systemic radionuclide treatment is allowed after pre-specified washout period

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

^{64}Cu-SAR-bisPSMA Dosimetry, Dose Escalation, and Cohort Expansion Phase

- To determine the safety and tolerability of ^{64}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-tumour 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

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 radiological progression free survival following treatment with ^{67}Cu-SAR-bisPSMA based on PCWG3

Current Status

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

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

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