(5100) COBRA: Assessment of safety and efficacy of ^{64}Cu-SAR-bisPSMA in patients with biochemical recurrence of prostate cancer following definitive therapy

Luke Nordquist[1], Eva Lengyelova[2], Daniel Saltzstein[3], David Josephson[4], Gregg E. Franklin[5], Glynn Morrish[2], Othon Gervasio[2], Michelle Parker[2], Robert M. Miller[2], Neal Shore[6]
[1]XCancer, Omaha, NE; [2]Clarity Pharmaceuticals, Sydney, Australia; [3]Urology San Antonio, San Antonio, TX; [4]Tower Urology, Los Angeles, CA; [5]New Mexico Cancer Center, Albuquerque, NM; [6]Carolina Urologic Research Center, Myrtle Beach, SC

Background

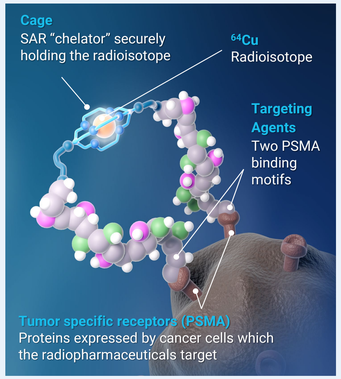
- Between 20-40% of patients with prostate cancer (PC) will relapse within 10 years of their primary PC treatment, as identified through rising prostate-specific antigen (PSA) levels[1]. Most relapses will occur within 5 years after definitive therapy[2]. Early diagnosis of biochemical recurrence (BCR) with accurate staging is essential to informing optimal treatment decision-making. Prostate-specific membrane antigen (PSMA) is used as an imaging target in PC. Current PSMA positron emission tomography (PET) agents have high specificity, but low sensitivity[3-5].
- ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA PET agents due to the bivalent structure of SAR-**bis**PSMA and longer half-life ($t_{1/2}$) of ^{64}Cu (12.7h), compared to monovalent PSMA PET agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$<2h)[3-6] (**Figure 1, Table 1**).
- Clinical evidence has demonstrated 2-3x higher tumor uptake and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11[6].
- This led to the development of the COBRA study: a phase I/II study assessing the safety and efficacy of ^{64}Cu-SAR-bisPSMA in PC patients with BCR and negative or equivocal standard of care (SOC) imaging.

Table 1: Cu-64 characteristics compared to Ga-68 and F-18[3,4]

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

*up to 72 h for dosimetry

Figure 1. SAR-bisPSMA stylized structure

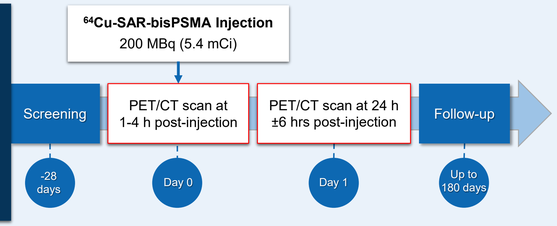


Methods

Study Design

Key Eligibility Criteria:

- Confirmed adenocarcinoma of prostate with subsequent definitive therapy
- Suspected recurrence of PC based on rising or detectable PSA
- Negative or equivocal findings for PC on conventional imaging per SOC within 60 days prior to Day 0



Primary Objective	*Primary Endpoint*
To investigate the safety and tolerability of ^{64}Cu-SAR-bisPSMA	Incidence and severity of treatment-emergent Adverse Events and Serious Adverse Events (SAEs) following the administration of ^{64}Cu-SAR-bisPSMA
To investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to correctly detect recurrence of PC	Assessed independently for Day 0 and Day 1: • Correct detection rate (CDR): proportion of true positive participants out of all scanned participants who had at least one evaluable reference standard datapoint • Region-level positive predictive value (PPV): proportion of true positive regions out of all positive regions on the ^{64}Cu-SAR-bisPSMA PET/computed tomography (CT) scan with corresponding evaluable reference standard

PET assessment and Reference Standard: The ^{64}Cu-SAR-bisPSMA PET/CT scans were interpreted by 3 independent, blinded, central readers. The findings were assessed against a composite Reference Standard (may consist of histopathology, follow-up SOC imaging and PSA levels) determined by an independent, blinded, central expert panel.

Results

Patient distribution: 52 patients received ^{64}Cu-SAR-bisPSMA (Safety Set) → 2 replacements (protocol deviations) → 50 proceeded to follow-up → 8 without reference standard → 42 with reference standard (Efficacy Set)

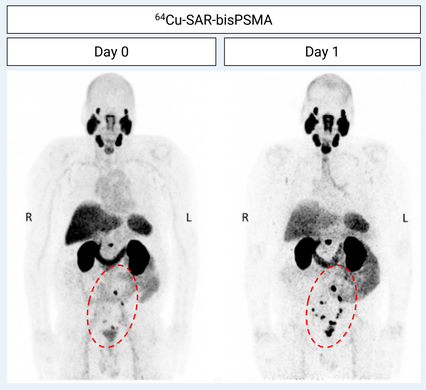
Safety

Table 2: Treatment-Emergent Adverse Events (TEAEs)

Unrelated TEAEs	N (%)
Participants with at least one TEAE	9 (17.3)
Related TEAEs	N (%)
Worsening Type 2 diabetes mellitus	1 (1.9)

- Safety analysis set: all patients who received ^{64}Cu-SAR-bisPSMA, **n=52**
- **Only one related TEAE was reported in one patient** (grade 2, worsening of type II diabetes), resolved.

Total number of lesions identified increased from Day 0 to Day 1



82% increase in the total number of lesions, from **70** (Day 0) to **129** (Day 1) *(average across 3 readers)*

Table 3. Number of lesions per participant with a positive ^{64}Cu-SAR-bisPSMA scan

^{64}Cu-SAR-bisPSMA PET	Day 0	Day 1
Mean range	2.4-2.8	2.8-4.1
SD range	2.4-3.6	3.1-4.5
Median	1.0	1.0-2.0
Min, Max	1, 15	1, 15
Sum of all lesions	53-80	82-153

The number of lesions per participant data only include patients who had a positive ^{64}Cu-SAR-bisPSMA PET. The table shows the ranges across the 3 readers. The median values across readers was the same on Day 0 (i.e. 1.0), therefore no ranges are provided.

Figure 2. Day 1 imaging identified additional lesions compared to Day 0 imaging. ^{64}Cu-SAR-bisPSMA PET showing positive LNs in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on Day 1.

Identification of pelvic lesion by ^{64}Cu-SAR-bisPSMA in a patient with equivocal entry scan using ^{18}F-DCFPyL, Pylarify®

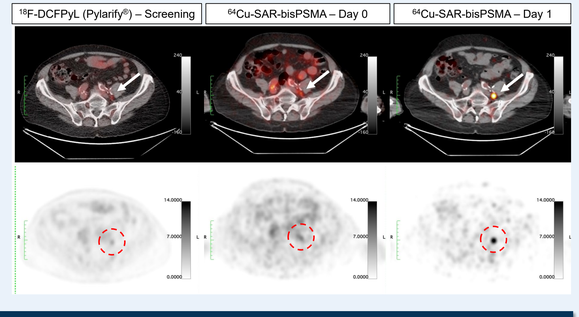


Figure 3. Identification of a lesion in the pelvic region using ^{64}Cu-SAR-bisPSMA on Day 1 imaging (right), negative on Day 0 imaging (center) and equivocal on screening ^{18}F-DCFPyL imaging (left). SUVmax of the lesion across scans (arrows in top images and red circles in bottom images) was 2.3, 4.3 and 17.5 (^{18}F-DCFPyL Day 0 and Day 1 ^{64}Cu-SAR-bisPSMA, respectively). Top images: PET/CT fusion. Bottom images: PET.

*^{64}Cu-SAR-bisPSMA imaging led to clinicians changing their intended treatment plan in **48%** of the patients.*

Increase in DR and CDR from Day 0 to Day 1

Table 4. Patient level DR, CDR and Region level PPV

^{64}Cu-SAR-bisPSMA PET	Day 0	Day 1
Patient Level DR (N=50)		
Positive patients, n (%)	22-29 (44-58)	29-40 (58-80)
Equivocal patients, n (%)	2-6 (4-12)	0-7 (0-14)
Negative patients, n (%)	15-25 (30-50)	6-21 (12-42)
Patient Level CDR (N=42)		
TP patients, n (%)	9-12 (21.4-28.6)	12-16 (28.6-38.1)
CDR % (95% CI)	21.4-28.6 (10.3-44.6)	28.6-38.1 (15.7-54.4)
Region Level PPV (N=42)		
TP regions, n (%)	9-14 (4.6-7.2)	13-17 (6.7-8.7)
FP regions, n (%)	14-20 (7.2-10.3)	17-35 (8.7-18.0)
PPV (95% CI)	39.1-44.8 (19.7-64.3)	32.7-43.3 (20.3-62.6)

The table shows the ranges across the 3 readers. DR: detection rate; CDR: correct detection rate; PPV: predictive positive value; TP: true positive; FP: false positive. N: number of participants.

34% more patients had a positive ^{64}Cu-SAR-bisPSMA scan on Day 1 (71%) vs. Day 0 (53%) imaging *(average across 3 readers)*

- Pelvic lymph nodes, had a Day 0 PPV range of 71.4–87.5% (95% CI 29.0–99.7) and Day 1 of 50.0–61.5% (15.7–86.1).
- The CDR and PPV results were substantially impacted by the large number of lesions that were detected, but unable to be biopsied (not clinically appropriate), coupled with the low sensitivity of the SOC scans that were used for co-localization.

^{64}Cu-SAR-bisPSMA detects lesions in the 2-millimeter range

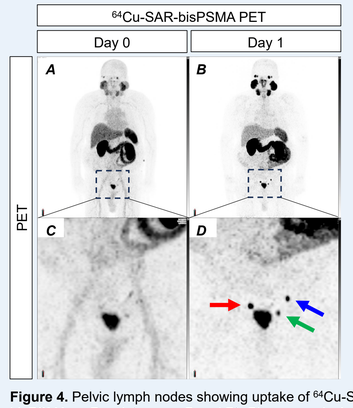


Figure 4. Pelvic lymph nodes showing uptake of ^{64}Cu-SAR-bisPSMA on Day 1 (arrows, B and D). Blue arrow: lesion size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1. Green arrow: lesion size also 3.8 mm x 4.4 mm, SUVmean 11.9, SUVmax 12.8 and TBR 75.3. Red arrow: size >5 mm. Inset in top images (A, B) displays pelvic region (bottom images, C and D).

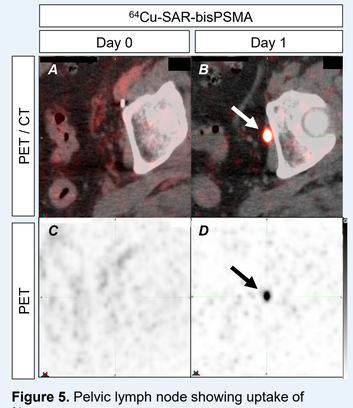


Figure 5. Pelvic lymph node showing uptake of ^{64}Cu-SAR-bisPSMA on Day 1 (arrows, B and D), with no uptake on Day 0 (A and C). The lesion shown in B and D is the same as shown in Figure 4, blue arrow (size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1).

Conclusions

COBRA showed for the first time that ^{64}Cu-SAR-bisPSMA is safe and effective in detecting PC lesions in patients with BCR. Only one TEAE was related to ^{64}Cu-SAR-bisPSMA (resolved). Next-day ^{64}Cu-SAR-bisPSMA PET localised disease in up to 80% of patients with negative or equivocal SOC imaging at study entry, detecting lesions as small as 2 mm. More lesions and more patients with a positive scan were identified on ^{64}Cu-SAR-bisPSMA PET compared to SOC scans, and on next-day vs. same-day imaging. These findings have important clinical implications as the identification of additional and small lesions can inform different treatment pathways for patients with BCR of PC.

References: 1. Ward and Moul. Nat Clin Pract Urol , 2005. 2. Pak et al. Int J Clin Onc. 2019. 3. Locametz FDA approved product information. Accessed on the 9 May 2024. 4. Pylarify FDA approved product information. Accessed on the 9 May 2024. 5. Posluma FDA approved product information Access on the 9 May 2024. 6. Lengyelova & Emmett et al. ASCO, 2023.