(1834) COBRA: Assessment of reader agreement for ^{64}Cu-SAR-bisPSMA PET 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], 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-bisPSMA and longer half-life ($t_{1/2}$) of ^{64}Cu (12.7 h), compared to monovalent PSMA PET agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$ < 2 h).[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 approved PSMA agents. [6,7]
- 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.

Figure 1. SAR-bisPSMA stylized structure

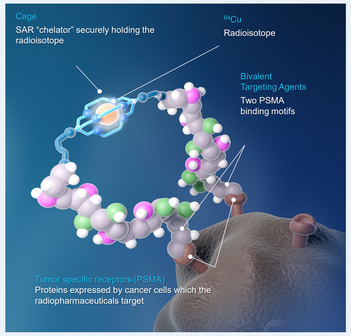


Table 1. Cu-64 characteristics compared to Ga-68 and F-18[3,4]

	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

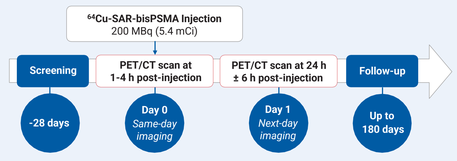
*up to 72 h for dosimetry

Methods

Study Design

Key Eligibility Criteria

- Confirmed adenocarcinoma of the 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 Objectives	Selected Primary Endpoints
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 same-day and next-day imaging: • Correct detection rate (CDR): proportion of true positive participants out of all scanned participants who had at least one evaluable reference standard datapoint

PET Assessment and Reference Standard:

- The ^{64}Cu-SAR-bisPSMA PET/CT scans were interpreted by the local investigator and 3 independent, blinded, central readers The findings of the central readers were assessed against a composite Reference Standard (may consist of histopathology, follow-up conventional imaging, and PSA levels) determined by an independent, blinded, central expert panel.
- Follow-up SOC PSMA PET scans were interpreted by 2 blinded central readers (recorded number of lesions), independent of the ^{64}Cu-SAR-bisPSMA PET readers.

Detection Rate:

Proportion of participants with a positive scan (presence of ≥ 1 PET-positive lesion on the scan) out of all scans.

Number of lesions:

A ^{64}Cu-SAR-bisPSMA PET-positive lesion was defined as focal uptake that was greater than physiologic background uptake in that tissue or greater than adjacent background if no physiologic uptake was expected and judged by the reader to be suspicious for disease. The number of PET-positive lesion(s) in each anatomical subregion was documented. The readers were required to evaluate the PET scans individually for the presence of pathological ^{64}Cu-SAR-bisPSMA uptake in the prostate bed/gland, pelvic lymph nodes, extra pelvic lymph nodes, visceral/soft tissue and bone.

Comparison of ^{64}Cu-SAR-bisPSMA PET to follow-up SOC PSMA PET

The ^{64}Cu-SAR-bisPSMA PET was interpreted by three blinded, independent central readers and the follow-up SOC PSMA PET was interpreted by two independent, central expert panel readers (distinct from the ^{64}Cu-SAR-bisPSMA PET readers). Each reader recorded the number of lesions on each scan and the number of lesions identified were compared. The readers interpreting the ^{64}Cu-SAR-bisPSMA scans had no access to the follow-up SOC PSMA scans/results, and vice versa.

Assessment of Intra- and Inter-Reader Agreement:

- Patient-level detection rate was used to assess intra- and inter-reader agreement, and to compare results between unblinded local and blinded central read of the ^{64}Cu-SAR-bisPSMA scans.
- Inter-reader agreement between 3 central readers was assessed using initial read results for all patients with Fleiss' overall multi-assessor kappa statistics.
- For assessment of intra-reader agreement, Cohen's pairwise kappa was used. Each central reader assessed a random subset of 16 same-day and 16 next-day scans for a second time after a washout period of at least three weeks following their initial read to minimize recall bias.

Results

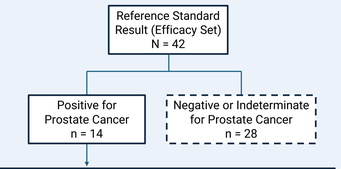
Correct Detection Rate of ^{64}Cu-SAR-bisPSMA was higher when using only histopathology as Reference Standard vs. follow-up conventional imaging, and on next-day imaging vs. same-day imaging

Participant distribution: 52 participants received ^{64}Cu-SAR-bisPSMA (Safety Set) → 50 proceeded to follow-up (Full Analysis Set, FAS) → 8 without reference standard → 42 with reference standard (Efficacy Set)

Table 2. Reference Standard Panel Results (Full Analysis Set)

	Total (N* = 50)
Reference Standard Result, N*	**50**
Positive, n (%)	14 (28)
Negative or Indeterminate, n (%)	28 (56)
Non-evaluable, n (%)	8 (16)
Histopathology Results, n†	**9**
Positive, n (%)	7 (77.8)
Negative, n (%)	2 (22.2)
Follow-Up Conventional Imaging Results, n†	**39**
Positive, n (%)	11 (28.2)
Negative or Equivocal, n (%)	28 (71.8)
PSA Response to Focal Therapy, n†	**8**
Confirmed PSA Response, n (%)	1 (12.5)
No Confirmed PSA Response, n (%)	7 (87.5)

***N** indicates the total number of participants in the Full Analysis Set. †**n** indicates the number of participants with non-missing data for the given parameter



- CDR was considerably higher when using the gold standard of histopathology as the reference standard (48.1% and 70.4% on same- and next-day imaging, respectively), compared to the composite reference standard (15.1% and 19.8% on same- and next-day imaging, respectively) **(Table 2)**
- One adverse reaction was reported: worsening of grade 2 diabetes, resolved

Table 3. Participant-Level DR and CDR (Reference Standard Comparison)

	^{64}Cu-SAR-bisPSMA Same-day imaging	^{64}Cu-SAR-bisPSMA Next-day imaging
Participant Level DR (N = 50) †		
Central readers: DR % (95% CI)	44-58% (30-71.8)	58-80% (95% CI 43.2-90)
Local reader: DR %	46%	56%
Participant Level CDR using Composite Reference Standard (n = 42) †		
CDR % (95% CI)	19.0-26.2 (8.6-42.0)	26.2-33.3 (13.9-49.5)
Participant Level CDR using Histopathology Only (n = 9) †		
CDR %	44.4-55.6	55.6-77.8
Participant Level CDR using Conventional Imaging Only (n = 39) *†		
CDR %	10.3-20.5	23.1-25.6

*n indicates the number of participants with available data for the given parameter. †Ranges across 3 blinded central readers. DR, detection rate; CDR, correct detection rate; TP, true positive

- The CDR results using the composite reference standard 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 conventional imaging scans that were used for the validation of ^{64}Cu-SAR-bisPSMA scan findings **(Table 3)**

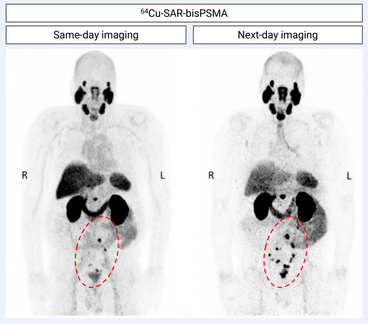


Figure 2. Next-day imaging identified additional lesions compared to same-day imaging. ^{64}Cu-SAR-bisPSMA PET showing positive lymph nodes in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on next-day imaging.

82% increase in the total number of lesions, from **70** on same-day to **129** on next-day imaging *(average across 3 readers)*

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

Detection rate on same- and next-day imaging with ^{64}Cu-SAR-bisPSMA was higher than that observed on follow-up conventional imaging, including SOC PSMA PET, by Day 90 and Day 180

Table 5. Detection Rates of Same- and Next-Day ^{64}Cu-SAR-bisPSMA PET and Follow-Up Conventional Imaging by Day 90 and Day 180

	^{64}Cu-SAR-bisPSMA Same-Day Imaging[1] N = 50	^{64}Cu-SAR-bisPSMA Next-Day Imaging[1] N = 50	Follow-Up Conventional Imaging by Day 90[2] n = 39	Follow-Up Conventional Imaging by Day 180[2] n = 30
Detection Rate, mean	52.7%	70.7%	23%	8.5%
Detection Rate, range	44-58%	58-80%	15-31%	7-10%
95% CI	30-71.8	43.2-90	NA	NA

1. ^{64}Cu-SAR-bisPSMA PET/CT scans interpreted by 3 blinded central readers. Mean and range across the 3 readers. 2. Follow-up conventional imaging scans interpreted by 2 blinded central readers independent of the ^{64}Cu-SAR-bisPSMA central readers. CI, confidence interval; NA, not applicable.

- Follow-up SOC PSMA PET was obtained in 20 participants (13 with ^{68}Ga-PSMA-11 and 7 with ^{18}F-DCFPyL)
- Median time from same-day ^{64}Cu-SAR-bisPSMA imaging to follow-up PSMA PET: 73.5 days (range, 29-180 days)
- More lesions and more patients with a positive scan identified by ^{64}Cu-SAR-bisPSMA vs. SOC PSMA PET, and on next-day vs. same-day imaging
- Results indicate that ^{64}Cu-SAR-bisPSMA is able to identify lesions from 29 days to more than 6 months earlier than SOC PSMA agents

Table 6. Detection Rate and Sum of Lesions Identified in Follow-Up SOC PSMA PET Subset of 20 COBRA participants

	^{64}Cu-SAR-bisPSMA Same-day imaging	^{64}Cu-SAR-bisPSMA Next-day imaging	Follow-Up SOC PSMA PET
Positive scan, n (%)*	14 (70)	18 (90)	12 (60)
Sum of lesions, avg.**	26.3	52.6	20.0

*Number (and percentage) of participants who had a positive scan confirmed by at least 1 reader (3 readers for ^{64}Cu-SAR-bisPSMA, 2 independent readers for follow-up SOC PSMA PET).
**Average of the "sum of lesions" (across readers) in participants with a positive scan for each respective tracer

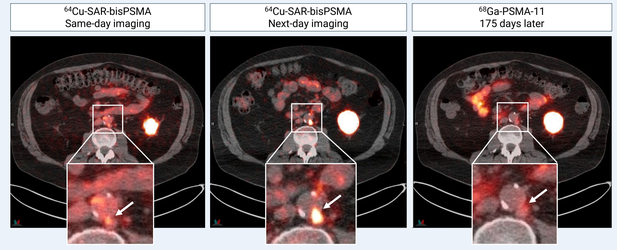


Figure 3. Retroperitoneal lymph node detected by ^{64}Cu-SAR-bisPSMA on next-day imaging (identified by all 3 central readers). Lymph node involvement was not identified on the ^{68}Ga-PSMA-11 scan performed 176 days post-Day 0 (i.e. 175 days post the ^{64}Cu-SAR-bisPSMA PET/CT that detected the LN) according to central read. Histopathology, performed on Day 190, confirmed the presence of prostate cancer in the extra-pelvic lymph node region in this patient. PET/CT fusion. Images below full scans represent inset highlighted on full scans.

Detection rate of central and local reads, inter- and intra-reader agreement of same- and next-day scans

Table 7. Inter- and Intra-Reader Agreement on Same-Day and Next-Day ^{64}Cu-SAR-bisPSMA PET

	Central Reader 1	Central Reader 2	Central Reader 3
Same-Day PET-positivity			
Inter-reader agreement*	Concordance reader 1 vs. 2: 82% Concordance reader 1 vs. 3: 70% Concordance reader 2 vs. 3: 80% Fleiss' Kappa for all 3 readers: 0.545 (0.411, 0.680)		
Intra-reader agreement**	Cohen's Kappa: 1.000 (1.000, 1.000)	Cohen's Kappa: 0.862 (0.603, 1.000)	Cohen's Kappa: 0.5 (0.076, 0.924)
Next-Day PET-positivity			
Inter-reader agreement*	Concordance reader 1 vs. 2: 82% Concordance reader 1 vs. 3: 80% Concordance reader 2 vs. 3: 66% Fleiss' Kappa for all 3 readers: 0.421 (0.256, 0.586)		
Intra-reader agreement**	Cohen's Kappa: 0.667 (0.241, 1.000)	Cohen's Kappa: 0.590 (0.078, 1.000)	Cohen's Kappa: 0.733 (0.389, 1.000)

*Pairwise concordance defined as: (# of concordant values across the 2 readers) / (# of concordant values + # of discordant values across the 2 readers). The numerator, denominator, and Concordance are shown for each pair.

Conclusions

- ^{64}Cu-SAR-bisPSMA PET demonstrated a high DR in patients with BCR of prostate cancer and negative or equivocal baseline standard of care imaging.
- More lesions and more patients with a positive scan were identified on ^{64}Cu-SAR-bisPSMA PET vs. SOC scans, and on next-day vs. same-day imaging.
- The CDR was considerably higher when using the gold standard of histopathology to verify ^{64}Cu-SAR-bisPSMA PET lesions vs. follow-up conventional imaging.
- More lesions were detected using ^{64}Cu-SAR-bisPSMA in a subset of participants who had follow-up SOC PSMA PET up to 180 days later, demonstrating that ^{64}Cu-SAR-bisPSMA may be able to identify lesions earlier than SOC PSMA PET agents.
- A high degree of inter- and intra-reader agreement across both scan days was observed, highlighting the reliability of ^{64}Cu-SAR-bisPSMA PET interpretations. The blinded and unblinded reads yielded similar detection rates.
- These findings have important clinical implications, as consistent and reliable image interpretations ensure consistent diagnoses, broad clinical applicability, and effective treatment planning, ultimately leading to improved patient outcomes. Furthermore, these results foster confidence in ^{64}Cu-SAR-bisPSMA as a new PET agent in biochemically recurrent prostate cancer.

References:
1. Ward JF, Moul JW. *Nat Clin Pract Urol.* 2005; 2(4): 174-82. 2. Pak S et al. *Int J Clin Oncol.* 2019; 24(10): 1238-1246. 3. Locametz. Prescribing Information. Novartis;2023. 4. Pylarify. Prescribing Information. Lantheus; 2023. 5. Posluma. Prescribing Information. Blue Earth Diagnostics; 2023. 6. Lengyelova et al. ASCO, 2023. 7. Nordquist et al. ASCO, 2024.
ClinicalTrials.gov Identifier: NCT05249127. This study is sponsored by Clarity Pharmaceuticals Ltd. Corresponding author: Dr. Luke Nordquist drluke@xcancer.com