^{64}Cu-SAR-bisPSMA PET/CT Compared to SOC PSMA PET/CT in Biochemical Recurrence of Prostate Cancer: A Close-Up of the Phase II COBRA Trial

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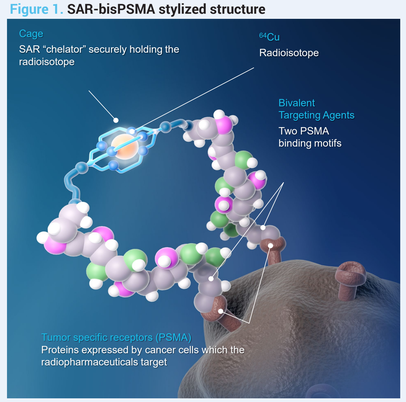
COBRA

Background

- Early diagnosis of prostate cancer (PC) biochemical recurrence (BCR) with accurate staging is essential to informing optimal treatment decision-making. Current PSMA positron emission tomography (PET) agents have high specificity, but low sensitivity.[1-3]
- ^{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 (12.7 h), compared to monovalent PSMA PET agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$ < 2 h).[1-4] **(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.[4-5]
- 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.

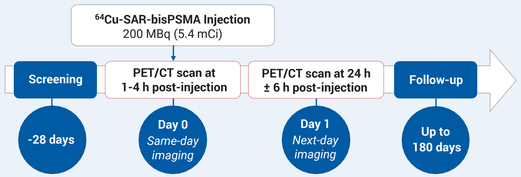
Figure 1. SAR-bisPSMA stylized structure



Methods

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: • Participant-level 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

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.

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 PC. 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 (LN), extra pelvic LNs, visceral/soft tissue and bone.

Results

Participant distribution: 52 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)

Correct Detection Rate, number of lesions, and number of participants with a positive scan were all higher on next-day vs. same-day ^{64}Cu-SAR-bisPSMA PET/CT

- **Participant-level detection rate** was 44-58% (95% CI 30-71.8) on same-day imaging vs. 58-80% (95% CI 43.2-90) on next-day imaging (ranges across 3 blinded central readers; N = 50 evaluable)
- **CDR using the composite reference standard** was 19.0-26.2% (95% CI 8.6-42.0) on same-day imaging vs. 26.2-33.3% (95% CI 13.9-49.5) on next-day imaging (ranges across 3 blinded central readers; N = 42 evaluable)
  - CDR was 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
- **Number of participants with a positive ^{64}Cu-SAR-bisPSMA scan increased** from 53% on same-day imaging to 71% on next-day imaging (average across 3 readers)
- **Total number of lesions seen on ^{64}Cu-SAR-bisPSMA increased** from 70 on same-day to 129 on next-day imaging (average across 3 readers)

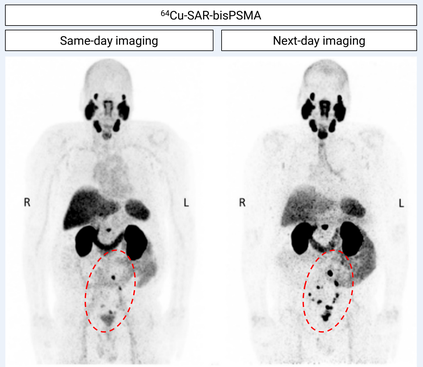


Figure 1. Next-day imaging identified additional lesions compared to same-day imaging. ^{64}Cu-SAR-bisPSMA PET showing positive LNs in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on next-day imaging.

82% increase in the total number of lesions on next-day vs. same-day imaging *(average across 3 readers)*

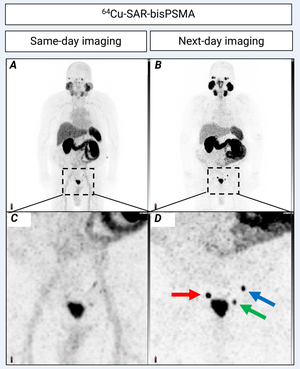


Figure 2. Pelvic LNs showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B and D). Blue arrow: lesion size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1. Green arrow: lesion size also 3.8 mm x 4.4 mm, SUVmean 11.9, SUVmax 12.8 and TBR 75.3. Red arrow: size > 5 mm. Inset in top images (A, B) displays in pelvic region (bottom images, C and D).

Correct Detection Rate was highest when using histopathology as the only Reference Standard vs. follow-up conventional imaging only or the Composite Reference Standard

Table 1. Participant-Level CDR (Reference Standard Comparison)

	^{64}Cu-SAR-bisPSMA Same-day imaging	^{64}Cu-SAR-bisPSMA Next-day imaging
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

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

^{64}Cu-SAR-bisPSMA PET/CT accurately detected more lesions up to 6 months earlier in participants who received follow-up SOC PSMA PET

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

Table 2. Detection Rate and Sum of Lesions Identified in Follow-Up SOC PSMA PET Subset of 20 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

*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

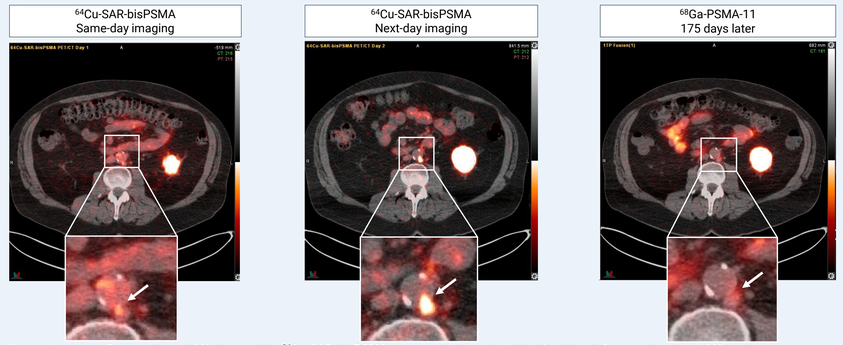


Figure 3 (above). Retroperitoneal LN detected by ^{64}Cu-SAR-bisPSMA on next-day imaging (identified by all 3 central readers). LN involvement was not identified on the ^{68}Ga-PSMA-11 scan performed 176 days post-Day 0 (i.e. 175 days post the ^{64}Cu-SAR-bisPSMA PET/CT that detected the LN) according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

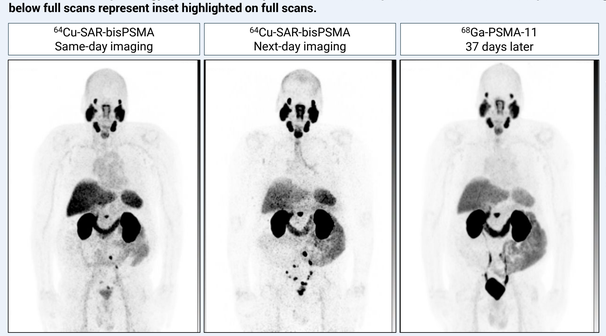


Figure 4 (left). Follow-up SOC PSMA scan from same participant as Figure 1. Multiple pelvic LNs detected by 64Cu-SAR-bisPSMA on same- and next-day imaging (identified by all 3 central readers). Follow-up images completed at 37 days post-Day 0 identified multiple pelvic lesions as positive according to central read.

Conclusions

The COBRA study showed that ^{64}Cu-SAR-bisPSMA is effective in detecting PC lesions in patients with BCR and negative or equivocal SOC imaging at study entry. Next-day ^{64}Cu-SAR-bisPSMA PET imaging localized disease in up to 80% of patients. More lesions and more participants with a positive scan were identified on ^{64}Cu-SAR-bisPSMA PET compared to SOC follow-up PSMA 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. These findings have important clinical implications as accurate staging and early identification of lesions can inform different treatment pathways for patients with BCR of PC.

References: 1. Locametz. Prescribing Information. Novartis;2023. 2. Pylarify. Prescribing Information. Lantheus; 2023. 3. Posluma. Prescribing Information. Blue Earth Diagnostics; 2023. 4. Lengyelova et. ASCO, 2023. 5. Nordquist et al. ASCO, 2024.

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