(44) COBRA: Assessment of the efficacy of ^{64}Cu-SAR-bisPSMA using histopathology as reference standard in patients with biochemical recurrence of prostate cancer following definitive therapy

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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 (12.7 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

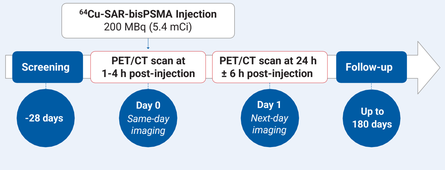
*up to 72 h for dosimetry

Methods

Study Design

Key Eligibility Criteria

- Confirmed adenocarcinoma of 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



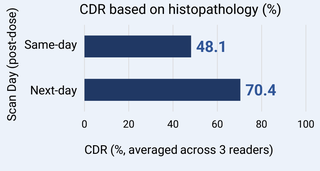
Primary Objective	Primary Endpoint
To investigate the safety and tolerability of ^{64}Cu-SAR-bisPSMA	Incidence and severity of treatment-emergent Adverse Events and Serious Adverse Events (SAEs) following the administration of ^{64}Cu-SAR-bisPSMA
To investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to correctly detect recurrence of PC	Assessed independently for 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 • 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)

High CDR based on histopathology used as reference standard



Up to 78% CDR using histopathology as the reference standard *(next-day imaging, results from 2 out of 3 readers)*

- CDR was considerably higher when using the gold standard of histopathology as the reference standard, highlighting the limitations of using less sensitive methods to verify the ^{64}Cu-SAR-bisPSMA PET findings.
- Of the 9 participants sampled (regions: 2 bone, 2 extra pelvic lymph nodes [LNs], 3 pelvic LNs and 2 prostate), 7 participants tested positive, and two participants' biopsies tested negative in the prostate bed for PC (both had undergone radical prostatectomy, which results in challenges to obtain biopsies for appropriate assessment). *All biopsies conducted outside the prostate bed were positive for PC on histopathology.*

Table 2. Patient level DR and CDR (reference standard comparison)

^{64}Cu-SAR-bisPSMA PET	Same-day imaging	Next-day imaging
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 *(Composite Ref. Standard; N=42)*		
TP patients, n (%)	8-11 (19.0-26.2)	11-14 (26.2-33.3)
CDR % (95% CI)	19.0-26.2 (8.6-42.0)	26.2-33.3 (13.9-49.5)
Patient Level CDR *(Histopathology Ref. Standard; N=9)*		
CDR %	44.4-55.6	55.6-77.8

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

- The CDR results using the composite reference standard (SOC imaging, histopathology and PSA decline) 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 the validation of the ^{64}Cu-SAR-bisPSMA scan findings.
- The table shows the ranges across the 3 readers. DR: detection rate; CDR: correct detection rate; TP: true positive; FP: false positive; N: number of participants.
- Safety: one adverse reaction reported (worsening of grade 2 diabetes, resolved).

Total number of lesions identified increased from same-day to next-day imaging

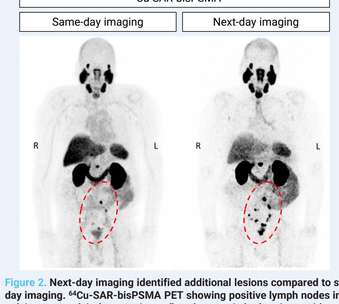


Figure 2. Next-day imaging identified additional lesions compared to same-day imaging. ^{64}Cu-SAR-bisPSMA PET showing positive lymph nodes in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on next-day imaging.

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

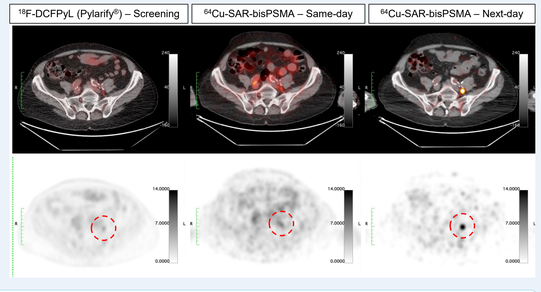
Table 3. Number of lesions per participant with a positive ^{64}Cu-SAR-bisPSMA scan

^{64}Cu-SAR-bisPSMA PET	Same-day imaging	Next-day imaging
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 same-day imaging (i.e. 1.0), therefore no ranges are provided.

Identification of pelvic lesion by ^{64}Cu-SAR-bisPSMA (equivocal entry scan using ^{18}F-DCFPyL, Pylarify®)

Figure 3. Identification of a lesion in the pelvic region using ^{64}Cu-SAR-bisPSMA on next-day imaging post-dose (right), negative on same-day imaging (center) and equivocal on screening ^{18}F-DCFPyL imaging (left). Maximum standardised uptake value (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, same- and next-day imaging ^{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

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

Figure 4. 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).

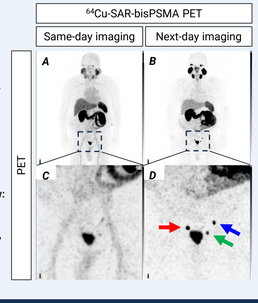
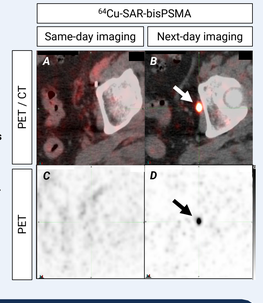


Figure 5. Pelvic LN showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B and D), with no uptake on same-day imaging (A and C). The lesion shown in B and D is the same as shown in Figure 4, blue arrow (size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1).



Conclusions

The COBRA study showed that ^{64}Cu-SAR-bisPSMA is safe and effective in detecting PC lesions in patients with BCR. Next-day ^{64}Cu-SAR-bisPSMA PET localized disease in up to 80% of patients with BCR and negative or equivocal SOC imaging at study entry, detecting lesions as small as 2 mm. Histopathology confirmed the presence of PC in lesions identified by ^{64}Cu-SAR- bisPSMA in up to 78% of cases in which biopsies were performed. 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. PET results led to clinicians changing the intended treatment plan in approximately half of the patients. 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 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. ASCO, 2023. 7. Nordquist et al. ASCO, 2024.

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