(MP13-01) COBRA: Assessment of ^{64}Cu-SAR-bisPSMA and standard of care prostate-specific membrane antigen Positron Emission Tomography 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

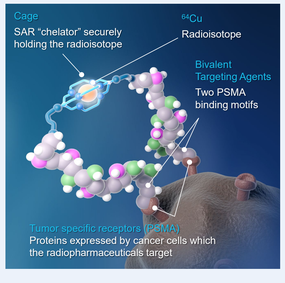


Table 1. Cu-64 characteristics compared to Ga-68 and F-18[3,4]

	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

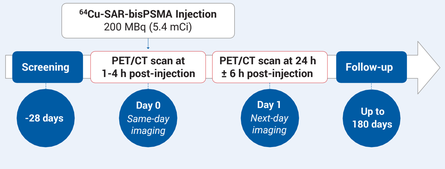
*up to 72 h for dosimetry

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. Follow-up SOC PSMA PET scans (interpreted by 2 blinded central readers independent of the ^{64}Cu-SAR-bisPSMA PET readers) were compared.

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

Higher patient level detection rate and total number of lesions identified on next-day vs. same-day imaging

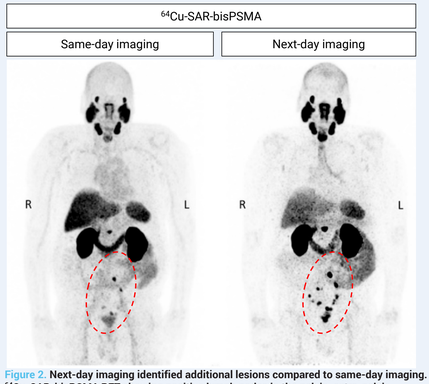


Figure 2. Next-day imaging identified additional lesions compared to same-day imaging. ^{64}Cu-SAR-bisPSMA PET showing positive lymph nodes in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on next-day imaging.

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 range across readers, number of participants (percentage): same-day imaging: 22-29 (44%-58%), next-day imaging 29-40 (58%-80%). N=50.

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

Table 2. 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

Table shows ranges across the 3 readers. Median values across readers were the same on same-day imaging (i.e. 1.0), therefore no ranges are provided.

CDR (range across 3 readers; N = 42 patients) was **19.0-26.2% on same-day imaging** and **26.2-33.3% on next-day imaging**. 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 SOC scans that were predominantly used for the validation of the ^{64}Cu-SAR-bisPSMA scan findings.

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

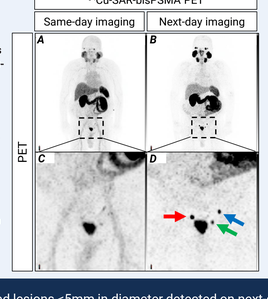


Figure 4. Pelvic lymph nodes showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B and D). Blue arrow: lesion size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1. Green arrow: lesion size also 3.8 mm x 4.4 mm, SUVmean 11.9, SUVmax 12.8 and TBR 75.3. Red arrow: size > 5 mm. Inset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

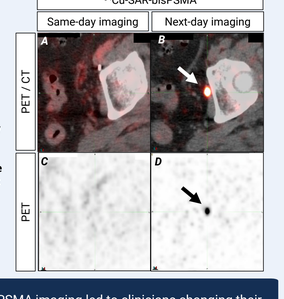


Figure 5. Pelvic lymph node showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B and D), with no uptake on same-day imaging (A and C). The lesion shown in B and D is the same as shown in Figure 4, blue arrow (size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1).

14% of patients had lesions <5mm in diameter detected on next-day imaging with ^{64}Cu-SAR-bisPSMA (mean SUVmax, 14.5; mean TBR, 88.3)

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

Pelvic nodal involvement identified by ^{64}Cu-SAR-bisPSMA (negative ^{68}Ga-PSMA-11 PET 175 days later)

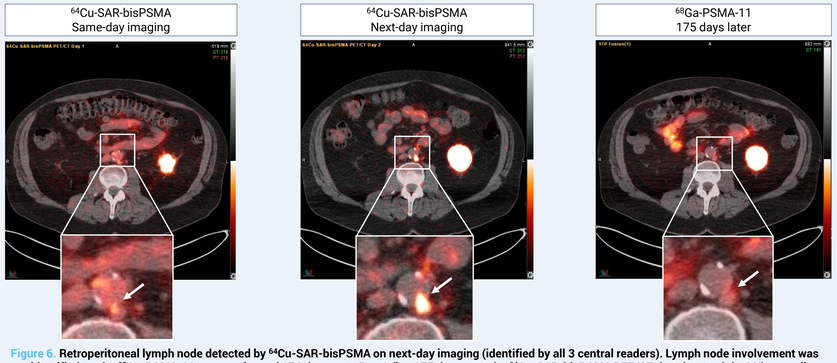


Figure 6. Retroperitoneal lymph node detected by ^{64}Cu-SAR-bisPSMA on next-day imaging (identified by all 3 central readers). Lymph node involvement was not identified on the ^{68}Ga-PSMA-11 scan performed 176 days post-Day 0 (i.e. 175 days post the ^{64}Cu-SAR-bisPSMA PET/CT that detected the LN) 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.

Earlier identification of lesions and increased detection rate using ^{64}Cu-SAR-bisPSMA vs. SOC PSMA PET

Table 3. Detection rate and sum of lesions identified in follow-up SOC PSMA PET subset (n=20)

	^{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.

- Follow-up SOC PSMA PET 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: 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

Conclusions

The COBRA study showed that ^{64}Cu-SAR-bisPSMA is effective in detecting PC lesions in patients with BCR. Next-day ^{64}Cu-SAR-bisPSMA PET imaging localized disease in up to 80% of patients with BCR and negative or equivocal SOC imaging at study entry. Lesions <5mm in diameter were identified by ^{64}Cu-SAR-bisPSMA in 14% of participants. 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. 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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