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

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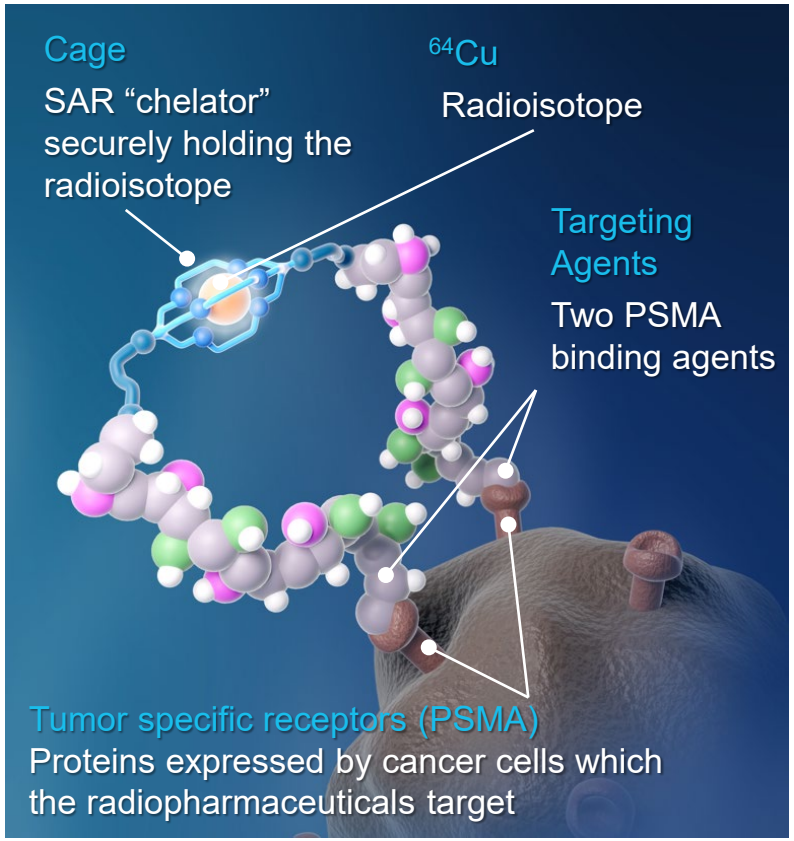
Background

- 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 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].

- Clinical evidence has demonstrated 2-3x higher tumor uptake and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to an approved PSMA agent[6].

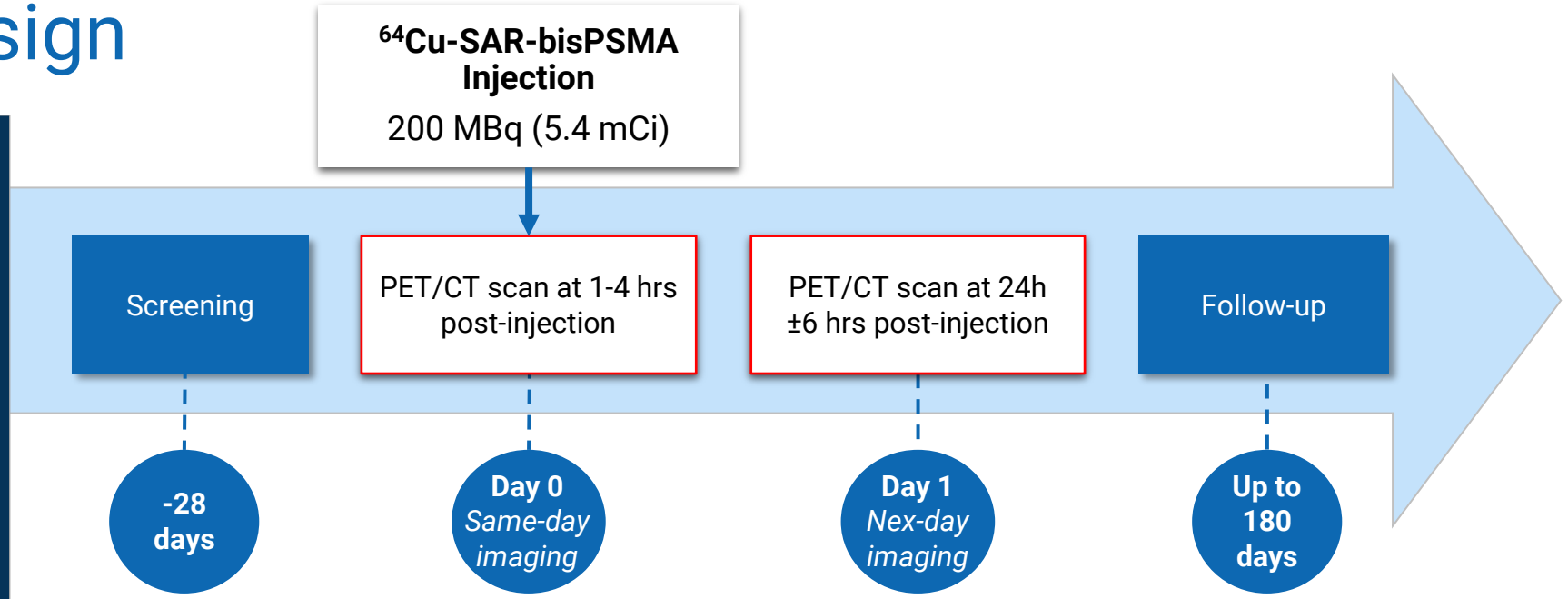


1. Ward and Moul. Nat Clin Pract Urol , 2005. 2. Pak et al. Int J Clin Onc. 2019. 3. Locametz FDA approved product information. Accessed on the 6 May 2024. 4. Pylarify FDA approved product information. Accessed on the 6 May 2024. 5. Posluma FDA approved product information Access on the 6 May 2024. 6.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

COBRA: Study design

Key Eligibility Criteria:

- Confirmed adenocarcinoma of prostate per original diagnosis and completed subsequent definitive therapy
- Suspected recurrence of PC based on rising PSA after definitive therapy based on:
  1. Detectable or rising PSA that is ≥ 0.2 ng/mL with a confirmatory PSA ≥ 0.2 ng/mL post radical prostatectomy; or,
  2. Increase in PSA level that is elevated by ≥ 2 ng/mL above the nadir post radiation therapy, cryotherapy or brachytherapy
- Negative or equivocal findings for PC on conventional imaging per standard of care (SOC) within 60 days prior to Day



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 (same-day imaging) and Day 1 (next-day imaging): • CDR, correct detection rate: proportion of true positive participants out of all scanned participants who had at least one evaluable reference standard datapoint • PPV, region-level positive predictive value: proportion of true positive regions out of all positive regions on the ^{64}Cu-SAR-bisPSMA PET/CT scan with corresponding evaluable reference standard

PET assessment end 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.

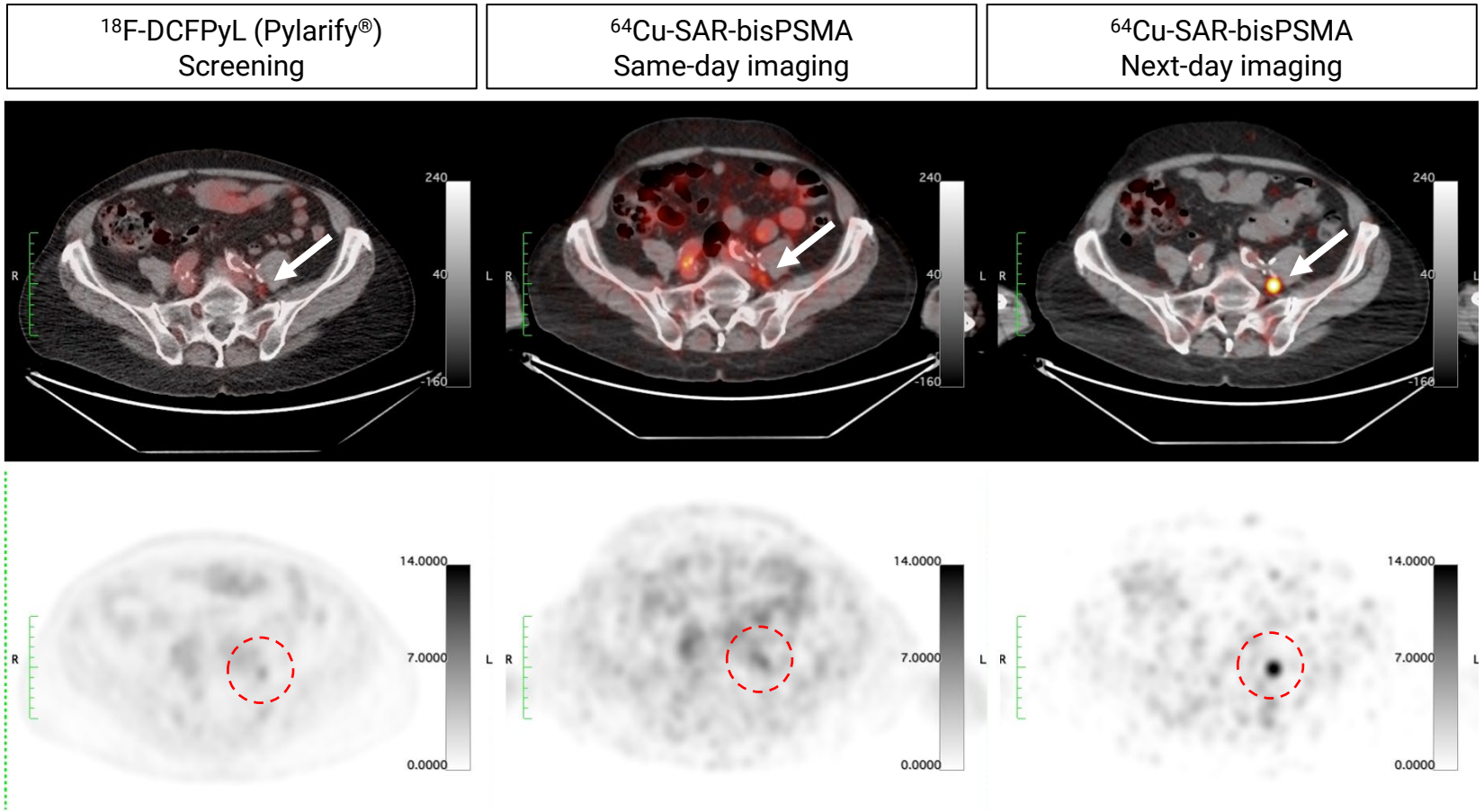
Demographics

Participant Distribution:

- 52 were enrolled in the study, received a single dose of ^{64}Cu-SAR-bisPSMA and were included in the Safety Analysis Set.
- 42 were evaluable for the efficacy endpoints.
- 32 completed the study as planned.
- 20 withdrew from the study early (13 protocol deviation, 4 physician decision, 2 withdrawal by subject, and 1 subject non-compliance).

Characteristics	N = 52 (%)
Age (years): median (range)	69 (53, 85)
Days from PC diagnosis, median (range)	2,547.0 (254, 7952)
ECOG status: N (%)	
0	49 (94.2)
1	3 (5.8)
Prior definitive therapy for prostate cancer: N (%)	
Radical prostatectomy (RP)	39 (75)
Radiotherapy (RT)	8 (15.4)
Other (includes RP + RT)	2 (3.8)
Unknown / Not reported	3 (5.8)
Gleason score: N (%)	
<8	39 (75)
≥8	13 (25)
PSA (ng/mL): median (range)	0.9 (0.25 to 17.6)
PSA at baseline, N (%)	
<0.5 ng/mL	11 (21.2)
0.5 - <1.0 ng/mL	17 (32.7)
1.0 - <2.0 ng/mL	4 (7.7)
2.0 - <5.0 ng/mL	10 (19.2)
≥5.0 ng/mL	10 (19.2)

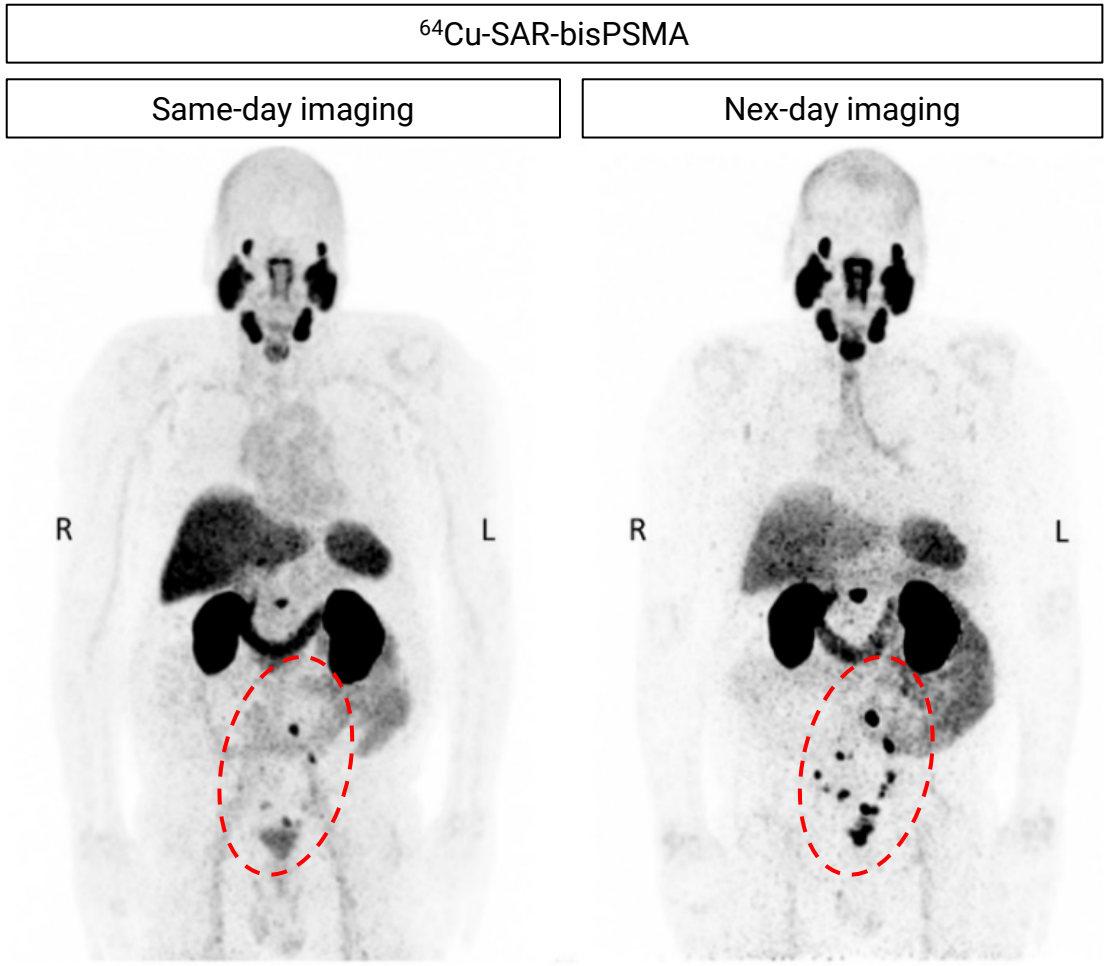
Identification of pelvic lesion by ^{64}Cu-SAR-bisPSMA (equivocal entry scan using ^{18}F-DCFPyL, Pylarify®)



- The ^{64}Cu-SAR-bisPSMA imaging led to clinicians changing their intended treatment plan in **48% of the patients**
- Only one adverse event was reported to be related to ^{64}Cu-SAR-bisPSMA (grade 2 worsening of type II diabetes, resolved)

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

More lesions and more patients with a positive scan were identified by ^{64}Cu-SAR-bisPSMA on next-day imaging



- In patients with a **negative or equivocal SOC scan**, the number of lesions identified by ^{64}Cu-SAR-bisPSMA increased from up to **80** to up to **153** (same-day vs. next-day imaging; **increase of 85%**)[1]

- Up to **58%** of patients had lesions identified by ^{64}Cu-SAR-bisPSMA on same-day imaging and up to **80%** patients on next-day imaging (**increase of 34%**)[2]

Figure 1. Nex-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[3].

1. Average increase across readers of 85% between days. Ranges across the readers for the total number of lesions detected: 53–80 on same-day vs. 82–153 on next-day imaging. Full Analysis Set: 42 patients.
2. Average increase across readers of 34% between days. Detection rate (DR) range across the readers on same-day imaging was 44–58% (95% CI 30–71.8), increasing on next-day imaging to 58–80% (95% CI 43.2–90). The CDR range across the readers same-day imaging was 21.4–28.6% (95% CI 10.3–44.6), increasing to 28.6–38.1% (95% CI 15.7–54.4) on next-day imaging. The range of the region-level PPV on same-day imaging was 39.1–44.8% (95% CI 19.7–64.3) and on next-day imaging was 32.7–43.3% (95% CI 20.3–62.6). The rate of biopsies was low (21%). The limited number of biopsies obtained coupled with the low sensitivity of the SOC imaging acquired during the 180-day follow-up resulted in a low number of ^{64}Cu-SAR-bisPSMA PET-positive lesions to be confirmed as true positives.
3. All images are displayed at Maximum Intensity Projection.

Key Efficacy Results: DR, CDR, PPV

Comparison of same-day vs. next-day imaging (average across readers)

- DR increased from **53%** to **71%**
- CDR increased from **25%** to **34%**
- Region level PPV remained relatively stable at **42%** and **39%**
- Specificity of PC detection in the pelvic lymph nodes remained high at **95% and 85%**

^{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 (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 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

The table shows the ranges across the 3 readers. Specificity rates (reported as a range with 95% CI in %): same-day imaging – pelvic region 93.8 to 96.9% (79.2 to 99.9), extra-pelvic region 93.9 to 97% (79.8 to 99.9), bone region 91.9 to 94.6% (78.1 to 99.3); next-day imaging – pelvic region 81.3 to 87.9% (63.6 to 96.6), extra-pelvic region 90.9 to 97% (75.7 to 99.9), bone region 78.4 to 97.3% (61.8 to 99.9).

Higher uptake and contrast in lesions on next-day vs. same-day imaging and detection of lesions in the 2-millimeter range

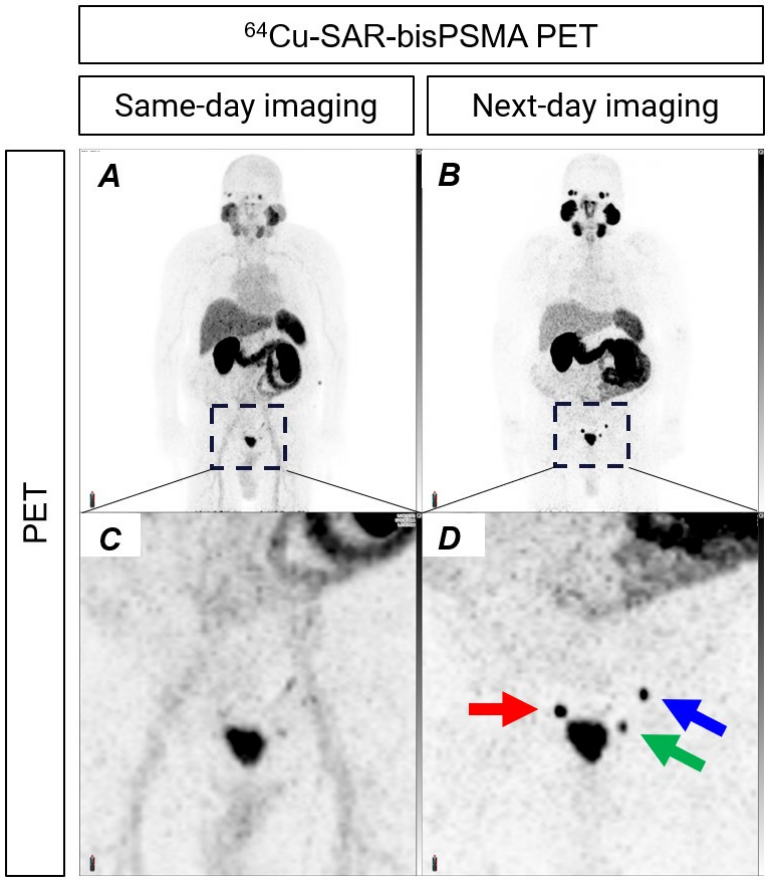
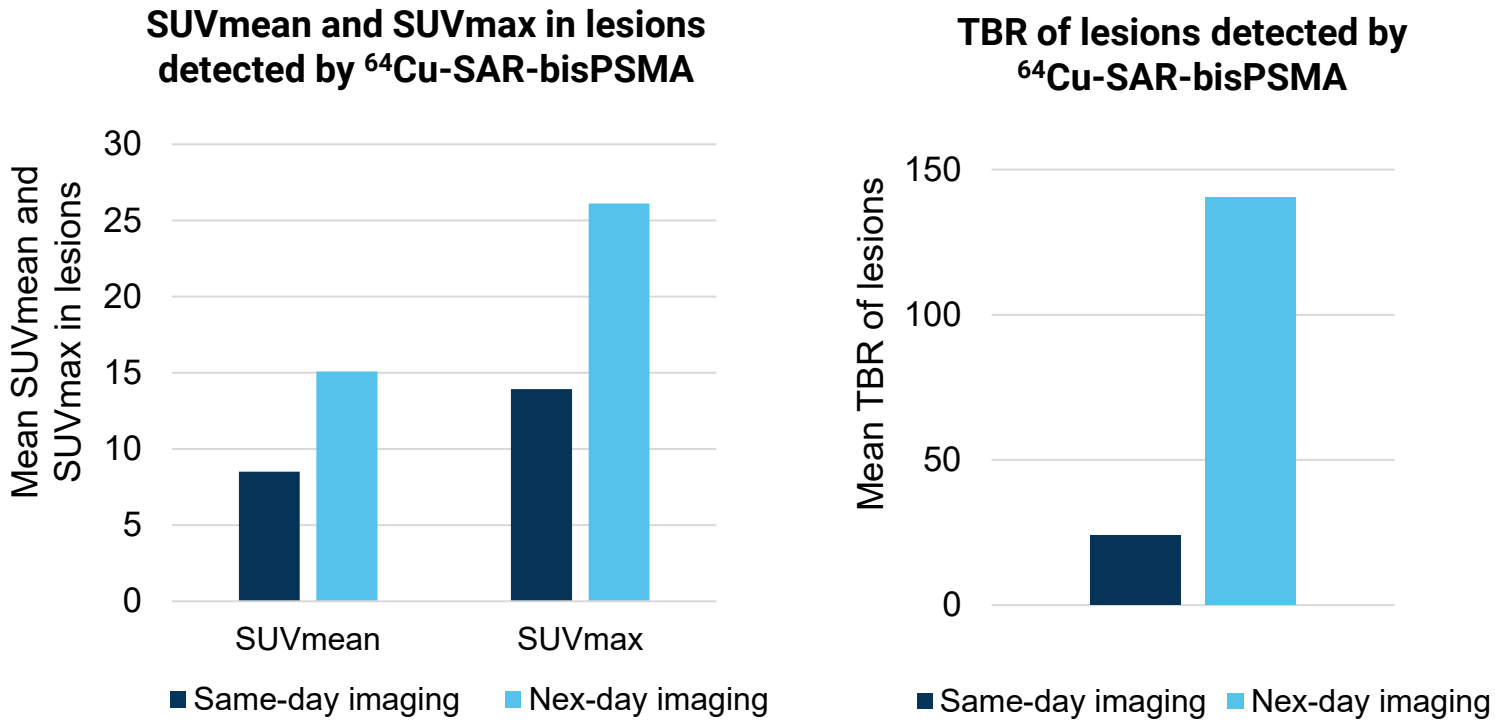


Figure 1. Pelvic lymph nodes showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B and D). Blue arrow: lesion size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1. Green arrow: lesion size also 3.8 mm x 4.4 mm, SUVmean 11.9, SUVmax 12.8 and TBR 75.3. Red arrow: size >5 mm. Inset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



>80% increase in mean SUVmean and SUVmax
(same-day vs. next-day imaging)

>5x increase in mean TBR
(same-day vs. next-day imaging)

Figure 2. SUVmean/max and TBR comparing same-day (Day 0) and next-day (Day 1) imaging. Average increase across 3 readers. SUVmean: mean standardised uptake value. SUVmax: maximum standardised uptake value. TBR: tumour-to-background ratio. The SUVmax, SUVmean and TBR were assessed in up to 25 lesions per patient on each ^{64}Cu-SAR-bisPSMA scan. Ranges across the readers for same-day and next-day imaging, respectively: SUVmean 6.6-9.9 and 14.7-15.8; SUVmax 13.9-14.0 and 22.2-33.4; TBR 23.2-25.4 and 118.1-181.7. TBR = SUVmax of the lesions / SUVmean of the gluteus region.

Conclusions

1. COBRA showed for the first time that ^{64}Cu-SAR-bisPSMA is safe and effective in detecting PC lesions in patients with BCR.
2. **Only one AE was related to ^{64}Cu-SAR-bisPSMA** (grade 2 worsening of type II diabetes, resolved).
3. 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**.
4. **More lesions, regions 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.**
5. **Higher uptake and contrast** were observed in lesions detected by ^{64}Cu-SAR-bisPSMA on **next-day imaging** compared to **same-day imaging**.
6. ^{64}Cu-SAR-bisPSMA PET results led to clinicians changing the **intended treatment plan in ~50% of the patients**.
7. 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.
8. A phase 3 study investigating ^{64}Cu-SAR-bisPSMA in BCR is currently in development