^{64}Cu-SAR-bisPSMA (PROPELLER) Positron Emission Tomography (PET) Imaging in Patients with Confirmed Prostate Cancer

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Background:

Prostate-Specific Membrane Antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in prostate cancer (PC). Recently, agents targeting this receptor have been commercialized to image PC due to their clinical utility against standard of care (SOC) and high specificity for PC. However, these products exhibit low sensitivity for PC potentially due to low tumor uptake and retention, or limitations of the short half-life of the isotopes being used.

^{64}Cu-SAR-bisPSMA is specifically designed to overcome these issues due to:

- the targeting moiety having two PSMA-targeting functional groups which have exhibited increased tumor uptake and retention;
- the copper-64 (^{64}Cu) isotope, which has a longer half-life (t1/2: 12.7h), longer shelf-life, greater flexibility for patient scheduling, and the ability to image at later timepoints, which has previously been shown to detect additional lesions; and
- ^{64}Cu has a shorter positron range (0.56mm), leading to improved scan resolution.

PROPELLER (NCT04839367) was a prospective, Phase 1, multi-center, blinded review, dose-ranging study evaluating safety and preliminary efficacy of ^{64}Cu-SAR-bisPSMA PET in patients with known primary PC.

The aims of PROPELLER were to:

- determine the safety and tolerability of ^{64}Cu-SAR-bisPSMA;
- determine the ability of ^{64}Cu-SAR-bisPSMA PET to detect primary PC;
- assess image quality at 100 MBq, 150 MBq and 200 MBq dosages of ^{64}Cu-SAR-bisPSMA; and
- explore how ^{64}Cu-SAR-bisPSMA compares to ^{68}Ga-PSMA-11 PET, a SOC radiotracer for imaging of PSMA-positive lesions in PC.

Methods:

Screening ^{68}Ga-PSMA-11 PET/CT

At screening, 30 patients with untreated, histopathology-proven, primary PC with intermediate- to high-risk features **completed a ^{68}Ga-PSMA-11 PET/CT** between 45–60min post injection per SOC protocols.

^{64}Cu-SAR-bisPSMA PET/CT

Patients were dosed 1:1:3 with 100 MBq, 150 MBq and 200 MBq of ^{64}Cu-SAR-bisPSMA, followed by a PET/CT at 2–4h post injection, respectively. **Safety was evaluated pre and post dose** for up to 11 weeks via adverse event (AE) reporting, vital signs, electrocardiograms (ECGs), blood and urine analysis.

Blinded PET reads

^{68}Ga-PSMA-11 and ^{64}Cu-SAR-bisPSMA PET/CT scans were evaluated by 2 independent, blinded, central readers for image quality, PC detection, intensity of tracer uptake in up to 5 concordant lesions per patient (maximum Standardized Uptake Values [SUVmax] and Tumor-to-Background Ratio [TBR]).

Prostatectomy/ Histopathology

Patients then proceeded to prostatectomy with pelvic lymph node dissection.

Safety Results:

^{64}Cu-SAR-bisPSMA was well tolerated in all 30 patients with only a single related AE of Grade 1 dysgeusia (metallic taste) reported in the 200 MBq cohort. There were no clinically significant changes in any laboratory measures or ECGs.

Imaging Results:

Both Readers scored 200 MBq of ^{64}Cu-SAR-bisPSMA as the dose providing the highest image quality. Interval between the ^{68}Ga-PSMA-11 and ^{64}Cu-SAR-bisPSMA scans was 2-50 days (median 20.5 days).

In the 200 MBq cohort:

- ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11 were able to detect primary PC in 100% and 77.8% of patients per Reader 1 and 85.7% and 83.3% of patients per Reader 2, respectively. The rest of the scans were indeterminate, no scan was deemed negative **(Figure 1)**.
- Concordant lesions on ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11 PET/CT showed 2.5 – 3 times higher uptake on ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11 in all parameters assessed **(Figure 2, Table 2)**.
- Reader 1 noted 38.9% of patients as having more lesions detected by ^{64}Cu-SAR-bisPSMA versus 22.2% of patients as having more lesions detected by ^{68}Ga-PSMA-11 PET/CT, while Reader 2 noted 42.9% of patients as having more lesions detected by ^{64}Cu-SAR-bisPSMA versus 14.3% of patients as having more lesions detected by ^{68}Ga-PSMA-11 PET/CT. In total, there were more lesions identified on ^{64}Cu-SAR-bisPSMA than on ^{68}Ga-PSMA-11 PET/CT according to both Readers **(Figure 3, Table 3)**.

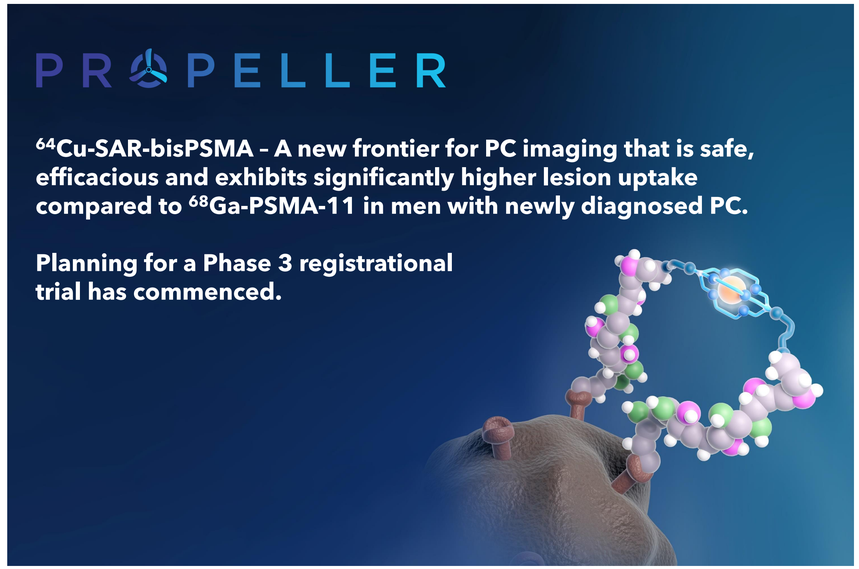

Figure 1. Primary PC PET results in the 200 MBq Dose Cohort (n=18)

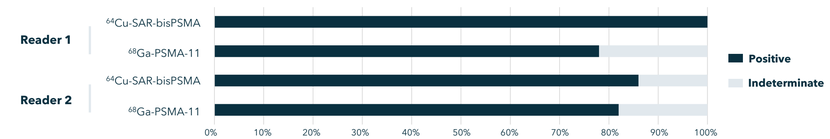

Figure 2. Intra-individual comparison of ^{68}Ga-PSMA-11 PET/CT (A) and 200 MBq of ^{64}Cu-SAR-bisPSMA PET/CT (B). Interval between serial imaging: 8 days

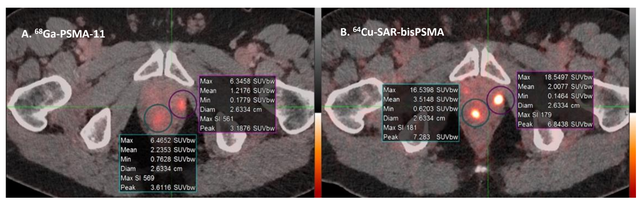

Figure 3. Readers did not detect uptake in pelvic lymph nodes on the ^{68}Ga-PSMA-11 PET/CT (C). PET/CT demonstrated uptake of ^{64}Cu-SAR-bisPSMA (D) in a left pelvic lymph node according to both Readers and PC was confirmed via histopathology. Arrows highlight the node detected on ^{64}Cu-SAR-bisPSMA PET/CT. Interval between serial imaging: 7 days

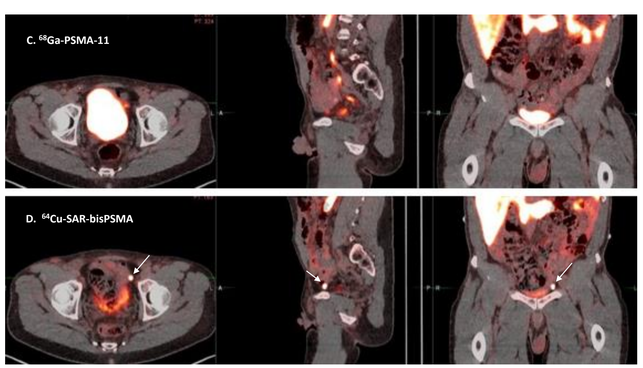

Table 1. Demographics and Baseline Characteristics (n=30)

Median (range) Age (years)	64 (50 to 75)	
TNM Stage	T1	4 (13.3%)
	T2	21 (70.0%)
	T3	4 (13.3%)
	N0	28 (93.3%)
	M0	28 (93.3%)
ISUP Grade Group	2	3 (10.0%)
	3	12 (40.0%)
	4	7 (23.3%)
	5	8 (26.7%)
Median (min, max) PSA Level (ng/mL)	8.21 (1.6, 36.0)	

Table 2. Uptake of ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11 in Concordant Lesions

200 MBq Cohort	Parameter	PET	N	Median	IQR	Median Difference	p-value*
Reader 1	**SUVmax**	^{64}Cu	17	31.4	27.45	14.85	p < 0.001
		^{68}Ga	17	10.08	13.92		
	TBR	^{64}Cu	17	49.07	67.69	27.15	P = 0.0015
		^{68}Ga	17	21.91	35.71		
Reader 2	**SUVmax**	^{64}Cu	13	41	46.09	27.03	p < 0.001
		^{68}Ga	13	14.58	14.98		
	TBR	^{64}Cu	13	76.34	66.37	45.37	p < 0.001
		^{68}Ga	13	23.9	33.05		

*Comparison of imaging methods undertaken with two-sided Wilcoxon signed-rank test.
Note: The lesions were averaged for each patient so that each patient contributes once to the summary statistics.

Table 3. Number of Lesions Detected on ^{64}Cu-SAR-bisPSMA vs ^{68}Ga-PSMA-11 per Reader per Participant Analysis

200 MBq Cohort	PET	Total # of Lesions Detected (all participants)	Mean Number of Lesions per Participant	Standard Deviation (SD)	Median Number of Lesions per Participant	Mean Difference	Median Difference	p-value**
Reader 1 (N=18)	^{64}Cu	41	2.3	1.4	2	0.28	0.0	0.4391
	^{68}Ga	36	2.0	1.4	1			
Reader 2 (N=14*)	^{64}Cu	31	2.2	1.5	2	0.64	0.0	0.069
	^{68}Ga	22	1.6	1.0	1			

*Only pairs of scans with both scans being evaluable were included in the analysis.
** Comparison of imaging methods undertaken with two-sided paired t-test.
The difference between imaging modalities is the number of lesions detected with ^{64}Cu-SAR-bisPSMA PET/CT relative to ^{68}Ga-PSMA-11 PET/CT within a participant (i.e. ^{64}Cu - ^{68}Ga). The trial was not powered to detect differences at an individual level.

Conclusions

^{64}Cu-SAR-bisPSMA is shown to be safe and effective for detecting PSMA-expressing lesions.

A 200 MBq dose of ^{64}Cu-SAR-bisPSMA was determined as optimal for future trials. ^{64}Cu-SAR-bisPSMA PET/CT showed a greater number of lesions and concordant lesions exhibited significantly higher uptake when compared to ^{68}Ga-PSMA-11 PET/CT in men with intermediate- to high-risk PC. Further trials to evaluate ^{64}Cu-SAR-bisPSMA as an imaging agent in patients with newly diagnosed and biochemical recurrence of PC using same day and next day imaging are underway.

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