PROPELLER - Comparison of PET/CT in Subjects with Confirmed Prostate Cancer Using ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11

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Background:

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in prostate cancer (PC). PSMA targeting PET tracers using ^{68}Ga or ^{18}F have been approved by the FDA to detect PC with improvements in sensitivity and specificity compared to traditional imaging by frequently identifying sub-centimeter lesions. However, these products still exhibit a relatively 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 a next-generation PET product in development for the imaging of PSMA-expressing PC lesions. In contrast to the short half-lives of ^{68}Ga ($t_{1/2}$=1.1h) and ^{18}F ($t_{1/2}$=1.8h), the longer half-life of ^{64}Cu ($t_{1/2}$=12.7h) may offer significant advantages, including:

- better resolution of images and detection of lesions due to the ^{64}Cu positron range (0.56mm) and potential for delayed imaging (up to 72h post administration);
- universal access to products through large scale central manufacturing of ready-to-use ^{64}Cu-SAR-bisPSMA; and
- improved product shelf-life of up to 48h to simplify patient scheduling.

Beyond the benefits of ^{64}Cu, SAR-**bis**PSMA has two PSMA-targeting functional groups, compared to the current generation of PSMA targeting agents, which only have a single targeting group. This can lead to improved tumor uptake and retention and thus, detection of additional smaller lesions. This is highly relevant in patients with suspected metastatic disease or recurrence, as it can lead to a change in management.

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 at 200 MBq;
- 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 standard-of-care (SOC) radiotracer for imaging of PSMA-positive lesions in PC.

Methods:

At screening, 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 standard of care (SOC) protocols. **30 patients** with a median age of 64 years (range: 50-75) with ISUP GG 2-5 and median PSA value of 8.21 ng/ml (range: 1.6-36) were enrolled.

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.

The **^{68}Ga-PSMA-11 and ^{64}Cu-SAR-bisPSMA PET/CT scans were evaluated** by 2 independent, blinded, central readers to determine image quality, primary PC detection, the number and location of lesions, intensity of tracer uptake in up to 5 concordant lesions using Standardized Uptake Values (SUVs) and tumor-to-background ratios (TBR).

Patients then proceeded to prostatectomy with pelvic lymph node dissection.

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)	

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 at any dose level.

PROPELLER

^{64}Cu-SAR-bisPSMA - a next-generation diagnostic agent that is safe, efficacious, has a longer half-life with favourable logistics and improved lesion uptake compared to the SOC ^{68}Ga-PSMA-11 PET/CT.

Initiation of a Phase 3 registrational trial is underway.

Table 1. Uptake of ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11 in concordant lesions

All Cohorts	Parameter	Imaging	N	Median	IQR	Min	Max	Median Difference	p-value*
Reader 1	SUVmax	^{64}Cu	28	30.26	46.9	8	100	14.23	p < 0.001
		^{68}Ga	28	13.53	12.79	2.7	55.1		
	SUVmean	^{64}Cu	28	21.2	32.23	5.4	69.9	9.26	p < 0.001
		^{68}Ga	28	9.12	8.71	1.8	37.6		
	TBR	^{64}Cu	28	53.55	84.45	10.3	294.1	27.94	p < 0.001
		^{68}Ga	28	24.29	36	9.6	134.4		
Reader 2	SUVmax	^{64}Cu	16	41.66	58.77	6.1	100	27.99	p < 0.001
		^{68}Ga	16	14.93	17.16	2.7	55.1		
	SUVmean	^{64}Cu	16	28.4	37.92	4.4	69.9	18.78	p < 0.001
		^{68}Ga	16	9.94	11.56	1.8	37.6		
	TBR	^{64}Cu	16	78.37	98.97	6.7	243.9	46.93	p < 0.001
		^{68}Ga	16	24.69	52.14	5	112.4		

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

Reader	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**
All Cohorts								
Reader 1 (N=29)	^{64}Cu	63	2.2	1.2	2	0.41	0.0	0.1005
	^{68}Ga	51	1.8	1.3	1			
Reader 2 (N=17*)	^{64}Cu	34	2	1.4	1	0.52	0.0	0.0748
	^{68}Ga	25	1.5	0.9	1			
200 MBq Cohort								
Reader 1 (N=18)	^{64}Cu	41	2.3	1.4	2	0.28	0.0	0. 4427
	^{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. 0749
	^{68}Ga	22	1.6	1.0	1			

**Comparison of imaging methods undertaken with two-sided Wilcoxon signed-rank test. Violation of normality assumption confirmed with Shapiro-Wilk Test for Normality (p<0.05).
Only participants who had evaluable scans for both imaging modalities were included in the analysis. 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). A negative value indicates more lesions detected with ^{68}Ga-PSMA-11 PET/CT than ^{64}Cu-SAR-bisPSMA PET/CT. The trial was not powered to detect differences at an individual level.

Imaging Results:

- 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.
- For both readers, 200 MBq scored the highest in terms of image quality.
  - Reader 1 found 83%, 67% and **89%** of scans to be acceptable at 100, 150 and **200 MBq** respectively.
  - Reader 2 found 17%, 17% and **39%** of scans to be acceptable at 100, 150 and **200 MBq** respectively.
- Across all cohorts, both Readers identified more lesions with ^{64}Cu-SAR-bisPSMA than with ^{68}Ga-PSMA-11 PET/CT and more lesions were identified at the 200 MBq cohort (numerical difference which is not statistically significant; the trial was not powered to detect differences in the number of lesions) **(Table 2, Figure2)**. The interval between the ^{68}Ga-PSMA-11 and ^{64}Cu-SAR-bisPSMA scans was 2-50 days (median 20.5 days).
- Concordant lesions on ^{64}Cu-SAR-bisPSMA and ^{68}Ga-PSMA-11 PET/CT consistently showed higher SUVmax, SUVmean and TBR with ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11 in all cohorts (statistically significant values for all parameters) **(Table 1, Figure 1, Figure 3)**.

Figure 1. Comparison of ^{64}Cu-SAR-bisPSMA PET/CT and ^{68}Ga-PSMA-11 PET/CT by Reader in all cohorts

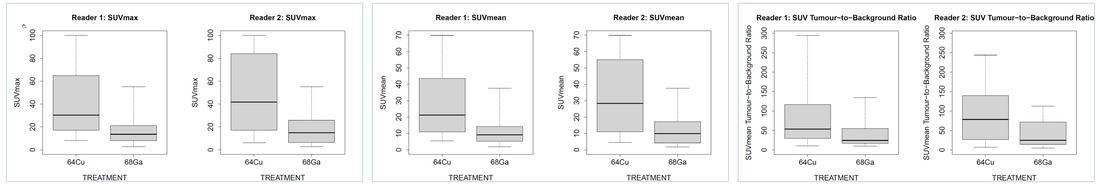


Figure 2. PET/CT demonstrated uptake of ^{64}Cu-SAR-bisPSMA at 200MBq (B) in a left pelvic lymph node according to both readers and PC was confirmed via histopathology. Readers did not detect uptake in pelvic lymph nodes on the ^{68}Ga-PSMA-11 PET/CT (A). Arrows highlight the additional node. Interval between serial imaging: 7 days

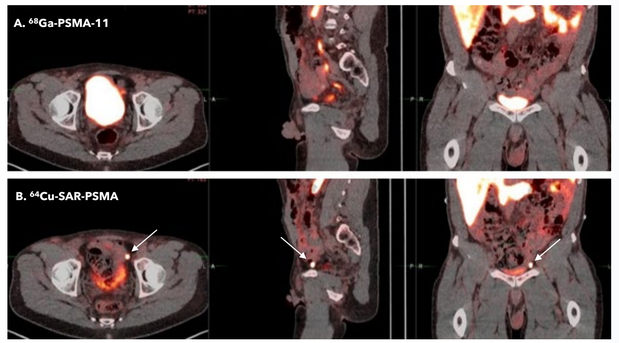
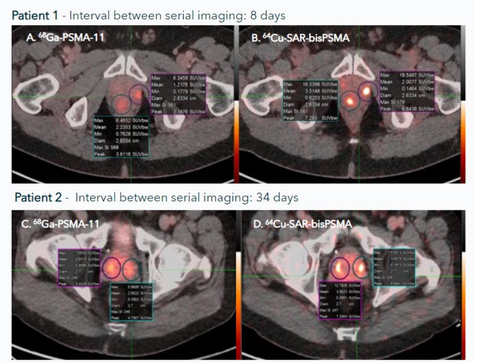


Figure 3. Intra-individual comparison of ^{68}Ga-PSMA-11 (A,C) and 200 MBq of ^{64}Cu-SAR-bisPSMA (B,D) PET/CT.



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 higher uptake on ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11 in all parameters 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.