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# A Phase II, Open-Label Study to Assess Safety and Management Change Using $^{68}\text{Ga}$ -THP PSMA PET/CT in Patients with High-Risk Primary Prostate Cancer or Biochemical Recurrence After Radical Treatment: The PRONOUNCED Study

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Our objectives were to assess the safety and clinical impact of a novel, kit-based formulation of  $^{68}\text{Ga}$ -tris(hydroxypyridinone) ( $^{68}\text{Ga}$ -THP) prostate-specific membrane antigen (PSMA) for PET/CT in guiding the management of patients with prostate cancer.

**Methods:** Patients were prospectively recruited to group A (high-risk untreated prostate cancer; Gleason score  $\geq 4 + 3$ , or prostate-specific antigen (PSA) level  $> 20$  ng/mL or clinical stage  $> \text{T2c}$ ), group B (biochemical recurrence and eligible for salvage treatment after radical prostatectomy with 2 consecutive rises in PSA with a 3-mo interval between reads and a final PSA level  $> 0.1$  ng/mL or a PSA level  $\geq 0.5$  ng/mL), or group C (biochemical recurrence with radical curative radiotherapy or brachytherapy at least 3 mo before enrollment, and an increase in PSA level  $> 2.0$  ng/mL above the nadir level after radiotherapy or brachytherapy). Patients underwent evaluation with PET/CT 60 min after intravenous administration of  $160 \pm 30$  MBq of  $^{68}\text{Ga}$ -THP PSMA. Safety was assessed through vital signs, cardiovascular profile, serum hematology, biochemistry, urinalysis, PSA, and adverse events (AEs). A change in management was reported when the predefined clinical management of the patient was altered as a result of the  $^{68}\text{Ga}$ -THP PSMA PET/CT findings. **Results:** Forty-nine patients were evaluated with PET/CT: 20 in group A, 21 in group B, and 8 in group C. No patients experienced serious AEs, discontinued the study because of AEs, or died during the study. Two patients had treatment-emergent AEs attributed to  $^{68}\text{Ga}$ -THP PSMA (pruritus in one patient and a rash at the intravenous catheter site in another). A management change secondary to the PET/CT findings occurred in 42.9% of all patients: 30% in group A, 42.9% in group B, and 75% in group C. **Conclusion:**  $^{68}\text{Ga}$ -THP PSMA was safe to use, with no serious AEs and no AEs resulting in withdrawal from the study.  $^{68}\text{Ga}$ -THP PSMA PET/CT changed the management of 42.9% of the study population, comparable to studies using other PSMA tracers. These data form the basis of a planned phase III study of  $^{68}\text{Ga}$ -THP PSMA in patients with prostate cancer.

**Key Words:** prostate cancer; PSMA; PET/CT;  $^{68}\text{Ga}$ -THP PSMA; phase II clinical trial

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**P**rostate-specific membrane antigen (PSMA) imaging with PET/CT has undergone rapid clinical acceptance across a variety of centers throughout the world within several years of first-in-humans studies (1). There is growing evidence of superiority over typical standard-of-care imaging such as CT and bone scanning, as well as over other PET tracers such as choline, but market authorization for use is still lacking (2–4).

Despite the growing number of articles published, relatively few studies have been performed in a clinical trial format. There is also limited systematically collected data on the safety of PSMA PET/CT (5).

There are several types of  $^{68}\text{Ga}$ -PSMA PET tracer being used worldwide (6). The greatest use has been with  $^{68}\text{Ga}$ -HBED PSMA, but other types include PSMA I&T and PSMA 617. The most common method of producing  $^{68}\text{Ga}$  PSMA tracers for clinical use includes a manual/semiautomated multistep process requiring heating and strict pH conditions to facilitate a multistep process that can take approximately 25 min to produce a dose (7). Cold-kit formulations such as  $^{68}\text{Ga}$ -tris(hydroxypyridinone) ( $^{68}\text{Ga}$ -THP) PSMA involve a single-step manufacturing process without the need for heating, requiring approximately 5 min to produce a dose (8).

$^{68}\text{Ga}$ -THP PSMA has been investigated in a phase I trial that evaluated 14 patients (9). Of these, 8 patients went on to have prostatectomy, and the tracer was able to identify tumor that was positive for PSMA expression on histopathology. In addition, in 6 patients who had a positive  $^{68}\text{Ga}$ -HBED PSMA PET/CT result,  $^{68}\text{Ga}$ -THP PSMA was able to demonstrate concordance in number of metastases. Some initial safety data were collected, with no adverse events (AEs) reported. Despite lower absolute uptake, the tumor-to-liver uptake ratio was similar to that of  $^{68}\text{Ga}$ -HBED PSMA (9).

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The aims of this study were to evaluate PSMA PET/CT in 3 clinical settings using a cold-kit formulation:  $^{68}\text{Ga}$ -THP PSMA. The primary objective was to assess the safety of  $^{68}\text{Ga}$ -THP PSMA in prostate cancer, and the secondary objective was to evaluate clinical impact by assessing whether the  $^{68}\text{Ga}$ -THP PSMA PET/CT findings brought about a change in the management of patients with prostate cancer.

## MATERIALS AND METHODS

This study was a prospective open-label phase II clinical trial in patients with newly diagnosed and recurrent prostate cancer (ClinicalTrials.gov identifier NCT03617588). The Institutional Review Board (Research and Ethics Committee) approved this study (reference 18/LO/0370), and all subjects gave written informed consent. The primary endpoint was evaluation of the safety of PSMA PET/CT (specifically AEs related to  $^{68}\text{Ga}$ -THP PSMA use), and the secondary endpoint was evaluation of a change in management plan after PET/CT.

Patients were identified from clinic and tumor board meetings from the primary site and from 3 other hospitals in London.

### Patients

**Inclusion Criteria.** The study group consisted of men older than 18 y old who were diagnosed with prostate cancer, had an Eastern Oncology Group performance status of 0–2 (10), and had not received hormone therapy related to prostate cancer within the previous 3 mo. The following criteria divided the study cohort into 3 distinct groups based on clinical setting.

Group A (new diagnosis, high risk) included men with newly diagnosed (histopathologically proven) prostate cancer of Gleason grade 4 + 3 or above, a prostate-specific antigen (PSA) level of more than 20 ng/mL, or a clinical stage greater than T2c and potentially operable disease.

Regarding group B (biochemical recurrence [BCR] after radical prostatectomy), the initial criterion for inclusion in the study was any patient with 3 rises in PSA after radical prostatectomy. This was amended to include a first diagnosis of BCR with 2 consecutive rises in PSA with a 3-mo interval between reads and a final PSA level of more than 0.1 ng/mL or a PSA level of more than 0.5 ng/mL at the time of recruitment.

Group C (BCR after radiotherapy) included men who had a first diagnosis of BCR with previous radical curative therapy with radiotherapy or brachytherapy at least 3 mo before enrollment, and with BCR based on an increase in PSA level to more than 2.0 ng/mL above the nadir level after radiotherapy or brachytherapy.

**Exclusion Criteria.** The exclusion criteria were receiving another investigational medical product from 1 mo before to 1 mo after administration of  $^{68}\text{Ga}$ -THP PSMA, known hypersensitivity to  $^{68}\text{Ga}$ -THP PSMA or any of its constituents, or an estimated glomerular filtration rate of less than 20 mL/min/1.73 m<sup>2</sup>.

### Protocol

Patients were recruited from June 2018 to July 2019 and underwent 4 visits as outlined in Table 1.

### Safety

AEs, regardless of suspected relationship to study treatment, were recorded throughout the study, from the  $^{68}\text{Ga}$ -THP PSMA administration until 30 d after the administration of  $^{68}\text{Ga}$ -THP PSMA. All AEs were followed up until resolution or until visit 4. Common terminology criteria grading was used for AEs (11).

Any related serious AEs that occurred at any time after 30 d after the administration of  $^{68}\text{Ga}$ -THP PSMA were reported.

Safety was assessed by means of physical examination, vital signs, cardiovascular profile (including 12-lead electrocardiography),

performance status, and laboratory evaluations (hematology, biochemistry, and urinalysis).

### $^{68}\text{Ga}$ -THP PSMA PET/CT

Radiopharmaceutical production of the  $^{68}\text{Ga}$ -THP PSMA was in accordance with good manufacturing practices and used a kit-based formulation, by a method previously described (8).

No patient preparation was required before the scan. The target administered activity of  $^{68}\text{Ga}$ -THP PSMA was 250 MBq  $\pm$  20% intravenously via a vein in the right upper limb.

PET/CT was performed on a GE Healthcare Discovery 710 time-of-flight scanner with Q.Clear reconstruction algorithm.

### Imaging Evaluation

All images were reviewed on GE Healthcare Advantage workstations by 2 nuclear medicine radiologists/physicians in consensus, both of whom had over 3 y of experience in reporting PSMA PET/CT findings and had undergone training that included a review of 50  $^{68}\text{Ga}$ -THP PSMA PET/CT studies performed at another site.

**Criteria for a Positive Scan.** Focal areas of tracer uptake that were greater than background activity and could not be explained by physiologic activity were attributed to prostate cancer or prostate cancer metastases.

**Criteria for a Negative Scan.** A negative scan was defined as one lacking any uptake that was higher than background activity and attributable to prostate cancer or prostate cancer metastases.

Disease distribution was classified as being in the prostate (or prostate bed), pelvic lymph nodes, extrapelvic lymph nodes, bones, or other sites, such as the liver parenchyma. The reviewing nuclear medicine radiologist was permitted to request additional imaging to clarify equivocal areas or potential synchronous diseases. Image reviewers were not masked to any existing standard-of-care imaging that had occurred (e.g., bone scanning, CT, or MRI) and were aware of all clinical details, including PSA value.

**Criteria for a Management Plan.** Management plans were created by the primary clinician who was evaluating the patient (urologist or oncologist). The initial management plan relied on standard-of-care clinical and imaging details as per local, national, and international guidelines. The revised management plan took all of the above factors into account, along with the additional information from the  $^{68}\text{Ga}$ -THP PSMA PET/CT study. A change in management was defined as a change that was influenced by, or altered directly in response to, the findings of the  $^{68}\text{Ga}$ -THP PSMA PET/CT study. A change that was primarily the result of non-PET factors, such as comorbidities, was not counted as a change in management.

### Statistics

The sample size was based on the degree of uncertainty in estimating the percentage of patients with a change in management, as measured by the CI. Because of the phase of the study, relatively wide CIs were allowed.

For group A, previous literature suggested that approximately 25% of patients would have a change in management (12). Assuming a 95% confidence level, 20 patients would be sufficient to estimate the secondary outcome that was within  $\pm 20\%$  of the population value.

For groups B and C, previous literature suggested that approximately 45% would have a change in management (13). With a 95% confidence level, 40 patients in the 2 groups combined would be sufficient to estimate the outcome that was within  $\pm 15\%$  of the population value. Two-sided 95% and 80% Clopper–Pearson exact CIs were calculated.

### Validation

Validation included a combination of histology correlation (22 patients) and, when available, follow-up of PSA levels beyond trial participation (31 patients).

**TABLE 1**  
Study Protocol Demonstrating Data Collected at Each of 4 Patient Visits

Event	Visit 1 prescan data (≤4 wk before scan)	Visit 2 (day of scan)	Visit 3, by telephone (next working day)	Visit 4, outpatient (~2 wk after scan)*
Eligibility confirmation	X			
Informed consent	X			
Demographics	X			
Medical history, including prostate cancer treatment history and imaging history	X	X		
Physical examination†	X	X		X
ECOG performance status	X			X
Concomitant medications	X	X	X	X
Management plan‡	X			X
Study registration	X			
Serum full blood count, urea, electrolytes, liver function tests, PSA	X			X
Urinalysis	X			X
Cardiovascular profile (electrocardiography)	X	X§		X
Vital signs	X	X		X
<sup>68</sup> Ga-THP PSMA PET/CT administration and imaging		X		
AEs		X	X	X

\*Window of 0–6 wk was permitted, depending on local clinical practice.

†Comprised height (visit 1 only), weight, body surface area, and description of external signs of cancer.

‡It was recognized that revised management plan might be decided on before outpatient appointment, and this was permitted. Deciding management plan outside of visit did not constitute protocol deviation.

§Electrocardiography: visit 2, approximately 1 h before scan.

||Vital signs: visit 2, before scan, during injection, after scan (for 2 h after injection), and before discharge.

ECOG = Eastern Cooperative Oncology Group.

## RESULTS

### Patients

Forty-nine patients underwent evaluation with <sup>68</sup>Ga-THP PSMA PET/CT, and 48 patients completed all visits, including the final safety visit. The median age of recruited patients was 67 y (range, 43–80 y).

Figure 1 outlines the number of patients at each stage of the trial, and Table 2 shows patient demographics and clinical characteristics.

### Safety

No serious AEs were reported, no patients were withdrawn from the trial because of AEs, and no deaths were reported. <sup>68</sup>Ga-THP PSMA was well tolerated.

Two patients (4.1%) had treatment-emergent AEs that were considered related to <sup>68</sup>Ga-THP PSMA PET/CT. These were grade 1 pruritus (duration, 22 d; 1 patient in group A) and a grade 1 catheter site rash (duration, 4 d; 1 patient in group B), according to the common terminology criteria for AEs. An additional 9 treatment-emergent AEs were reported, not related to <sup>68</sup>Ga-THP administration.

No clinically significant variations in serum hematology, clinical chemistry, or urinalysis parameters were detected, and no AEs were identified from these parameters.

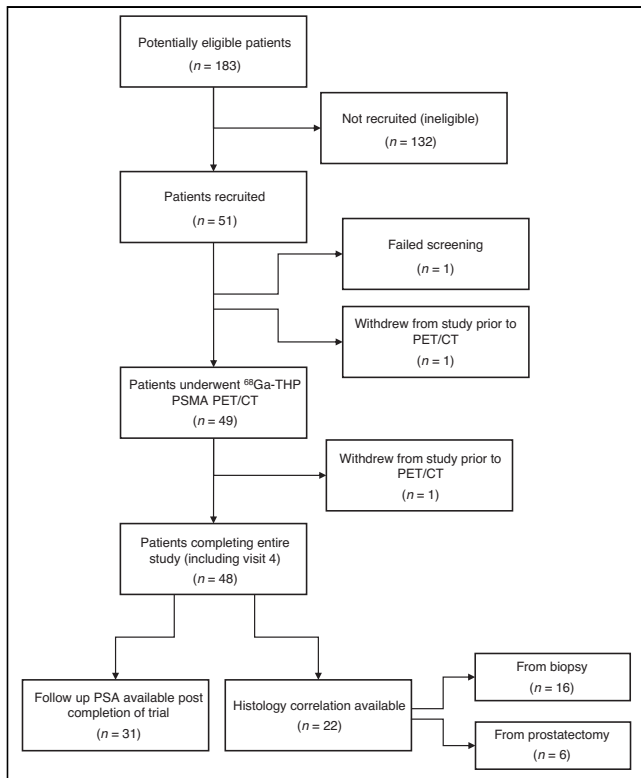
There were no clinically significant changes in vital signs for any patients during the study. No AEs were recorded from electrocardiography findings.

### Imaging Findings

All imaging was of diagnostic quality. In 2 patients, image interpretation was more challenging because of a high body mass index, because the injected activity was at the lower end of the acceptable range, and because of the arms-down position in a patient who could not elevate the arms above the head.

A minor halo artifact was frequently encountered, but the images could be reviewed without scatter correction to reduce the effect of this artifact.

<sup>68</sup>Ga-THP PSMA PET/CT was positive in 27 patients (55.1%). Most patients in group A had focal uptake in the prostate gland. In 2 of these patients, focal increased uptake in the prostate was difficult to localize on PET/CT, leading to a positivity rate of 90% in this



**FIGURE 1.** Number of patients in each stage of trial.

group. Fifteen patients had prostate disease only, 1 had prostate–plus–seminal vesicle involvement, 1 had prostate–plus–pelvic lymph node involvement, and 1 had prostate involvement plus involvement of the lymph nodes below and above the diaphragm (Fig. 2).

Only 3 of 21 patients in group B were positive for disease (14.3%). One had uptake in the prostatectomy bed, 1 had prostate disease and pelvic lymph node involvement (PSA, 1.77 ng/mL), 1 had pelvic lymph node and bone metastases (PSA, 0.6 ng/mL), and 1 had bone metastases only (PSA, 2.54 ng/mL).

Positive scans in this group were demonstrated only when PSA at the time of the scan was more than 0.5 ng/mL (Figs. 2 and 3).

Patients in group C tended to have a higher proportion of positive scans than did patients in group B (6/8, 75%). Disease was identified in the treated prostate in 50% of the patients in this group, and disease was identified in a relatively greater proportion of lymph nodes (pelvic and extrapelvic) and bones in this group than in groups A and B. <sup>68</sup>Ga-THP was positive in the prostate alone in 3 patients; in the prostate and lymph nodes above and below the diaphragm in 1 patient; in the pelvic and retroperitoneal lymph nodes in 1 patient; and in the pelvic, extrapelvic, and bone in 1 patient (Fig. 2).

In 3 patients, additional imaging was requested. The first request was for a <sup>68</sup>Ga-HBED PSMA study for short-interval follow-up of a small-volume mildly avid pelvic node; this node was negative on <sup>68</sup>Ga-HBED PSMA. The second request was for MRI of the liver to evaluate solitary focal uptake in the liver; this study revealed imaging features typical of a hemangioma. The third request was for MRI of the spine to evaluate focal uptake in the L5 vertebral body; this study showed no metastases, and the uptake at L5 was deemed to be secondary to degenerative change.

Patients demonstrated the typical physiologic distribution of this tracer, which has been described previously (9).

In some patients, areas of uptake were relatively mild in the prostate, and manipulation of the window setting was required to evaluate further. Requirement of manipulation due to mild uptake was also noted during training with <sup>68</sup>Ga-THP PSMA cases before the trial, suggesting that both background and tumor activity may be less than in patients being evaluated with <sup>68</sup>Ga-HBED PSMA.

### Change in Management

There were 21 changes from the original management plan in total across all 3 groups. Of these, 6 occurred in group A (30%), 8 in group B (42.9%), and 6 in group C (75%), giving a 51.7% change in management in groups B and C combined (Table 3).

Most of the changes throughout the 3 groups were intermodality (16/21)—for example, from prostatectomy to radiotherapy, or from radical or salvage local treatment to systemic treatment. A change from salvage treatment of the prostate bed to surveillance was also considered an intermodality change.

A minority of changes were intramodality—that is, a change from prostatectomy with lymph node dissection to prostatectomy alone or an adjustment of the radiotherapy fields to include lymph nodes.

Management changes occurred at all PSA levels (Fig. 4).

An example of a positive <sup>68</sup>Ga-THP PSMA PET/CT finding with a resulting change in management is shown in Figure 5.

### Validation

In all 22 patients with a histopathologic reference standard (6 from prostatectomy and 16 from biopsy) within 3 mo of the date of the <sup>68</sup>Ga-THP PSMA PET/CT study, disease within the prostate identified on <sup>68</sup>Ga-THP PSMA PET/CT could be correlated with a site of disease on histology. In all patients for whom follow-up PSA measurements were available after trial participation (14 with a management change and 17 without), PSA was reduced.

In the 2 group A patients for whom disease was difficult to identify, prostatectomy was performed on one and revealed pT2 Gleason 4 + 3 acinar adenocarcinoma with a tumor volume of 0.2 cm<sup>2</sup>, and a pretrial biopsy in the other demonstrated a Gleason 4 + 5 tumor with a maximum length of 7 mm (involving 40% of the core), which was ultimately treated with radiotherapy.

### DISCUSSION

This was the first phase II clinical trial using <sup>68</sup>Ga-THP PSMA (a kit-based formulation) and showed a lack of serious AEs and a lack of patients discontinuing the study due to AEs. The confirmed safety profile when reviewing serum hematology, chemistry, urinalysis, vital signs, and electrocardiography further fortified the safety profile of this tracer. These were all important findings when considering a phase III study with this tracer.

The lack of serious AEs is concordant with published data on safety using other PSMA agents (<sup>68</sup>Ga-PSMA-11, <sup>18</sup>F-PSMA-11, and <sup>18</sup>F-DCFPyL) (5,14,15). The <sup>68</sup>Ga PSMA-11 data showed no clinically reported AEs. With <sup>18</sup>F-PSMA-11, no clinically relevant changes in vital parameters were observed and no patients reported any side effects. The DCFPyL study showed no serious AEs, and no AEs related to heart rate or blood pressure were seen. One patient reported 2 AEs that were classified as unlikely to be attributable to the radiotracer, and another patient had a fall in platelet count attributed to treatment for prostate cancer.

This study demonstrated that clinically significant levels of management change occurred after <sup>68</sup>Ga-THP PSMA PET/CT

**TABLE 2**

Demographic and Baseline Characteristics in Group A (New Diagnosis, High-Risk) and in Groups B and C (Combined Recurrence After Radical Prostatectomy and After Radiotherapy)

Characteristic	Newly diagnosed (group A)	BCR (groups B and C)	Total
Patients (n)	20	29	49
Age			
Median	68.5	66.0	67.0
Minimum	49	43	43
Maximum	76	80	80
Race (n)*			
White	13 (65.0%)	21 (72.4%)	34 (69.4%)
Afro-Caribbean	7 (35.0%)	5 (17.2%)	12 (24.5%)
Asian	0 (0.0%)	3 (10.3%)	3 (6.1%)
ECOG performance status (n)			
0	19 (95.0%)	29 (100.0%)	48 (98.0%)
1	1 (5.0%)	0 (0.0%)	1 (2.0%)
PSA before scan (µg/L)			
Mean	25.2	1.6	11.2
SD	27.00	2.32	20.70
Median	13.8	0.4	4.2
Range	5–90	0–10	0–90
Initial Gleason score			
≤3 + 4	1 (5.0%)	15 (51.7%)	16 (32.7%)
≥4 + 3	19 (95.0%)	14 (48.3%)	33 (67.3%)

\*Prostate cancer aggressiveness can vary according to race.

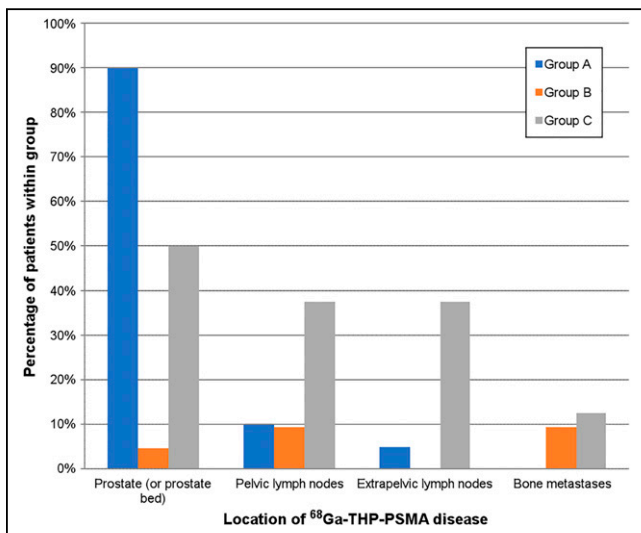
in high-risk patients and in those with BCR (42.9% change in management across all groups).

In the primary high-risk group, a change in management occurred in 30% of patients. This finding is comparable to the findings from a recent study performed with the same tracer; that study showed that management changed in 24% of high-risk patients (12). The

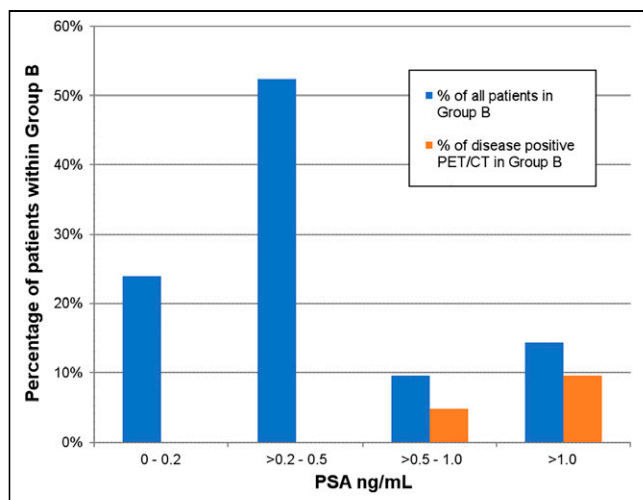
management change rate in high-risk patients in a randomized multicenter study using <sup>68</sup>Ga-HBED PSMA was 28% (4,12).

In the BCR groups combined, a management change occurred in 51.7% of patients. This was comparable to the findings of the meta-analysis of studies performed with PSMA in the recurrence setting by Han et al. and slightly higher than the proportion of management change we described previously using <sup>68</sup>Ga-HBED PSMA (13).

There were fewer changes in the postprostatectomy group (42.9%) than in the postradiotherapy group (75%). This may in part have been due to the large proportion of patients scanned at very low PSA levels in group B; 23.8% of patients in this group had a PSA of 0.1–0.2 ng/mL and 52.4% had a PSA of 0.2–0.5 ng/mL and an associated low number of positive scans. The low PSA levels at the time of scanning in the postprostatectomy group was driven by the definition of BCR in this group, reflecting clinicians’ threshold to consider offering early salvage radiotherapy. In the BCR group evaluated by Kulkarni et al., there were no positive scans in the population with a PSA of less than 0.5 ng/mL, and that study reported higher rates of management change at higher PSA levels (12). Derlin et al. did demonstrate positive findings at very low PSA levels: 20.0% for a PSA value of more than 0.2 to less than 0.5 ng/mL, and 22.2% for a PSA value of 0.01–0.2 ng/mL (16). This finding is in contrast to the findings from other published data using <sup>68</sup>Ga-HBED PSMA, which showed 38% of scans to be positive when PSA was less than 0.5 ng/mL in BCR (17). Others have also demonstrated higher positive rates at very low PSA levels, and this is one of the key strengths of PSMA over other PET tracer such as <sup>18</sup>F/<sup>11</sup>C-choline. However, our previous study using



**FIGURE 2.** Locations of <sup>68</sup>Ga-THP uptake positive for tumor in groups A–C.



**FIGURE 3.** Proportion of patients in group B and proportion of positive scans in this group, stratified according to serum PSA level.

$^{68}\text{Ga}$ -HBED PSMA demonstrated a positive rate of 15.8% in a PSA range of 0.2–0.5 ng/mL (18). As a possible explanation, many studies have not excluded hormone use before the scan (which would increase PSMA upregulation/scan positivity), and another important consideration is that  $^{68}\text{Ga}$ -THP PSMA has faster renal clearance of THP and potentially lower affinity than  $^{68}\text{Ga}$ -HBED PSMA (12). Both PSMA tracers would need to be investigated in the same population with low PSA levels or at least in a matched-pair analysis to evaluate further.

The higher rate of management change in the postradiotherapy BCR group (group C) may have been in part due to the greater proportion of positive PET/CT results in this group, as well as the greater number of available options to treat these patients, including salvage prostatectomy, salvage focal therapy, further salvage radiotherapy/brachytherapy, systemic therapies, or watchful waiting.

The cold-kit manufacturing method of this tracer has several potential benefits if permitted to enter mainstream clinical use. A short manufacturing time is helpful in the context of a short-half-life radiotracer, and less complex radiopharmacy production may allow more patients to be scanned with produced doses.

This study had some limitations. The endpoint chosen for this trial—management change—has been used in multiple studies evaluating PSMA PET/CT (19–21). In a well-designed clinical trial, use of the same endpoint as in other studies allows for potential progression of PSMA tracers toward regulatory approval; although a survival or progression endpoint is more objective, it may take years to be reached. There remains a lack of evidence that a management change improves survival or another surrogate endpoint. However, the increased accuracy of disease detection implies more personalized and appropriate management for the stage of disease and reduction of the risks and side effects of ineffective treatments.

There is a lack of full validation within this and many studies on PSMA PET/CT (19–21). Although histology was available in some patients, mainly those with recent biopsy and those who underwent prostatectomy soon after the PET/CT, histology was not available in all patients and other sites of disease, such as lymph nodes, were not sampled to provide systematic validation. Such sampling is often not feasible, particularly in the BCR setting. Diagnostic accuracy assessment was not within the scope of this phase II trial but is planned to be evaluated in a larger phase III study.

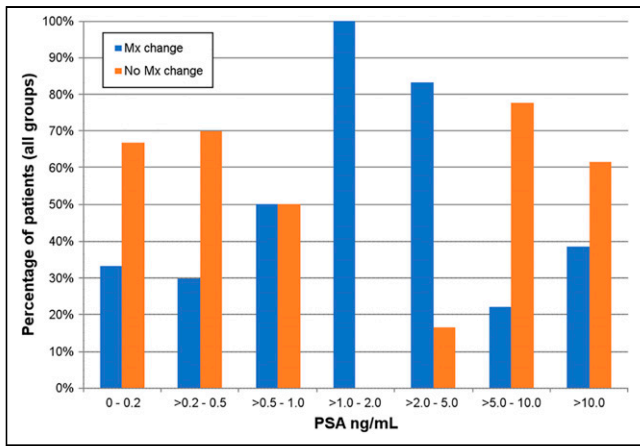
The study design involved recording the intended management plan after and on the basis of  $^{68}\text{Ga}$ -THP PSMA PET/CT, and factors related to clinician–patient consultations may have led to an executed management different from that recorded in the study.

In one patient for whom lymph node dissection was not performed, the lack of uptake in nodes partly informed the decision not to proceed with lymphadenectomy, even though the clinician and patient were aware that a negative scan did not exclude disease

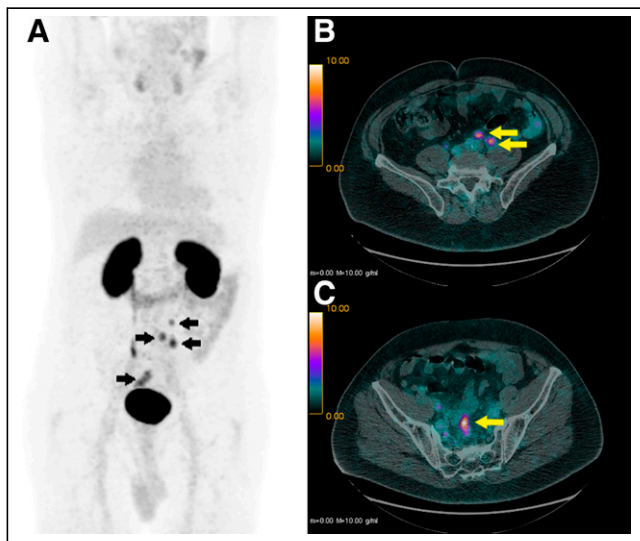
**TABLE 3**  
Scan Positivity and Management Change per Patient Group

Group	Positive	Intermodality change	Intramodality change	Other (imaging/short-interval follow-up)	Total management change per group
A	18 (90%)	4 (RP to RT [1], RT to RP [1], RT to RT with field change [1], RP to hormones [1])	1 (RP with lymph node dissection to RP alone)	1 (spine MRI)	30.0%
B	3 (14.3%)	6 (RT to surveillance [4], RT to hormones [2])	1 (RT to RT with field change)	2 (liver MRI [1], short-interval repeat PET/CT [1])	42.9%
C	6 (75%)	6 (salvage RP/focal therapy of prostate to hormones/chemotherapy [3], hormones to template biopsy for consideration of salvage RP/focal therapy [2], salvage RP/focal therapy of prostate to surveillance [1])	0	0	75.0%
Total	27 (55.1%)	16	2	3	42.9%

RP = radical prostatectomy; RT = radiotherapy.



**FIGURE 4.** Proportion of patients with management (Mx) change (all groups) stratified according to PSA level.



**FIGURE 5.**  $^{68}\text{Ga}$ -THP PSMA PET/CT in 62-y-old man in group C. (A) Maximum-intensity projection, with arrows showing  $^{68}\text{Ga}$ -THP PSMA-avid lymph nodes in pelvis and retroperitoneum. (B) Axial PET/CT image, with arrows showing some small-volume retroperitoneal lymph nodes. (C) Axial PET/CT image, with arrow showing some small-volume pelvic nodal disease. Patient's management changed from potential salvage options (prostatectomy or focal therapy) to systemic treatment with hormones.

entirely. This example touches on the complex issue of PSMA-guided targeted therapy and the need for robust histopathologic studies to confirm the limits of disease detection within nodes.

## CONCLUSION

$^{68}\text{Ga}$ -THP PSMA (kit formulation) was well tolerated and safe to use, with no serious AEs and no AEs resulting in withdrawal from this phase II study.  $^{68}\text{Ga}$ -THP PSMA PET/CT changes the management of prostate cancer patients in BCR (42.9%) and, to a lesser degree, in primary high-risk disease. The levels of management change described in this prospective trial are comparable to those found by others who have evaluated PSMA in these prospective and retrospective clinical settings. These data form the basis of a planned phase III study of  $^{68}\text{Ga}$ -THP PSMA in patients with prostate cancer.

## DISCLOSURE

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## KEY POINTS

**QUESTION:** Is  $^{68}\text{Ga}$ -THP PSMA PET/CT safe to use, and does it change the management of patients with prostate cancer?

**PERTINENT FINDINGS:** This phase II, open-label prospective clinical trial showed  $^{68}\text{Ga}$ -THP PSMA PET/CT to be well tolerated and safe to use. Management was changed in 30% of patients with untreated high-risk disease and in 51.7% of patients with recurrent disease.

**IMPLICATIONS FOR PATIENT CARE:** These data show the potential utility of  $^{68}\text{Ga}$ -THP PSMA in untreated and recurrent disease, and the safety data serve as the basis for a planned phase III study.

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