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Received: 16 August 2023 | Revised: 13 September 2023 | Accepted: 18 September 2023

DOI: 10.1002/ijc.34749

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER

The real-world outcomes of Lutetium-177 PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer: Turkish Oncology Group multicenter study

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Abstract

Metastatic castration-resistant prostate cancer (mCRPC) remains a challenging condition to treat despite recent advancements. This retrospective study aimed to assess the activity and tolerability of Lutetium-177 (Lu-177) PSMA-617 radioligand therapy

Abbreviations: ARPIs, androgen receptor pathway inhibitors; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; SD, stable disease; SPECT, single-photon emission computed tomography; SUV, standardized uptake value.

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[Correction added on 14 October 2023, after first online publication: The affiliation of Fatih Tamer has been corrected and renumbered.]

[Correction added on 15 November 2023, after first online publication: In Figures 2 to 4, the captions have been updated in this version.]

(RLT) in mCRPC patients across multiple cancer centers in Turkey. The study included 165 patients who received at least one cycle of Lu-177 PSMA-617 RLT, with the majority having bone metastases and undergone prior treatments. Prostate-specific antigen (PSA) levels were assessed before each treatment cycle, and the biochemical response was evaluated in accordance with the Prostate Cancer Work Group 3 Criteria. The PSA decline of ≥50% was classified as a response, while an increase of ≥25% in PSA levels was indicative of progressive disease. Neither response nor progression was considered as stable disease. The Lu-177 PSMA-617 RLT led to a significant PSA response, with 50.6% of patients achieving a >50% decrease in PSA levels. Median overall survival (OS) and progression-free survival were 13.5 and 8.2 months, respectively. Patients receiving Lu-177 PSMA-617 RLT in combination with androgen receptor pathway inhibitors (ARPIs) had a higher OS compared to those receiving Lu-177 PSMA-617 RLT alone (18.2 vs 12.3 months, $P = .265$). The treatment was generally well-tolerated, with manageable side effects such as anemia and thrombocytopenia. This study provides real-world evidence supporting the effectiveness and safety of Lu-177 PSMA-617 RLT in mCRPC patients, particularly when used in combination with ARPIs. These findings contribute to the growing body of evidence on the potential benefits of PSMA-targeted therapies in advanced prostate cancer.

KEYWORDS

lutetium-177, prostate cancer, PSMA-617, radioligand therapy

What's new?

Despite modern treatment advances, metastatic prostate cancer remains incurable. Here, the authors evaluated the activity and tolerability of radioligand therapy in a retrospective study including 165 patients from cancer centers across Turkey. They found that treatment with lutetium-177 (Lu-177) PSMA-617 was well-tolerated with manageable side effects. Just over half the patients had a >50% decrease in PSA levels. Median overall survival was 13.5 months, and patients who received antiandrogen drugs as well as radioligand therapy had higher survival rates.

1 | INTRODUCTION

Metastatic prostate cancer remains incurable despite the introduction of multiple new agents in recent years. Androgen deprivation therapy, in combination with an androgen receptor pathway inhibitor or docetaxel, is the initial treatment of choice for most men with metastatic prostate cancer.[1] However, the majority of patients eventually experience disease progression, resulting in what is known as mCRPC.[2]

The landscape of treatment modalities in mCRPC is constantly evolving. Second-generation androgen receptor-targeted agents enzalutamide and abiraterone, and chemotherapy agents docetaxel and cabazitaxel delay disease progression and improve overall survival.[3] Radioligand therapy (RLT) using PSMA-targeted Lutetium-177 (Lu-177) is an emerging treatment option for patients with PSMA-positive disease. VISION trial evaluated the efficacy and safety of Lu-177 PSMA-617 in patients with mCRPC who had previously received 1 to 2 lines of androgen receptor pathway inhibitor (ARPI) and 1 to 2 lines of taxane chemotherapy. In this trial, co-primary endpoints of imaging-based progression-free survival (8.7 vs 3.4 months, hazard ratio [HR] for progression 0.40, 95% CI 0.29-0.57) and overall survival (15.3 vs 11.3 months, HR for death 0.62, 95% CI 0.52-0.74) were both improved with Lu-177 PSMA-617 as compared to standard care in the 831 patients with mCRPC.[4] In the phase 2 TheraP trial, when compared with cabazitaxel, Lu-177 PSMA-617 resulted in higher PSA responses with fewer grade 3 or 4 adverse events in patients with mCRPC.[5] The results of these trials suggest that Lu-177 PSMA-617 RLT is a safe and effective treatment for patients with mCRPC who have limited treatment options.

While randomized clinical trials are indispensable for evaluating new therapies, they may not be fully informative for wider patient populations because of restrictions in eligibility criteria and strict protocol defined algorithms. In this regard, real-life experiences complement randomized clinical trial data for a better appreciation of a treatment effect. In this study, we aimed to determine the activity and tolerability of Lu-177 PSMA-617 vipivotide tetraxetan treatment administered across multiple cancer centers in Turkey where lutetium Lu-177 PSMA-617 became immediately available after the release of the preliminary data from retrospective analyses.[6,7]

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2 | MATERIALS AND METHODS

2.1 | Patient selection

This is a retrospective study designed and executed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients with histologically confirmed progressive mCRPC who showed PSMA expression of their lesions through PSMA-targeted imaging, and had received at least one cycle of Lu-177 PSMA-617 RLT were eligible. Patients were required to have disease progression with at least 1 line of an ADT plus ARPI such as abiraterone and enzalutamide or chemotherapy such as docetaxel and cabazitaxel. There were no restrictions on the number of treatments administered for mCRPC and Eastern Cooperative Oncology Group (ECOG) performance status. The decision to administer Lu-177 PSMA-617 RLT was made by the interdisciplinary tumor board at each therapy center which comprised of a medical oncologist, urologist, radiation oncologist, pathologist, radiologist and a nuclear medicine specialist. The decision on the number of cycles for each patient and the reasons for discontinuation of therapy were multifactorial and tailored to the unique circumstances of each individual. Patient response, tolerability and disease status all played a role in determining the course of treatment.

Concomitant use of an ARPI during Lu-177 PSMA treatment was optional. A total of 18 Centers across Turkey volunteered to participate in this retrospective study. Patients treated with Lu-177 PSMA-617 between May 2017 and July 2020 were eligible. In the study, the baseline demographic and clinical characteristics of the patients, previous treatments, risk categories based on Gleason grading, and Lu-177 PSMA treatment strategies were retrospectively examined. The Gleason score grades prostate cancer based on cell appearance, ranging from 2 to 10, where lower scores indicate less aggressiveness and better differentiation, while higher scores suggest more aggressive cancer.

2.2 | Administration and monitoring of Lu-177 PSMA-617

The procedures and dosing for administering Lu-177 PSMA-617 were at the discretion of the participating centers. All centers however followed recommendations outlined in the VISION Trial[4] and were closely monitored for quality control by experienced radiochemists at local sites. The nuclear medicine specialist also conducted a double check to ensure that the radiochemical purity, identity, pH value, ethanol content, endotoxin content and sterility were all within acceptable levels.

Briefly, Lu-177 PSMA-617 was slowly injected into the patient's veins over a period of 1 to 30 min followed by a saline or ringer solution rinse. Subsequent cycles were performed at intervals of 8 weeks. Patients received 150 to 200 mCi Lu-177 PSMA-617 in each cycle.

To confirm the uptake and retention of Lu-177 PSMA-617 in tumor tissue, whole-body scintigraphy and additional Single-photon emission computed tomography/computed tomography (SPECT/CT) were performed at least once 24 to 48 h after injection. Once patients met the local regulatory guidelines (with a radiation level of <3.5 mSv/h measured at a distance of 2 m), they were discharged from the nuclear medicine ward.

2.3 | Response assessment

The prostate-specific antigen (PSA) was measured before each cycle. Biochemical PSA response was determined according to the Prostate CancerWork group 3 Criteria: a PSA decline ≥50% was considered as a response (PR) and ≥ 25% PSA increase as a progressive disease (PD). Neither PR nor PD was considered as stable disease (SD).[2]

Patients were radiologically evaluated every two to four cycles by Ga-68 PSMA Positron emission tomography (PET/CT). The 30% reduction in the SUV max value was defined as regression, an increase of 30% or more standardized uptake value (SUV) max value or observation of a new lesion was accepted as progression. Not meeting these criteria was accepted as a stable disease. Additional scanning with bone scans, chest and abdominal CTs, and FDG PET-CT were optional. Hemograms, liver and kidney function tests, serum PSA and electrolytes were checked before each treatment.

2.4 | Safety

History and physical examination and blood work including hemoglobin, white blood cells, platelets, liver function tests, creatinine and alkaline phosphatase were done at each participating center shortly before each cycle. Toxicity was categorized using the Common Toxicity Criteria for Adverse Events (version 4.03). In addition, all serious adverse events were reported.

2.5 | Statistical analysis

Statistical analyses were performed using IBM SPSS software version 28. Descriptive statistics were presented as frequency (percent), mean ± SD or median (min-max). The χ^2 test was used to compare the proportions in different categorical groups. The time from the onset of Lu-177 PSMA to death from any cause was defined as overall survival (OS); to radiological progression or death was defined as progression-free survival (PFS). Survival estimates were calculated with the Kaplan-Meier method. The log-rank test was used to identify the independent effects on OS and PFS. A P value of <.05 was used to infer statistical significance.

3 | RESULTS

3.1 | Baseline characteristics

A total of 165 patients with mCRPC were treated with Lu-177 PSMA-617 at the participating 18 centers in Turkey. The mean age was

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69.8 ± 8.3 years (median: 70, range: 45-88). Sixteen (9.7%) patients had previously undergone radical prostatectomy. One hundred twenty-three (74.5%) patients had distant metastases at the time of diagnosis. Of the 165 patients included in the study, 126 (76.4%) patients had bone metastases only, while 39 (23.6%) patients had visceral involvement (15 lung, 14 liver and 10 others). The ECOG performance score was zero in 17 (10.3%) patients, one in 108 (65.6%), two in 37 (22.4%) and three in 3 (1.8%) patients. According to Gleason grading, 8 (4.8%) patients had low/very low risk, 50 (30.4%) patients had intermediate risk and 107 (64.8%) patients had high/very high risk.

Lu-177 PSMA-617 was second-line therapy in 31 (18.8%) patients, third-line in 54 (32.7%) and fourth-line in 80 (48.5%). Previous therapies are outlined in Table 1. First-line therapy was Docetaxel in 80 (48.5%) and androgen deprivation therapy (ADT) alone in 76 (46.1%). Second-line therapies consisted of docetaxel in 62 (37.6%), enzalutamide in 49 (29.7%) and abiraterone in 38 (23%). Abiraterone and enzalutamide were the most used therapies in the third line.

All 165 patients received at least one cycle of Lu-177 PSMA-617 with a median of 3 (1-8) cycles. Of the total, 95.7, 60.6, 47.3, 19.4, 17, 10.3 and 7.3% completed two through 8 cycles of therapy. Lu-177 PSMA-617 was given alone in 121 (73.3%) and concurrently with abiraterone or enzalutamide in 44 (26.7%) patients (Table 1).

3.2 | PSA response

PSA response evaluation was available for 158 out of 165 patients. Overall, 80 (50.6%) patients showed a PSA response of >50% decrease compared to baseline, while 55 (34.8%) patients showed PSA progression. In 23 individuals (14.6%), PSA was rated as stable (Figure 1). Considering all the first 3 cycles, treatment was discontinued in 87 (52.7%) patients; in 55 due to disease progression, and in 32 patients due to side effects or patient-related factors. Treatment was stopped in 7 (all due to adverse effects), 58 (49 progression and 9 adverse effects) and 22 (6 progression, 16 adverse effects) patients after the first, second and third cycles, respectively. PSA response was achieved after a median of 2 (1-4) cycles. PSA response rates in each of the 8 cycles were 17.6%, 33.3%, 37.8%, 65.7%, 72.4%, 70%, 73.3% and 91.7%, respectively (Figure 2). It was shown that PSA response rate was 63.3% in patients who received Lu-177 PSMA-617 as the second line, 58.5% as the third line and 40% as the fourth line treatment ($P = .036$). The ECOG performance status of 0 and 1 were linked to a better biochemical response than 2-3 (56.3% vs 33.3%, $P = .013$). The metastasis site at the beginning of lutetium therapy (only bone vs visceral or visceral plus bone, $P = .22$) was not significantly associated with overall PSA response. The response rate was significantly higher in patients receiving combined therapy with abiraterone or enzalutamide than in patients receiving Lu-177 PSMA-617 alone (69.8% vs 43.5%, $P = .003$).

TABLE 1 Baseline characteristics of the patients.

Characteristics	Frequency (%), n = 165
Age, mean ± SD, years	69.8 ± 8.3
Risk categories based on Gleason grading	
Low/very low	8 (4.8)
Intermediate	50 (30.4)
High/very high	107 (64.8)
Radical prostatectomy	16 (9.7)
Metastasis at diagnosis	123 (74.5)
Previous treatments	
First line	
Docetaxel	80 (48.5)
ADT	76 (46.1)
Enzalutamide	5 (3)
Abiraterone	4 (2.4)
Second line	
Docetaxel	62 (37.6)
Enzalutamide	49 (29.7)
Abiraterone	38 (23)
ADT	3 (1.8)
EP	2 (1.2)
Cabazitaxel	2 (1.2)
Third line	
Abiraterone	35 (21.2)
Enzalutamide	24 (14.5)
Docetaxel	19 (11.5)
Cabazitaxel	13 (7.9)
Estramustine	1 (0.6)
Lu-177 PSMA line	
Second	31 (18.8)
Third	54 (32.7)
Fourth	80 (48.5)
ECOG PS at first Lu-177 PSMA cycle	
0	17 (10.3)
1	108 (65.6)
2	37 (22.4)
3	3 (1.8)
Metastasis site at Lu-177 PSMA treatment	
Only bone metastasis	126 (76.4)
Visceral/bone plus visceral metastasis	39 (23.6)
Lu-177 PSMA cycle, median (min-max)	3 (1-8)
Treatment strategy	
Lu-177 PSMA only	121 (73.3)
Lu-177 PSMA plus Abiraterone /Enzalutamide	44 (26.7)

Abbreviations: ADT, androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EP, etoposide and cisplatin; PSMA, prostate-specific membrane antigen.

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3.3 | Safety

Adverse effects after each Lu-177 PSMA-617 cycle are detailed in Table 2. Treatment was discontinued in 32 (19.4%) patients due to 3 to 4 grade side effects, and 3 (1.8%) patients died due to side effects. Acute renal injury, thrombocytopenic central nervous system bleeding, febrile neutropenia and sepsis all contributed to the deaths of one patient each. Overall, the most common adverse effect was anemia. Grade 1 or 2 anemia was frequently encountered. Grade 3 anemia was observed in 3 (1.9%), 8 (5.6%), 6 (6%), 4 (5.1%), 1 (3.1%) and 1 (3.6%) patients in the first 6 cycles, respectively. Grade 4 anemia was not found. One patient had grade 3 leukopenia after the fourth cycle, while one patient had grade 4 leukopenia after the first cycle. Five patients experienced grade 3 and one experienced grade 4 thrombocytopenia. Only one patient experienced a grade 3 creatinine rise after the first cycle, but no grade 2 or 4 creatinine increases were found after any cycle. There were no signs of grade 3 or 4 hepatocellular toxicity, but only two individuals had grade 2 ALT elevation.

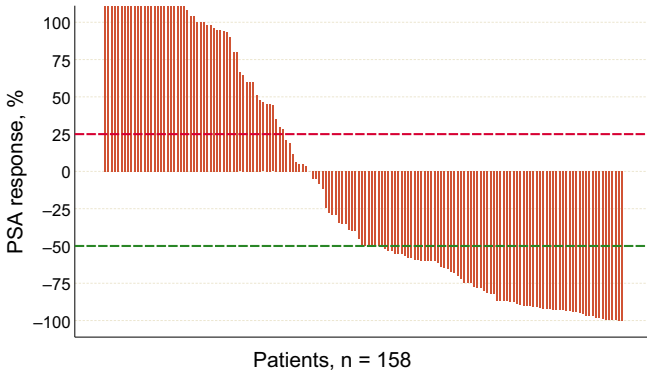

FIGURE 1 Waterfall plots of maximum PSA change (%) from baseline over total follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Survival analyses

The median follow-up period from the beginning of lutetium treatment was 9.1 (0.03-55.6) months. During follow-up, the disease progressed in 118 (71.5%) patients, and 93 (56.4%) patients died. Twenty (12.1%) patients died following the initial treatment cycle. The median OS and PSF were 13.5 (8.7-18.3) and 8.2 (6.7-9.7) months, respectively. The 3-year OS was 23.8% (14.8-32.8) and the 3-year PFS was 13.8% (7.1-20.5).

The median OS was 19.6 (1.8-37.3) months for patients who received Lu-177 PSMA-617 treatment in the second line, 12.7 (5.2-20.3) months in the third line, and 12.3 (8.4-16.3) months in the fourth line ($P = .588$) (Figure 3A). The median PFS was 13.3 (1.7-24.8), 8.6 (7.6-9.6) and 5.7 (3.7-7.7) months in patients who received Lu-177 PSMA-617 therapy in the second, third and fourth lines, respectively ($P = .293$) (Figure 4A). ECOG performance status of

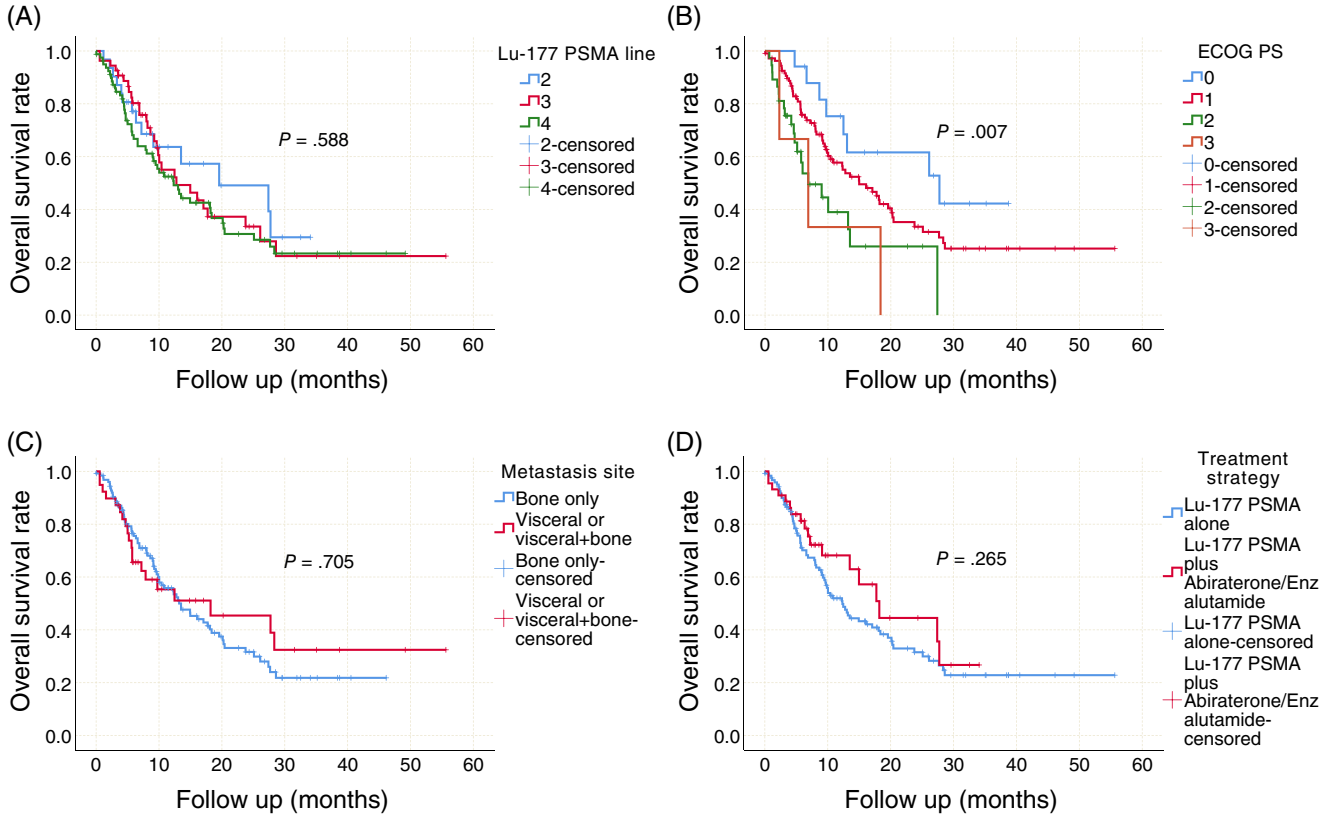

FIGURE 2 Overall survival based on (A) Lu-177 PSMA treatment sequences; (B) ECOG performance scores at initial lutetium therapy; (C) metastasis sites at Lu-177 PSMA treatment and (D) treatment strategies. [Color figure can be viewed at wileyonlinelibrary.com]

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TABLE 2 Main adverse effects after Lu-177 PSMA cycles.

	After Lu-177 PSMA cycle, n (%)							
Adverse effects	**I (n = 159)[a]**	**II (n = 142)**	**III (n = 100)**	**IV (n = 78)**	**V (n = 32)**	**VI (n = 28)**	**VII (n = 17)**	**VIII (n = 12)**
Anemia								
Grade 1	95 (20.1)	81 (57)	55 (55)	47 (60.3)	16 (50)	15 (53.6)	13 (76.5)	12 (100)
Grade 2	29 (18.2)	29 (20.4)	22 (22)	13 (16.7)	6 (18.8)	4 (14.3)	0 (0)	0 (0)
Grade 3	3 (1.9)	8 (5.6)	6 (6)	4 (5.1)	1 (3.1)	1 (3.6)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia								
Grade 1	30 (18.9)	23 (16.3)	18 (18)	13 (16.7)	4 (12.5)	6 (21.4)	0 (0)	2 (16.7)
Grade 2	2 (1.3)	7 (5)	3 (3)	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia								
Grade 1	6 (3.8)	15 (10.6)	11 (11)	11 (14.1)	3 (9.4)	2 (7.1)	2 (11.8)	1 (8.3)
Grade 2	1 (0.6)	2 (1.4)	1 (1)	1 (1.3)	0 (0)	1 (3.6)	0 (0)	0 (0)
Grade 3	3 (1.9)	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)
Grade 4	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nephrotoxicity[b]								
Grade 1	12 (7.5)	10 (7.1)	6 (6)	6 (7.7)	2 (6.3)	1 (3.6)	1 (5.9)	1 (8.3)
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatotoxicity[b]								
Grade 1	9 (5.7)	13 (9.2)	7 (7)	6 (7.8)	1 (3.1)	0 (0)	0 (0)	0 (0)
Grade 2	0 (0)	1 (0.7)	0 (0)	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviation: PSMA, prostate-specific membrane antigen.

[a]Six patients' laboratory results are missing.

[b]Evaluations were based on creatinine increase for nephrotoxicity and alanine transaminase increase for hepatotoxicity.

two at first Lu-177 PSMA-617 cycle was associated with decreased OS ($P = .007$) and PFS ($P = .016$) (Figures 3B and 4B). No statistically significant difference in OS ($P = .705$) or PFS ($P = .704$) was observed between patients with only bone metastases and those with visceral or visceral plus bone metastases at the start of lutetium therapy (Figures 3C and 4C). The median OS was 18.2 (12.7-23.6) months in patients receiving Lu-177 PSMA-617 combined with abiraterone or enzalutamide, and 12.3 (9.3-15.3) months in patients receiving Lu-177 PSMA-617 alone ($P = .265$) (Figure 3D). Median PFS was significantly higher in the combined treatment group than in patients treated with Lu-177 PSMA-617 alone (11.9 [10-13.9] vs 7.4 [5.4-9.5] months, $P = .031$) (Figure 4D).

4 | DISCUSSION

Lu-177-PSMA-617 RLT is a novel treatment method that delivers beta particle radiation to PSMA-expressing cells and their surrounding environment. Although it was first introduced in 2015, the results of randomized controlled studies investigating the efficacy of this treatment have only been published in the last 2 years.[4,5,8] The current research examined the real-life safety and effectiveness of Lu-177 PSMA-617 RLT in mCRPC patients across many centers. This study represents the most extensive real-life analysis of a multicenter approach for Lu-177 PSMA-617 RLT in prostate cancer that has been conducted to date. The efficacy, safety and potential benefits of Lu-177 PSMA-617, particularly when used in combination with antiandrogen agents, in real-life patients have not been extensively studied despite its growing acceptance in recent years. In this study patients receiving new-generation antiandrogenic agents in combination with Lu-177 PSMA-617 RLT were also included.

Our cohort of patients with metastatic prostate cancer showed a significant advantage in PFS and OS with Lu-177 PSMA-617 treatment, providing 8.2 months of PFS and 13.5 months of OS. Previous retrospective studies have mainly utilized Lu-177 treatment for patients with advanced prostate cancer who have exhausted other

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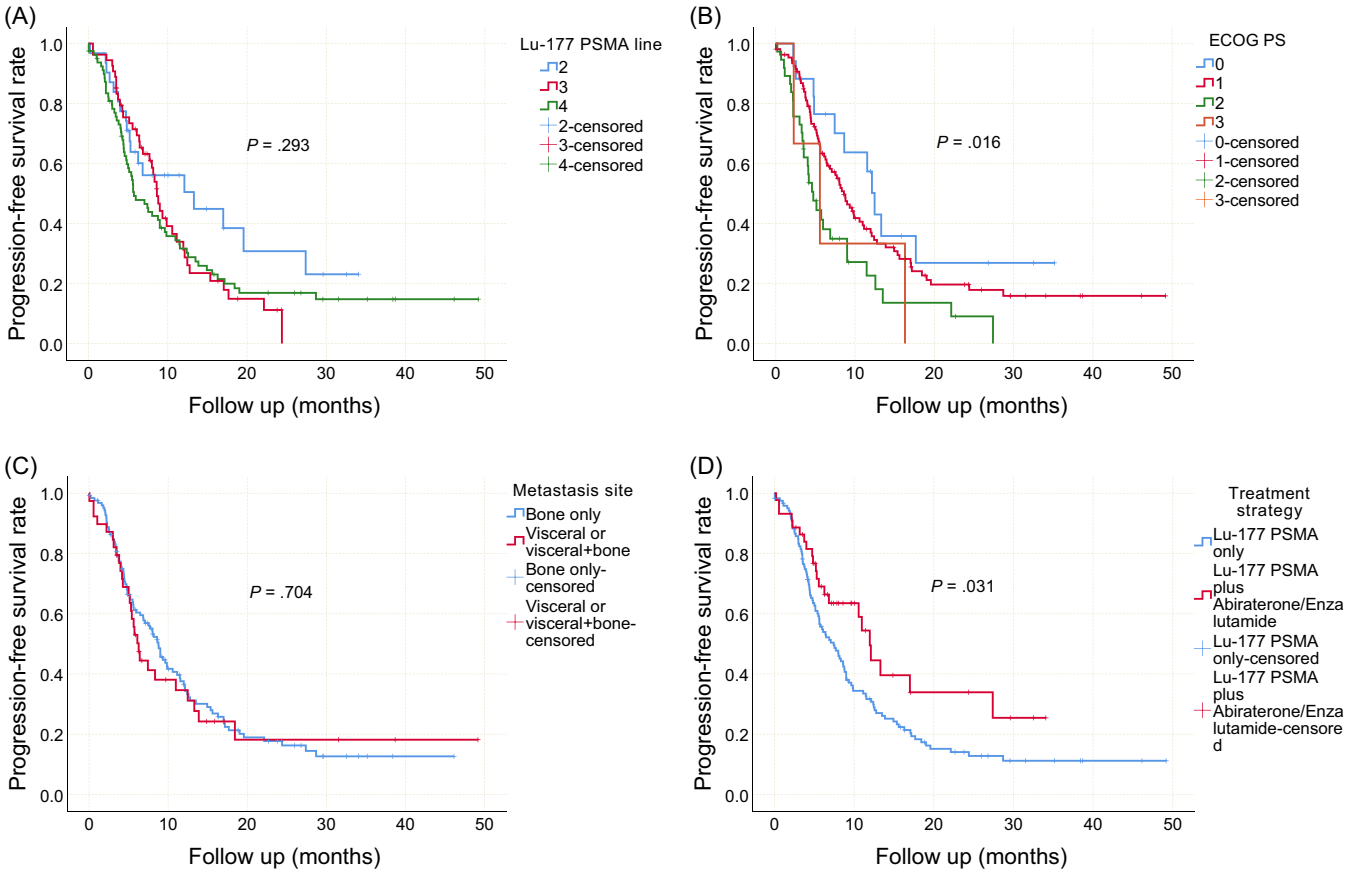

FIGURE 3 Progression-free survival based on (A) Lu-177 PSMA treatment sequences; (B) ECOG performance scores at initial lutetium therapy; (C) metastasis sites at Lu-177 PSMA treatment and (D) treatment strategies. [Color figure can be viewed at wileyonlinelibrary.com]

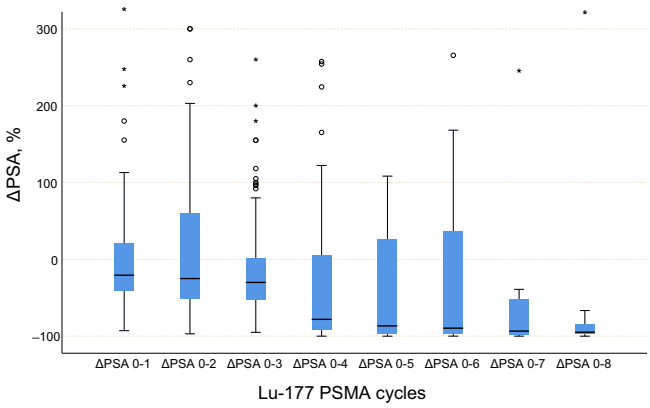

FIGURE 4 Box plots showing PSA response rates in each of the 8 cycles from baseline up to the end of treatment. [Color figure can be viewed at wileyonlinelibrary.com]

treatment options, reporting an average OS of 5-15 months.[5,9-11] These findings are consistent with the results of our study. Additionally, the Phase III VISION study, which focused on heavily treated patients, also demonstrated comparable results, with a PFS of 8.7 months and OS of 15.3 months.[4]

The phase II TheraP study investigated Lu-177 PSMA-617 in chemotherapy-naive patients who had received one to two lines of antiandrogens. At the ASCO 2022 meeting, updated survival results indicated that Lu-177 treatment yielded 19.1 months of OS and 7.1 months of PFS, surpassing those shown in earlier studies.[5] This led to a query as to whether administering Lu-177 treatment in earlier stages would be more efficacious. Furthermore, a post hoc exploratory analysis of the VISION trial showed greater benefits for patients who had not received a second prior taxane (HR for OS 0.59 [0.46, 0.75] vs 0.73 [0.53, 0.99]).[12] Our study also produced comparable outcomes to the TheraP results, with OS and PFS rates of 19.6 months and 13.3 for patients who received Lu-177 PSMA as their second-line treatment.

In our study, patients who were treated with new-generation ARPi (enzalutamide or abiraterone acetate) alongside Lu-177 PSMA-617 had higher OS compared to those who received Lu-177 PSMA-617 alone. The median OS was 18.2 months for the combination therapy group, whereas it was 12.3 months for the Lu-177 PSMA-617 alone group. However, it is uncertain whether this result is due to the synergistic effect of the combination therapy or because the former group received the Lu-177 PSMA-617 treatment earlier. The ENZA-p trial and PSMAddition studies are expected to provide more clarity on this matter.[13,14]

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In the TheraP trial, more than half of the participants experienced a decline of over 50% in their PSA levels, while in the VISION trial, this was the case for 46% of patients.[4] In our own cohort, we observed a similar trend, with 50.6% of patients achieving a PSA decline of over 50%. The PSA response was typically observed after a median of two treatment cycles, and those who received Lu-177 PSMA-617 in combination with their ARPi had a more favorable response.[4,5]

In clinical trials, the most common grade 3 or 4 adverse events reported were hematological toxicity (28.7%), fatigue (5.6%) and renal toxicity (3.3%). The incidence was relatively low with dry mouth and radiation dermatitis being reported in <1% of patients. In terms of the incidence and grades of radiation-related adverse events, the VISION trial reported that 17% of patients experienced grade 3 or 4 adverse events, which included lymphopenia (8%), thrombocytopenia (5%) and anemia (3%).[4] The THERAP trial, which included 200 patients, reported similar side effects, with the most commonly reported being nausea (32%), fatigue (23%) and vomiting (19%). Radiation-related adverse events occurred in 15% of patients, the most common types being lymphopenia (6%), thrombocytopenia (5%) and anemia (4%).[5] In our patient group, 19.4% experienced grades 3 to 4 adverse events, and three patients died due to treatment-related complications. Among the observed side effects, anemia was the most frequent, which aligns with previous studies, whereas thrombocytopenia was relatively rare in our cohort, with only five patients affected. This finding contrasts with previous research, which reported higher incidence rates ranging from 17% to 40%, but this led to the death of one patient.[5,8,15] In general, studies have shown that the safety profile of Lu-177 PSMA-617 is generally favorable, with mild to moderate side effects that can be effectively managed with supportive care. However, the possibility of severe or life-threatening adverse reactions, such as MDS or kidney damage has been reported.[15]

This study has several notable limitations that need to be acknowledged. Firstly, its retrospective design poses a significant limitation, as it may limit the ability to draw causal inferences and establish causality. Additionally, the use of data collected from multiple centers introduces potential heterogeneity, which may affect the generalizability of the findings. Furthermore, the presence of missing data due to the unavailability is another limitation. Another important limitation to note is the lack of patient-reported outcomes, which may limit the ability to fully capture patients' experiences with the treatment. As a result, the side effect profile was solely interpreted based on the available data in the patient's medical records, which may not accurately reflect the true incidence and severity of adverse events.

5 | CONCLUSIONS

PSMA-targeted treatment has emerged as a promising therapeutic approach for prostate cancer patients, particularly for those with advanced or metastatic disease. Results shown in this multi-center real-life study support the findings in previous clinical studies showing improved progression-free and overall survival rates. Data are emerging indicating that Lu-177 PSMA-617″ could be more effective when used in earlier lines. However, there are still concerns about the potential side effects of the treatment, and further research is needed to determine its long-term safety and efficacy. Despite these challenges, PSMA-targeted treatment offers hope for improving the outcomes and quality of life for prostate cancer patients and represents an exciting area of ongoing research and development in the field of oncology.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. Conceptualization: Elvina Almuradova. Data curation: Elvina Almuradova, Mustafa Seyyar, Hacı Arak, Fatih Tamer, Umut Kefeli, Sinan Koca, Erdem Sen, Tugba Akin Telli, Fatih Karatas, Ivo Gokme, Nazım Serdar Turhal, Teoman Sakalar, Murat Ayhan, Ferhat Ekinci, Emre Hafizoglu, Seda Kahraman, Oguzhan Kesen, Caglar Unal, Ozkan Alan, Serdar Celik, Emre Yekeduz, Ozgür Omur, Erhan Gokmen. Formal analysis: Elvina Almuradova. Investigation: Elvina Almuradova, Mustafa Seyyar, Hacı Arak, Fatih Tamer, Sinan Koca, Erdem Sen, Tugba Akin Telli, Fatih Karatas, Ivo Gokme, Nazım Serdar Turhal, Teoman Sakalar, Murat Ayhan, Ferhat Ekinci, Emre Hafizoglu, Seda Kahraman, Oguzhan Kesen, Caglar Unal, Ozkan Alan, Serdar Celik, Emre Yekeduz, Ozgür Omur, Erhan Gokmen. Methodology: Elvina Almuradova, Erhan Gokmen. Project administration: Elvina Almuradova, Nazım Serdar Turhal, Ozgür Omur, Erhan Gokmen. Resources: Elvina Almuradova, Mustafa Seyyar, Hacı Arak, Fatih Tamer, Sinan Koca, Erdem Sen, Tugba Akin Telli, Fatih Karatas, Ivo Gokme, Nazım Serdar Turhal, Teoman Sakalar, Murat Ayhan, Ferhat Ekinci, Emre Hafizoglu, Seda Kahraman, Oguzhan Kesen, Caglar Unal, Ozkan Alan, Serdar Celik, Emre Yekeduz, Ozgür Omur, Erhan Gokmen. Software: Elvina Almuradova. Supervision: Elvina Almuradova, Erhan Gokmen. Validation: Elvina Almuradova, Mustafa Seyyar, Hacı Arak, Fatih Tamer, Sinan Koca, Erdem Sen, Tugba Akin Telli, Fatih Karatas, Ivo Gokme, Nazım Serdar Turhal, Teoman Sakalar, Murat Ayhan, Ferhat Ekinci, Emre Hafizoglu, Seda Kahraman, Oguzhan Kesen, Caglar Unal, Ozkan Alan, Serdar Celik, Emre Yekeduz, Ozgür Omur, Erhan Gokmen. Visualization: Elvina Almuradova. Writing—original draft: Elvina Almuradova, Erhan Gokmen. Writing—review & editing: Elvina Almuradova, Mustafa Seyyar, Hacı Arak, Fatih Tamer, Sinan Koca, Erdem Sen, Tugba Akin Telli, Fatih Karatas, Ivo Gokme, Nazım Serdar Turhal, Teoman Sakalar, Murat Ayhan, Ferhat Ekinci, Emre Hafizoglu, Seda Kahraman, Oguzhan Kesen, Caglar Unal, Ozkan Alan, Serdar Celik, Emre Yekeduz, Ozgür Omur, Erhan Gokmen.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The utilization of the collected data from each institution for inclusion in this project has received formal approval. Furthermore, in strict

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adherence to the principles outlined in the Declaration of Helsinki, written informed consent was diligently obtained from all participating subjects. Lastly, the study has been officially sanctioned by the Medical Research Ethics Committee of Ege University under Decision number 21-2.1T/55.

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How to cite this article: Almuradova E, Seyyar M, Arak H, et al. The real-world outcomes of Lutetium-177 PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer: Turkish Oncology Group multicenter study. *Int J Cancer*. 2024;154(4):692-700. doi:10.1002/ijc.34749

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