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[^{177}Lu]Lu-PSMA-617 Versus Docetaxel in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer: Final Survival Analysis of a Phase 2 Randomized, Controlled Trial

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The prostate-specific membrane antigen (PSMA) inhibitor [^{177}Lu]Lu-PSMA-617 has been previously demonstrated to be noninferior to docetaxel in achieving a biochemical response in chemotherapy-naïve metastatic castration-resistant prostate cancer patients. Here, we report the final analysis of overall survival (OS) for a phase 2 randomized, controlled trial. **Methods:** Forty chemotherapy-naïve, PSMA-positive metastatic castration-resistant prostate cancer patients were randomly assigned to [^{177}Lu]Lu-PSMA-617 (n = 20) or docetaxel (n = 20). Thirty-five patients received treatment per the protocol. Survival analysis was done using Kaplan–Meier curves and the Cox regression model. **Results:** The mean follow-up duration was 33.4 mo. In intention-to-treat analysis, the median OS for the [^{177}Lu]Lu-PSMA-617 and docetaxel arms was 15.0 mo (95% CI, 9.5–20.5 mo) and 15.0 mo (95% CI, 8.1–21.9 mo), respectively (P = 0.905). In per-protocol analysis, the median OS was 19.0 mo (95% CI, 12.3–25.7 mo) versus 15.0 mo (95% CI, 8.1–21.9 mo), respectively (P = 0.712). No significant difference in OS was observed between the 2 arms across the analyzed subgroups. **Conclusion:** Long-term outcomes with [^{177}Lu]Lu-PSMA-617 administered earlier in the prechemotherapy setting are comparable to those with docetaxel.

Key Words: mCRPC; [^{177}Lu]Lu-PSMA-617; docetaxel; overall survival; randomized, controlled trial

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Prostate cancer is the most common cancer in men, with a projected 288,300 new cases and 34,700 deaths in the United States in 2023 (*1*). Despite androgen deprivation, around 10%–20% of prostate cancer patients progress to a more aggressive castration-resistant state (*2*). Although a few drugs have been shown to improve survival outcomes in metastatic castration-resistant prostate cancer (mCRPC), it continues to remain a therapeutic challenge (*3,4*). [^{177}Lu]Lu-PSMA-617 has recently emerged as a viable treatment option for mCRPC (*5*). Subsequent to the landmark TheraP and VISION trials, [^{177}Lu]Lu-PSMA-617 has been recommended as a third-line treatment for mCRPC patients after progression with at least one taxane and one androgen-receptor pathway inhibitor (*6–8*). However, data on earlier lines vis-à-vis other treatment options remain limited.

The use of [^{177}Lu]Lu-PSMA-617 in the chemotherapy-naïve setting was evaluated previously in a randomized, phase 2 trial. In this trial, we randomized chemotherapy-naïve mCRPC patients with highly prostate-specific membrane antigen (PSMA)–expressing lesions to [^{177}Lu]Lu-PSMA-617 or docetaxel. The trial demonstrated the noninferiority of [^{177}Lu]Lu-PSMA-617 versus docetaxel for the primary endpoint of biochemical response rate in a per-protocol analysis (60% vs. 40%, respectively, P = 0.250). Further, whereas the progression-free survival was also similar between the 2 interventions, [^{177}Lu]Lu-PSMA-617 resulted in less frequent serious adverse events than docetaxel (*9*). Here, we report the results of the final overall survival (OS) analysis after a mean follow-up of about 3 y.

MATERIALS AND METHODS

This investigator-initiated, randomized, parallel-group, open-label, phase 2 noninferiority trial was performed between December 2019 and March 2021. Chemotherapy-naïve patients with mCRPC and high PSMA expression were recruited. High PSMA expression was defined as tracer avidity in which at least 80% of the lesions were significantly (≥1.5 times) more avid than normal liver on [^{68}Ga]Ga-PSMA-11 PET/CT and none of the lesions had uptake less than that of the liver. The full inclusion and exclusion criteria have been described previously and briefly outlined in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org) (*9*). Informed written consent was obtained from the patients before inclusion. The study was approved by the Institute Ethics Committee (INT/IEC/2019/001972) and followed the Helsinki Declaration guidelines. The trial was prospectively registered at the Clinical Trials Registry–India (CTRI/2019/12/022282).

Forty eligible patients were randomly assigned in a 1:1 ratio to either [^{177}Lu]Lu-PSMA-617 (6.0–7.4 GBq/cycle intravenously, up to 4 cycles, 8–12 wk apart) or docetaxel (75 mg/m^2/cycle intravenously, up to 10 cycles, 3 wk apart). The primary endpoint of best prostate-specific antigen response rate, and secondary endpoints comprising best objective response rate, molecular response rate, progression-free survival, toxicity, and quality-of-life outcomes, have been reported previously (*9*). The final endpoint, that is, OS, was planned to be analyzed after 70% data maturity, that is, at least 28 events. OS was estimated from the time of treatment initiation to death due to any cause.

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The primary analysis was by intention to treat and included all randomized patients. A per-protocol sensitivity analysis was also done by including only those patients who underwent at least half the allocated treatment—that is, received at least 2 cycles of ^{177}Lu-PSMA-617 or at least 5 cycles of docetaxel. Statistical analyses were done using IBM SPSS Statistics (version 20.0 for Microsoft Windows) and Stata (version 14.2). Categoric variables were expressed as numbers and percentages, and the χ^2 test was used for intergroup comparison. Survival analysis was done using the Kaplan–Meier curve method and the Cox proportional-hazards model. The proportional-hazards assumption was checked by the Schoenfeld residuals test. Mean follow-up was calculated using the reverse Kaplan–Meier method. The log-rank test was used to compare the median OS between groups. A 2-tailed P value of less than 0.05 was considered statistically significant.

RESULTS

Between December 2019 and March 2021, 40 chemotherapy-naïve mCRPC patients underwent randomization. Twenty patients each were assigned to the [^{177}Lu]Lu-PSMA-617 and docetaxel arms, with similar characteristics at baseline (Supplemental Table 2). Of these, 35 patients received treatment per the protocol: 15 of 20 patients in the [^{177}Lu]Lu-PSMA-617 arm and 20 of 20 patients in the docetaxel arm (Supplemental Fig. 1). Five patients in the [^{177}Lu]Lu-PSMA-617 arm could not complete 2 cycles—because of disease progression in 2 patients, disease-related death in 2 patients, and treatment-related severe myelosuppression in 1 patient.

As of May 31, 2023, the patients had a mean follow-up of 33.4 mo (95% CI, 28.0–38.9 mo). Further posttrial treatments were received by 9 of 20 (45%) patients in the [^{177}Lu]Lu-PSMA-617 arm, compared with 12 of 20 (60%) patients in the docetaxel arm ($P = 0.342$) (Table 1). Notably, 30% of the patients in the [^{177}Lu]Lu-PSMA-617 arm could switch over to docetaxel, in contrast to 5% of the patients in the docetaxel arm who could receive [^{177}Lu]Lu-PSMA-617 subsequently ($P = 0.038$).

Twenty-nine of the 40 (72.5%) patients died in the course of follow-up. Two patients each in the [^{177}Lu]Lu-PSMA-617 and docetaxel arms were alive at the last cutoff date; however, 7 patients (3 in the [^{177}Lu]Lu-PSMA-617 arm and 4 in the docetaxel arm) were lost to follow-up. The proportional-hazards assumption was met with a nonsignificant Schoenfeld residuals test ($P = 0.638$). In intention-to-treat analysis, the median OS for the [^{177}Lu]Lu-PSMA-617 and docetaxel arms was 15.0 mo (95% CI, 9.5–20.5 mo) and 15.0 mo (95% CI, 8.1–21.9 mo), respectively ($P = 0.905$) (Fig. 1). In the per-protocol analysis, the median OS for the [^{177}Lu]Lu-PSMA-617 arm was 19.0 mo (95% CI, 12.3–25.7 mo), versus 15.0 mo (95% CI, 8.1–21.9 mo) for the docetaxel arm ($P = 0.712$) (Fig. 2). No significant difference in OS was observed between the 2 arms across the analyzed subgroups (Table 2).

TABLE 1
Posttrial Treatments

Treatment option	[^{177}Lu]Lu-PSMA-617 arm* ($n = 20$)	Docetaxel arm ($n = 20$)
Docetaxel	6 (30)	0 (0)
Abiraterone	1 (5)	3 (15)
Enzalutamide	5 (25)	9 (45)
Rucaparib	1 (5)	0 (0)
Carboplatin	1 (5)	0 (0)
[^{177}Lu]Lu-PSMA-617	0 (0)	1 (5)
[^{225}Ac]Ac-PSMA-617	1 (5)	0 (0)

*Few patients received more than one subsequent treatment. Data are number followed by percentage in parentheses.

DISCUSSION

[^{177}Lu]Lu-PSMA-617 has been previously shown to improve survival outcomes in the postchemotherapy mCRPC setting (*6,7*). To the best of our knowledge, this is one of the first trials evaluating [^{177}Lu]Lu-PSMA-617 in the chemotherapy-naïve space. An important highlight of this study was the use of docetaxel as an active comparator. This is in contrast to other upcoming trials with [^{177}Lu]Lu-PSMA radioligand therapy in the prechemotherapy setting (but after one line of androgen-receptor pathway inhibitor) wherein control group patients are switched over to another drug of the same class (PSMAfore and SPLASH). The fact that a second-line androgen-receptor pathway inhibitor often has limited activity (especially in the presence of a first-line novel androgen-receptor inhibitor such as enzalutamide) was the reason why we compared [^{177}Lu]Lu-PSMA-617 and docetaxel in a noninferiority design in our trial (*10*). We have demonstrated earlier that [^{177}Lu]Lu-PSMA-617 is not inferior to docetaxel in terms of the short-term outcome, that is, biochemical response rate (*9*). The current results indicate that even the long-term outcome with [^{177}Lu]Lu-PSMA-617 administered earlier in the prechemotherapy setting is comparable to that with docetaxel.

The toxicity profiles of both arms in this trial have been extensively reported. Briefly, adverse events of grade 3 or higher occurred less frequently with [^{177}Lu]Lu-PSMA-617 (30%) than with docetaxel (50%). This finding was also accompanied by an improvement in the quality of life of the patients receiving [^{177}Lu]Lu-PSMA-617 (*9*).

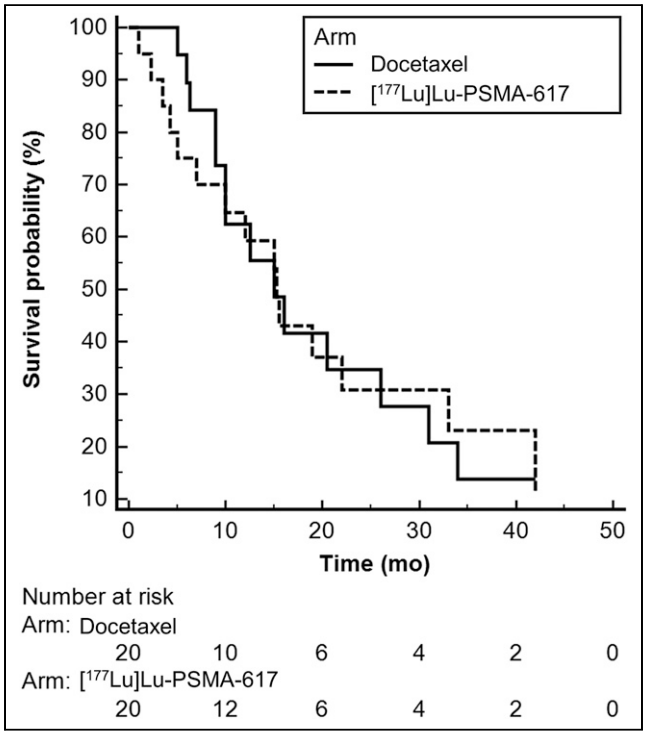

FIGURE 1. Kaplan–Meier curves for OS in intention-to-treat analysis.

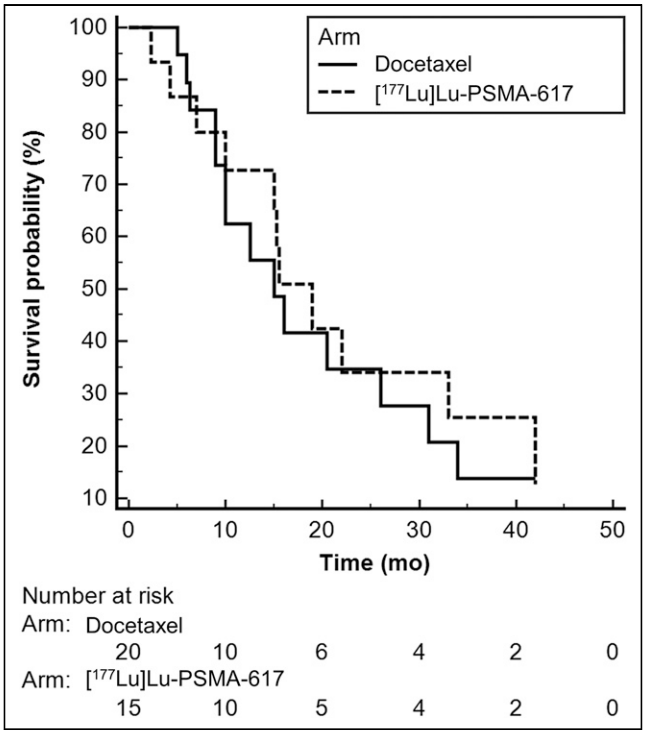

FIGURE 2. Kaplan–Meier curves for OS in per-protocol analysis.

Further, whereas a similar number of patients received subsequent therapies in both arms, the better safety with [^{177}Lu]Lu-PSMA-617 allowed a higher proportion of patients to cross over to docetaxel. In contrast, only one patient in the docetaxel arm could receive [^{177}Lu]Lu-PSMA-617 subsequently. These results indicate that contrary to the previous perception, early institution of [^{177}Lu]Lu-PSMA-617 does not significantly impair the ability to tolerate future treatments. Given its comparable efficacy over the short term as well as the long term, administration of [^{177}Lu]Lu-PSMA-617 in the prechemotherapy setting therefore has the added advantages of less frequent treatment cycles, less toxicity, and preservation of patients' quality of life.

In the current trial, we observed a median OS of 15 mo in both the [^{177}Lu]Lu-PSMA-617 arm and the docetaxel arm. However, this OS was similar to that reported with the [^{177}Lu]Lu-PSMA-617 arm in the phase 3 VISION trial in the postchemotherapy setting (*7*). Given that our trial was conducted in the prechemotherapy space, a longer OS was expected. A few factors could have adversely impacted our results: a higher percentage of patients with extensive skeletal metastases, more frequent prior treatments with both abiraterone and enzalutamide in the [^{177}Lu]Lu-PSMA-617 arm, a higher percentage of patients with extrapulmonary visceral metastases, lack of a baseline 2-[^{18}F]FDG PET/CT scan to exclude patients with discordant PSMA-negative/2-[^{18}F]FDG-positive lesions, and a treatment delay due to the coronavirus disease 2019 pandemic (*9*). Despite these factors, the comparability of the outcomes with [^{177}Lu]Lu-PSMA-617 and docetaxel adds value to our study.

The OS results with [^{177}Lu]Lu-PSMA-617 in our chemotherapy-naïve patients need to be seen further in the context of our other patients who were previously treated with chemotherapy. In a separate analysis comprising such heavily pretreated patients, we observed a median OS of 9.0 mo (*11*). The longer median OS in our chemotherapy-naïve patients therefore roughly translates to a hazard ratio of 0.60, that is, a 40% reduction in the risk of death. This is in agreement with the findings of a recent metaanalysis comparing [^{177}Lu]Lu-PSMA radioligand therapy efficacy outcomes in chemotherapy-naïve versus chemotherapy-treated patients. In this pooled analysis comprising more than 2,000 patients, taxane-naïve patients had a 1.8 times improved odds of a biochemical response, a 40% reduced risk of progression, and a 46% reduced

TABLE 2
Subgroup Regression Analyses for OS in [^{177}Lu]Lu-PSMA-617 Versus Docetaxel Arms

Variable	HR	95% CI	*P*
Age			
<70 y (*n* = 24)	0.99	0.39–2.52	0.976
≥70 y (*n* = 16)	1.09	0.33–3.64	0.882
Gleason score			
<8 (*n* = 14)	1.77	0.47–6.61	0.397
≥8 (*n* = 26)	0.70	0.28–1.78	0.454
Prior androgen-receptor pathway inhibitor			
No (*n* = 14)	0.37	0.09–1.48	0.159
Yes (*n* = 26)	1.94	0.75–4.99	0.172
Extent of skeletal disease			
<10 lesions (*n* = 8)	2.54	0.35–18.45	0.357
≥10 lesions (*n* = 32)	0.77	0.33–1.78	0.540
Visceral metastasis			
No (*n* = 31)	0.86	0.36–2.08	0.744
Yes (*n* = 9)	2.47	0.57–10.69	0.226

HR = hazard ratio.

risk of death after [^{177}Lu]Lu-PSMA radioligand therapy compared with their taxane-treated counterparts (*12*).

The current analysis has one key limitation. The study sample size was based on the primary endpoint of prostate-specific antigen response rate and was not adequately powered for other analyses. Nevertheless, this remains one of the first trials reporting final survival outcomes with [^{177}Lu]Lu-PSMA-617 in the chemotherapy-naïve setting. The use of an active comparator agent, a prolonged follow-up, and mature data for OS constitute major strengths of this study.

CONCLUSION

On the basis of the results of this phase 2 study, long-term outcomes with [^{177}Lu]Lu-PSMA-617 administered earlier in the pre-chemotherapy setting are comparable to those with docetaxel. Further trials powered for survival analyses are required to validate our observations.

KEY POINTS

QUESTION: How does [^{177}Lu]Lu-PSMA-617 impact OS vis-à-vis docetaxel in chemotherapy-naïve mCRPC patients?

PERTINENT FINDINGS: This randomized, controlled phase 2 trial assigned 40 chemotherapy-naïve, PSMA-positive mCRPC patients in a 1:1 ratio to [^{177}Lu]Lu-PSMA-617 or docetaxel. Over a mean follow-up of 33.4 mo, the median OS for the [^{177}Lu]Lu-PSMA-617 and docetaxel arms was 15.0 mo (95% CI, 9.5–20.5 mo) and 15.0 mo (95% CI, 8.1–21.9 mo), respectively ($P = 0.905$). No significant difference in OS was observed between the 2 arms across the analyzed subgroups.

IMPLICATIONS FOR PATIENT CARE: Showing long-term outcomes comparable to those of docetaxel in the chemotherapy-naïve mCRPC setting, [^{177}Lu]Lu-PSMA-617 can be a potential alternative earlier in the disease course.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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