Journal of Nuclear Medicine, published on May 11, 2023 as doi:10.2967/jnumed.123.265414

[^{177}Lu]Lu-PSMA-Radioligand Therapy Efficacy Outcomes in Taxane-Naïve Versus Taxane-Treated Patients with Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Metaanalysis

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Radioligand therapy (RLT) with ^{177}Lu-prostate-specific membrane antigen (PSMA) inhibitors ([^{177}Lu]Lu-PSMA) is currently approved for patients with metastatic castration-resistant prostate cancer (mCRPC) after progression with at least 1 taxane and 1 androgen-receptor–pathway inhibitor. However, the impact of prior chemotherapy on [^{177}Lu]Lu-PSMA-RLT outcomes is debatable, with various studies showing inconsistent results. This study was conducted to precisely evaluate the impact of prior taxane chemotherapy on response and survival outcomes in mCRPC patients after [^{177}Lu]Lu-PSMA-RLT. **Methods:** This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Searches in PubMed, Scopus, and Embase were made using relevant key words, and articles up to December 2022 were included. The endpoints included prostate-specific antigen (PSA) response rate (RR), progression-free survival, and overall survival (OS). Individual patient data were pooled when feasible. Univariate odds ratios (ORs) and hazard ratios (HRs) were extracted from the individual articles, and pooled estimates and 95% CIs were generated using metaanalysis. **Results:** Thirteen articles comprising 2,068 patients were included. In 6 articles (553 patients), taxane-naïve patients had significantly better odds of biochemical response after [^{177}Lu]Lu-PSMA-RLT (pooled OR, 1.82; 95% CI, 1.21–2.71). Individual patient data metaanalysis for PSA RRs in 3 articles revealed a significantly higher PSA RR in the taxane-naïve versus taxane-treated patients (57.1% vs. 39.5%; difference, 17.6%; 95% CI, 5.6%–28.9%). Further, taxane-naïve status was also a predictor of significantly better progression-free survival (5 articles; 1,027 patients; pooled HR, 0.60; 95% CI, 0.51–0.69) and OS (8 articles; 1,594 patients; pooled HR, 0.54; 95% CI, 0.43–0.68) after [^{177}Lu]Lu-PSMA-RLT. There was no evidence of publication bias. **Conclusion:** mCRPC patients with no prior taxanes had significantly better outcomes after [^{177}Lu]Lu-PSMA-RLT than did taxane-treated patients. Further trials evaluating [^{177}Lu]Lu-PSMA-RLT in the taxane-naïve setting are now required.

Key Words: mCRPC; [^{177}Lu]Lu-PSMA; radioligand therapy; chemotherapy; metaanalysis

J Nucl Med 2023; 00:1–6
DOI: 10.2967/jnumed.123.265414

Prostate cancer is currently ranked as the second most common cancer and the fifth leading cause of cancer-related death in men globally (*1*). Metastatic prostate cancer, particularly castration-resistant disease, presents a considerable therapeutic challenge (*2,3*). Over the past 2 decades, few drugs have shown efficacy and a proven survival benefit in metastatic castration-resistant prostate cancer (mCRPC) (*4*). However, more often than not, disease progression eventually ensues. In this context, radioligand therapy (RLT) with ^{177}Lu-labeled prostate-specific membrane antigen ([^{177}Lu]Lu-PSMA) inhibitors has emerged as a viable treatment option.

PSMA is a type II transmembrane glycoprotein that is overexpressed in almost all prostate cancer cells, thereby making it an ideal target for therapy in mCRPC (*5*). In the landmark phase 3 VISION trial, [^{177}Lu]Lu-PSMA-617-RLT has been proven to improve overall survival (OS), when added to the standard of care, in patients with end-stage, PSMA-positive mCRPC previously treated with at least 1 androgen-receptor–pathway inhibitor (ARPI) and 1 taxane regimen (*6*). The phase 2 trial, TheraP, also demonstrated better biochemical and radiologic response outcomes, as well as longer progression-free survival (PFS), with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel in mCRPC patients having previously progressed on docetaxel (*7*). Subsequently, [^{177}Lu]Lu-PSMA-617-RLT was granted Food and Drug Administration approval for progressive end-stage PSMA-positive mCRPC. The recent American Society of Clinical Oncology update also recommended its use as a treatment option in patients with PSMA-positive mCRPC who have progressed on 1 prior line of ARPI and at least 1 line of prior chemotherapy (*8*).

Despite these successes, there is a need to further optimize patient selection for PSMA-RLT to ensure better outcomes. The impact of prior taxane chemotherapy on [^{177}Lu]Lu-PSMA-RLT outcomes is debatable at present, with various studies showing inconsistent results (*9*). Given that the current treatment guidelines recommend [^{177}Lu]Lu-PSMA-RLT in only the postchemotherapy setting, it is essential to address this conundrum. This systematic review and metaanalysis was therefore conducted to precisely evaluate the effect of prior taxane chemotherapy on biochemical response and survival outcomes in patients with mCRPC treated with [^{177}Lu]Lu-PSMA-RLT.

MATERIALS AND METHODS

This systematic review was conducted as per a prespecified protocol (supplemental materials; available at http://jnm.snmjournals.org) in

Received Jan. 5, 2023; revision accepted Mar. 10, 2023.
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Published online May. 11, 2023.

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*10*).

Search Strategy and Study Selection

Two reviewers made independent systematic searches in PubMed, Scopus, and Embase for articles published until December 19, 2022. The search key words used were (lutetium OR Lu) AND (PSMA OR "prostate specific membrane antigen") AND (chemotherapy OR taxane) AND (response OR survival OR prognosis). The reviewers also undertook a manual search and searches through the references of various articles. We selected studies that assessed the impact of prior taxane chemotherapy on prostate-specific antigen (PSA) response in patients with mCRPC after treatment with [^{177}Lu]Lu-PSMA-RLT using univariate binary logistic regression analysis. Studies that provided the PSA response rates (RRs) in the taxane-naïve and taxane-treated patients separately were also included. PSA response was defined as per the Prostate Cancer Clinical Trials Working group 3 criteria—that is, at least a 50% decline in serum PSA levels from baseline (*11*). We also included studies with [^{177}Lu]Lu-PSMA-RLT that evaluated prior taxane chemotherapy status as predictors for PFS or OS using the univariate Cox proportional-hazards model. PFS was estimated from the date of the first [^{177}Lu]Lu-PSMA-RLT till documented PSA progression or radiologic progression or death. OS was estimated from the date of first treatment till death from any cause. No restriction was placed on country, language, or date of publication or on the type of ligand used for therapy; both [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T were considered. Only full-length articles that included at least 30 patients were included in this review. Reviews, case reports, letters to the editor, conference abstracts, and articles reporting exclusively on dosimetry or toxicity were excluded. In the case of multiple studies from the same center, the study with the largest number of patients was included; however, if 2 studies from the same center assessed different outcomes, they were also included separately. Studies with RLT other than [^{177}Lu]Lu-PSMA, such as ^{90}Y-PSMA, ^{225}Ac-PSMA, or tandem [^{225}Ac]Ac-PSMA/[^{177}Lu]Lu-PSMA, were also excluded. Discrepancies, if any, were resolved in consultation with the third reviewer. Institutional review board approval was not required since only prior published studies were evaluated.

Data Extraction

The following data were extracted from the included articles by 2 reviewers independently: name of first author; publication year; study design; sample size; baseline patient characteristics such as age and serum PSA; treatment characteristics such as agent administered, number of cycles, interval between each cycle, and activity administered per cycle; and available treatment outcomes (namely PSA RR or PFS or OS). For evaluating the impact of prior chemotherapy on treatment outcomes, we extracted the univariate odds ratios (ORs) for PSA response and the univariate hazard ratios (HRs) for PFS and OS in taxane-naïve versus taxane-treated patients, as available. Natural logarithmic transformations of the ratios (OR or HR) and their corresponding 95% CIs were done, and SEs for the ratios in the individual articles were calculated (*12*).

Quality assessment of the included studies was done as per the adapted Newcastle–Ottawa scale for single-arm cohort studies by 2 reviewers independently. The scale consists of 2 parameters—selection and outcome—with a total score of at least 4 for a study to be considered of good quality (*13*).

Statistical Analysis

All statistical analyses were performed using RevMan (version 5.3; Nordic Cochrane Centre) and Stata (version 14.2; Stata Corp.). Statistical heterogeneity was assessed using I^2 statistics, with an I^2 value of 30%–50% representing moderate heterogeneity and more than 50% suggesting substantial heterogeneity. The pooled OR and HR estimates were calculated using the generic inverse-variance method with random-effects model. Forest plots were generated to summarize the results. Sensitivity analysis was done to explore heterogeneity, if any, by calculating the pooled estimates after consecutively excluding each study from the metaanalysis. Subgroup analyses were based on the type of the study, sample size, and RLT agent used. Funnel plots and Egger regression tests were also undertaken to assess for publication bias. A P value of less than 0.05 was considered statistically significant.

RESULTS

Study Characteristics

In total, 591 articles were found through a systematic search of the databases: 148 from PubMed, 148 from Scopus, and 295 from Embase. After screening of titles and abstracts and removal of duplicate records, 47 full-text articles were assessed for eligibility. Thirteen articles were finally included, comprising 2,068 patients (Fig. 1; Supplemental Tables 1–2) (*14–26*). All studies were single-arm interventional studies and, barring 2 studies (*19,20*), were retrospective. All studies included mCRPC patients who had progressive disease despite prior treatments with antiandrogens with or without chemotherapy and who had been administered [^{177}Lu]Lu-PSMA-RLT as salvage or compassionate treatment. The prior taxane chemotherapy status was available for 2,067 patients, of whom 590 (28.5%) were taxane-naïve and 1,477 (71.5%) had received prior taxane. The median of the median and mean age of the patients in the evaluable articles was 71.6 y (range, 30–92 y). The median of the median and mean pretreatment PSA of the patients was 214 ng/mL (range, 0.07–11,830 ng/mL). Most studies used RLT with [^{177}Lu]Lu-PSMA-617 (n = 8); however, 3 studies used [^{177}Lu]Lu-PSMA-I&T (*17,25,26*) and 2 other studies used both agents in their respective cohorts (*16,21*). [^{177}Lu]Lu-PSMA-RLT was administered intravenously at activities of up to 11.6 GBq/cycle (usually 6.0–7.4 GBq/cycle), 3–12 wk apart over 1–20 cycles. The patients were followed up for a median of 9.9 mo (range, 0.5–72 mo). The characteristics of the included articles are detailed in Supplemental Table 1. The impact of prior chemotherapy

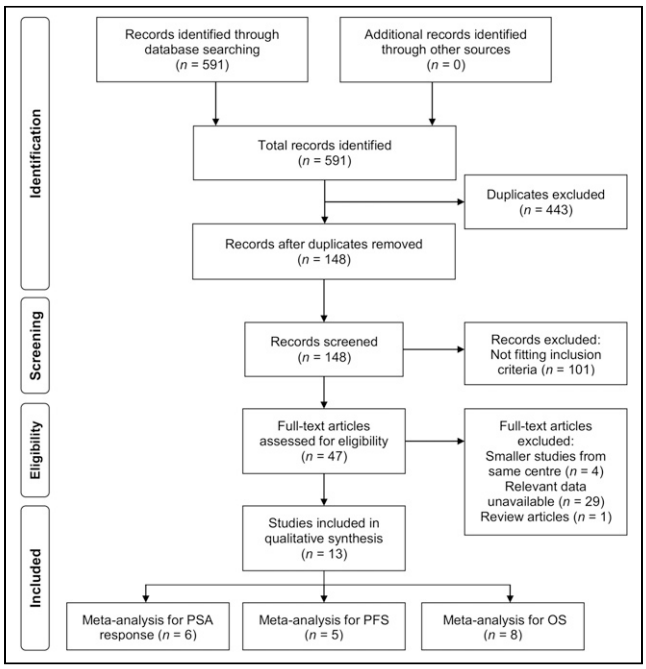

FIGURE 1. Flowchart describing study selection process.

TABLE 1
Prior Chemotherapy Status and Impact on Response and Survival Outcomes in Included Studies (Taxane-Naïve vs. Taxane-Treated Patients)

Study	Sample size (*n*)	Prior status		Univariate OR for PSA response	Univariate HR for PFS	Univariate HR for OS
		Taxane-naïve (*n*)	Taxane-treated (*n*)			
Bräuer (*14*)	59	12 (20.3%)	47 (79.7%)	NS	NS	0.62 (0.22–1.79)
Rahbar (*15*)	145	66 (45.5%)	79 (54.5%)	1.94 (0.87–4.33)*	NS	NS
Barber (*16*)	167	84 (50.3%)	83 (49.7%)	1.97 (0.99–3.95)†	0.59 (0.41–0.83)	0.39 (0.25–0.62)
Heck (*17*)	100	16 (16.0%)	84 (84.0%)	1.33 (0.45–3.93)	Excluded‡	Excluded‡
Ahmadzadehfar (*18*)	416	102 (24.5%)	314 (75.5%)	NS	NS	0.67 (0.51–0.87)
Yadav (*19*)	90	6 (6.7%)	84 (93.3%)	1.29 (0.24–6.82)	NS	NS
Khreish (*20*)	254	66 (26.0%)	188 (74.0%)	NS	0.71 (0.53–0.97)	0.63 (0.39–1.01)
Meyrick§ (*21*)	191	72 (37.7%)	118 (61.8%)	NS	0.58 (0.42–0.80)	0.29 (0.18–0.47)
Rasul (*22*)	61	19 (31.1%)	42 (68.9%)	1.27 (0.42–3.80)	NS	NS
Widjaja (*23*)	71	12 (16.9%)	59 (83.1%)	4.08 (1.00–16.63)	NS	NS
Yadav (*24*)	121	20 (16.5%)	101 (83.5%)	NS	0.63 (0.34–1.13)	0.50 (0.27–0.91)
Hartrampf (*25*)	92	28 (30.4%)	64 (69.6%)	NS	NS	0.67 (0.40–1.13)
Karimzadeh (*26*)	301	87 (28.9%)	214 (71.1%)	NS	0.53 (0.40–0.69)‖	0.67 (0.45–0.98)‖

*OR for PSA RR evaluated in 99 patients: 44 taxane-naïve and 55 taxane-treated.
†OR for PSA RR evaluated in 132 patients: 70 taxane-naïve and 62 taxane-treated.
‡Results excluded because corresponding estimates were available in larger study from same center (*26*).
§Prior chemotherapy status available for 190 patients.
‖HR for PFS and OS evaluated in 295 patients: 84 taxane-naïve and 211 taxane-treated.
NS = not specified.
Data in parentheses are percentages or 95% CIs.

on treatment outcomes in the individual studies is summarized in Table 1. All included studies were of good quality as per the Newcastle–Ottawa scale, with 11 of the 13 articles having a total score of 6 each (Table 2).

TABLE 2
Quality Assessment of Included Studies Using Adapted Newcastle–Ottawa Scale

Study	Selection	Outcome	Total score
Bräuer (*14*)	3	2	5
Rahbar (*15*)	3	2	5
Barber (*16*)	3	3	6
Heck (*17*)	3	3	6
Ahmadzadehfar (*18*)	3	3	6
Yadav (*19*)	3	3	6
Khreish (*20*)	3	3	6
Meyrick (*21*)	3	3	6
Rasul (*22*)	3	3	6
Widjaja (*23*)	3	3	6
Yadav (*24*)	3	3	6
Hartrampf (*25*)	3	3	6
Karimzadeh (*26*)	3	3	6

Pooled OR for PSA Response

The PSA RRs, that is, the proportions of patients achieving at least a 50% decline in serum PSA from baseline, ranged from 34% to 61% in the evaluable articles. Six articles consisting of 553 patients provided univariate ORs to assess the impact of prior taxane chemotherapy status on PSA response (*15–17,19,22,23*). These included 167 (30.2%) taxane-naïve patients and 386 (69.8%) taxane-treated patients. The estimated pooled OR for PSA response in taxane-naïve versus taxane-treated patients was 1.82 (95% CI, 1.21–2.71; $P = 0.004$). No statistical heterogeneity was observed ($I^2 = 0\%$, $P = 0.810$) (Fig. 2A).

Individual patient data for PSA RRs were available in 3 articles comprising 303 patients (*16,17,23*). The pooled PSA RR after [^{177}Lu]Lu-PSMA-RLT was significantly higher in the taxane-naïve patients than in patients who received chemotherapy (56/98 [57.1%] vs. 81/205 [39.5%]; difference, 17.6%; 95% CI, 5.6%–28.9%; $P = 0.004$).

Pooled HR for PFS

In the evaluable articles, the median PFS ranged from 4.0 to 12.0 mo. The impact of prior chemotherapy status on PFS was evaluated in 5 articles (1,027 patients) comprising 326 (31.7%) taxane-naïve and 701 (68.3%) taxane-treated patients (*16,20,21,24,26*). Three of these articles evaluated PFS based on PSA progression (*20,24,26*), one assessed radiologic PFS (*16*), and another evaluated both PSA PFS and radiologic PFS (*21*). The pooled HR estimate for overall PFS in taxane-naïve versus taxane-treated patients was 0.60 (95% CI, 0.51–0.69; $P < 0.001$) (Fig. 2B). No significant statistical

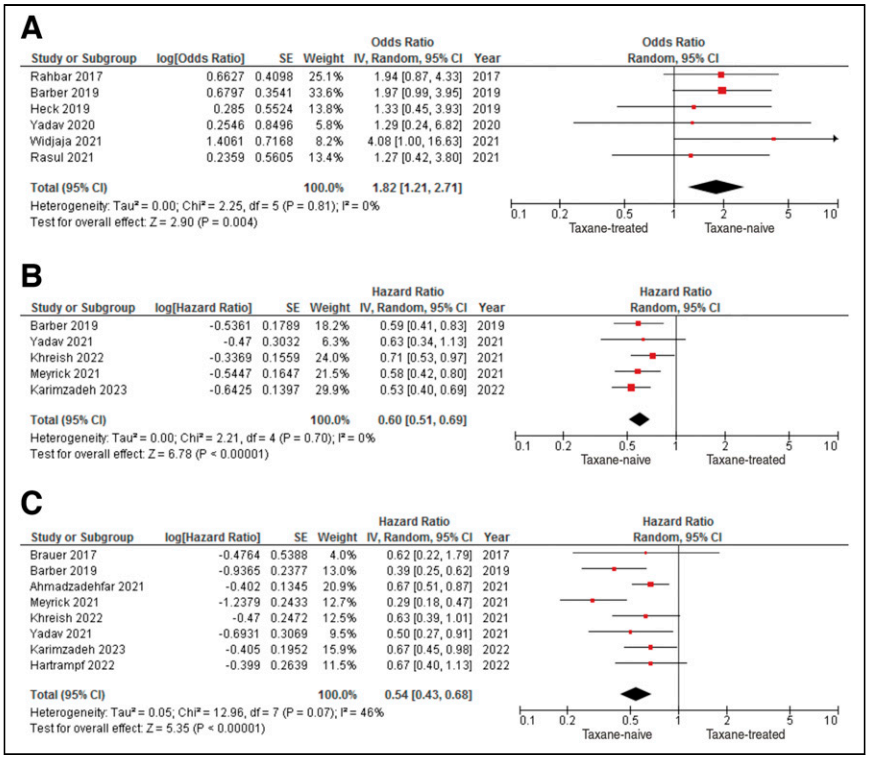

FIGURE 2. Forest plots showing pooled estimates of univariate OR for PSA response (A), univariate HR for PFS (B), and univariate HR for OS (C) in taxane-naïve vs. taxane-treated patients after ^{177}Lu-PSMA-RLT.

heterogeneity was noted (I^2 = 0%, P = 0.70). The corresponding pooled HR estimates for PSA PFS and radiologic PFS were 0.60 (95% CI, 0.51–0.71; $P < 0.001$; I^2 = 0%) and 0.55 (95% CI, 0.43–0.70; $P < 0.001$; I^2 = 0%), respectively.

Pooled HR for OS

The median OS in the included articles ranged from 8.0 to 27.1 mo. Eight articles comprising 1,594 patients evaluated the impact of prior chemotherapy in predicting OS using univariate analysis (*14,16,18,20,21,24–26*). The estimated pooled univariate HR for taxane-naïve patients (n = 468/1,594, 29.4%) versus taxane-treated patients (n = 1,126/1,594, 70.6%) was 0.54 (95% CI, 0.43–0.68; $P < 0.001$) (Fig. 2C). Moderate statistical heterogeneity was observed (I^2 = 46%, P = 0.07). Sensitivity analysis indicated that the source of heterogeneity was the study by Meyrick et al. (*21*). After exclusion of this particular result from the metaanalysis, the pooled HR for OS was 0.61 (95% CI, 0.52–0.71; $P < 0.001$) and did not exhibit any statistical heterogeneity (I^2 = 0%, P = 0.58).

Subgroup Analyses

Table 3 shows the results of subgroup analyses of the pooled estimates based on the study design, sample size, and RLT agent used. Significantly better PFS and OS outcomes were observed with both [^{177}Lu]Lu-PSMA-617 (HR for PFS, 0.69; HR for OS, 0.64) and [^{177}Lu]Lu-PSMA-I&T (HR for PFS, 0.53; HR for OS, 0.67) in the taxane-naïve than in the taxane-treated patients.

Publication Bias

Visual assessment of funnel plots for the efficacy outcomes did not indicate any publication bias. Egger regression test results were not statistically significant (Fig. 3).

DISCUSSION

With the results of the landmark VISION and TheraP trials, [^{177}Lu]Lu-PSMA-RLT has been proven to improve outcomes in mCRPC patients in the postchemotherapy setting (*6,7*). Given its encouraging efficacy and safety profiles in end-stage mCRPC, use in earlier treatment lines is expected to result in even better outcomes. However, the absence of definite evidence of improvement in outcomes has so far hindered the acceptability of [^{177}Lu]Lu-PSMA-RLT earlier in the disease course. Further, retrospective

TABLE 3
Subgroup Analyses of Pooled Estimates

	Pooled OR for PSA response		Pooled HR for PFS		Pooled HR for OS	
Variable	95% CI	I^2	95% CI	I^2	95% CI	I^2
Study design						
Retrospective	1.85 (1.22–2.81)	0%	0.56 (0.47–0.67)	0%	0.53 (0.41–0.68)	53%
Prospective	1.29 (0.24–6.82)	NA	0.71 (0.53–0.97)	NA	0.63 (0.39–1.01)	NA
Sample size						
<100 patients	1.87 (1.07–3.25)	0%	NA	NA	0.66 (0.42–1.05)	0%
≥100 patients	1.76 (0.98–3.16)	0%	NA	NA	0.52 (0.39–0.68)	60%
RLT agent						
^{177}Lu-PSMA-617	1.87 (1.07–3.25)	0%	0.69 (0.53–0.91)	0%	0.64 (0.51–0.78)	0%
^{177}Lu-PSMA-I&T	1.33 (0.45–3.93)	NA	0.53 (0.40–0.69)	NA	0.67 (0.49–0.91)	0%

NA = not applicable.

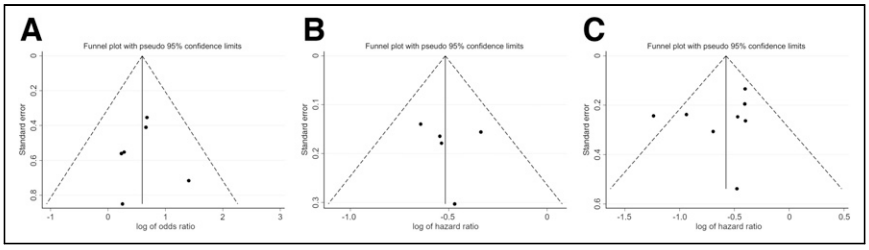

FIGURE 3. Funnel plots evaluating publication bias for PSA RR (A), PFS (B), and OS (C)

studies evaluating [^{177}Lu]Lu-PSMA-RLT outcomes in taxane-naïve versus taxane-treated patients have so far given conflicting results (*14–26*). To address this evidence gap, this systematic review and metaanalysis comprehensively pooled 13 studies to evaluate the impact of prior chemotherapy status on [^{177}Lu]Lu-PSMA-RLT outcomes. Our results clearly indicate that [^{177}Lu]Lu-PSMA-RLT resulted in significantly better PSA response, PFS, and OS when administered in the taxane-naïve setting than in the post-taxane setting. Specifically, in taxane-naïve patients receiving [^{177}Lu]Lu-PSMA-RLT, the odds of having a PSA response were 1.8 times better than in taxane-treated patients, with a reduction of 40% and 46% in the risk of progression and deaths, respectively.

Nevertheless, the results of this metaanalysis, although highly relevant, are no substitute for those of a randomized controlled trial. To date, only a single prospective phase 2 trial has evaluated [^{177}Lu]Lu-PSMA-RLT in taxane-naïve mCRPC. The trial compared [^{177}Lu]Lu-PSMA-617 with docetaxel in 40 taxane-naïve mCRPC patients and showed that [^{177}Lu]Lu-PSMA-617 had response outcomes similar and noninferior to docetaxel. Further, patients receiving [^{177}Lu]Lu-PSMA-617 experienced fewer grade 3–5 adverse events (30% vs. 50%, respectively), with a significantly better quality of life, than those receiving docetaxel (*27*). These results, when coupled with those of our metaanalysis, support the notion that [^{177}Lu]Lu-PSMA-RLT can safely be instituted in the prechemotherapy space, at least in the second-line setting (post-ARPI) in mCRPC, with better long-term outcomes. Upcoming phase 3 trials with [^{177}Lu]Lu-PSMA-RLT in the taxane-naïve setting—such as PSMAfore (NCT04689828) and SPLASH (NCT04647526)—will help elucidate its impact on survival outcomes.

The reasons underlying better outcomes with [^{177}Lu]Lu-PSMA-RLT in the taxane-naïve setting need exploration. In a series of 167 patients, Barber et al. observed that the patients receiving [^{177}Lu]Lu-PSMA-RLT and, previously, taxane-based chemotherapy had more aggressive baseline features than did their taxane-naïve counterparts, such as a higher tumor burden, lower hemoglobin levels, poorer performance status, and a greater number of prior treatments (*16*). A baseline poor performance status before [^{177}Lu]Lu-PSMA-RLT affects tolerance of the complete RLT course and negatively impacts survival outcomes. Further, chemotherapy-induced systemic toxicities often result in a relatively lower threshold for tolerating RLT-related adverse events, thereby further compromising patient tolerance of RLT. It is known that higher cumulative activities of [^{177}Lu]Lu-PSMA-RLT are necessary for an adequate tumor-absorbed dose and for causing a tumor response (*28,29*). Poor tolerance and the resultant inability to complete the RLT course in taxane-treated patients, especially in the face of highly aggressive, high-volume disease, is therefore likely to contribute to poor post-RLT outcomes, often coupled with added toxicity. In contrast, taxane-naïve patients are likely to have a better performance status, less aggressive disease, fewer toxicities, better tolerance to [^{177}Lu]Lu-PSMA-RLT, and, hence, better efficacy and safety outcomes.

Another parameter bearing significance is tumor heterogeneity, especially in the presence of visceral metastases. In the era of extensive use of novel ARPIs, the prevalence of visceral metastasis in mCRPC has increased manifold, with a possible contribution from the prolonged androgen suppression leading to neuroendocrine transdifferentiation (*30*). PSMA expression in these metastases is often low and accompanied by increased metabolic activity on 2-[^{18}F]FDG PET/CT (*31*). Patients with these low–PSMA-expressing or discordant metastases therefore respond poorly to [^{177}Lu]Lu-PSMA-RLT and are better suited for chemotherapy (*32,33*). On the basis of our observations, we believe that mCRPC patients after progression with ARPIs can safely and effectively be treated with [^{177}Lu]Lu-PSMA-RLT in cases of adequate PSMA expression and preferably in the absence of visceral metastases. If patients progress on [^{177}Lu]Lu-PSMA-RLT or already have discordant visceral metastases at initial presentation, chemotherapy might be an option. A crossover randomized controlled trial comparing the sequencing of [^{177}Lu]Lu-PSMA-RLT and taxane chemotherapy in the post-ARPI setting will be necessary to validate our hypothesis.

The current metaanalysis is not without limitations. The number of studies included for each outcome analyzed was quite limited to obtain definitive conclusions. Most studies were retrospective and single-armed and thus had an inherent high risk of bias. Further, the numbers of taxane-naïve and taxane-treated patients were not equally matched. Pooled estimates of univariate ORs and HRs might also have been affected by other clinical variables.

CONCLUSION

The current metaanalysis comprehensively pooled the largest series—to our knowledge—of taxane-naïve mCRPC patients treated with [^{177}Lu]Lu-PSMA-RLT. Our results highlight the better response and long-term survival outcomes with [^{177}Lu]Lu-PSMA-RLT in such patients with no prior exposure to taxane chemotherapy. Although data from phase 3 trials are awaited, our results show a promising role for [^{177}Lu]Lu-PSMA-RLT in the taxane-naïve space. This will be especially beneficial for those patients who are ineligible for or unwilling to undergo chemotherapy because of its potential toxicities and adverse impact on quality of life. Further trials evaluating [^{177}Lu]Lu-PSMA-RLT in the taxane-naïve setting are now required.

DISCLOSURE

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

KEY POINTS

QUESTION: Will [^{177}Lu]Lu-PSMA-RLT be more effective when administered before taxane chemotherapy than after?

PERTINENT FINDINGS: This systematic review and metaanalysis comprised 13 articles with 2,068 patients. In 6 articles comprising 553 patients, taxane-naïve patients had significantly better odds of a biochemical response after [^{177}Lu]Lu-PSMA-RLT (pooled OR, 1.82; 95% CI, 1.21–2.71). A taxane-naïve status was also a predictor of significantly better PFS (5 articles; 1,027 patients; pooled HR, 0.60; 95% CI, 0.51–0.69) and OS (8 articles; 1,594 patients; pooled HR, 0.54; 95% CI, 0.43–0.68) after [^{177}Lu]Lu-PSMA-RLT.

IMPLICATIONS FOR PATIENT CARE: Although [^{177}Lu]Lu-PSMA-RLT has been proven effective in end-stage disease, our results suggest even better outcomes in patients with no prior exposure to chemotherapy.

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