When to use 177Lu-PSMA-617 in metastatic prostate cancer: before or after taxanes?

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Metastatic castration-resistant prostate cancer (mCRPC) remains a significant clinical challenge, with patients often progressing despite initial androgen receptor pathway inhibitor (ARPI) therapies. Recent research has explored the role of lutetium-177 PSMA-617 (177Lu-PSMA-617), a radioligand therapy targeting prostate-specific membrane antigen (PSMA), in improving outcomes for these patients. Two pivotal Phase 3 trials, VISION and PSMAfore, provide critical insights into the efficacy and optimal sequencing of 177Lu-PSMA-617 in the mCRPC treatment landscape.

KEY TAKEAWAYS

- The Pivot: 177Lu-PSMA-617 demonstrates efficacy in both taxane-naive and taxane-pretreated mCRPC, expanding its potential role in earlier lines of therapy.
- The Data: In taxane-naive patients, 177Lu-PSMA-617 significantly prolonged radiographic progression-free survival (median 11.6 months vs 5.59 months for ARPI change; HR 0.49). In taxane-pretreated patients, it extended overall survival (median 15.3 vs 11.3 months; HR 0.62) and imaging-based progression-free survival (median 8.7 vs 3.4 months; HR 0.40).
- The Action: Clinicians should consider 177Lu-PSMA-617 as an effective treatment option for PSMA-positive mCRPC, both before and after taxane-based chemotherapy, based on patient characteristics and prior ARPI progression.

Understanding Metastatic Castration-Resistant Prostate Cancer

Metastatic castration-resistant prostate cancer (mCRPC) represents an advanced stage of prostate cancer where the disease continues to progress despite androgen deprivation therapy. Patients with mCRPC face a poor prognosis, and treatment options aim to extend survival and improve quality of life. Prostate-specific membrane antigen (PSMA) is a protein highly expressed on the surface of prostate cancer cells, making it an attractive target for diagnostic imaging and therapeutic interventions 1,2.

Lutetium-177 (^{177}Lu)-PSMA-617 is a radioligand therapy designed to deliver beta-particle radiation directly to PSMA-expressing cancer cells and their surrounding microenvironment. This targeted approach has shown promise in clinical trials, leading to its evaluation in different stages of mCRPC progression 1,2.

The VISION Trial: ^{177}Lu-PSMA-617 in Later-Line Therapy

The VISION trial was an international, open-label, phase 3 study that investigated ^{177}Lu-PSMA-617 in patients with mCRPC who had previously received at least one androgen-receptor-pathway inhibitor (ARPI) and one or two taxane regimens. Patients were required to have PSMA-positive gallium-68 (Ga)-labeled PSMA-11 positron-emission

tomographic-computed tomographic scans 1.

A total of 831 patients were randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus protocol-permitted standard care, or standard care alone. Standard care excluded chemotherapy, immunotherapy, radium-223, and investigational drugs. The primary endpoints were imaging-based progression-free survival (PFS) and overall survival (OS) 1.

Key Findings from VISION

The VISION trial demonstrated significant benefits for patients receiving ^{177}Lu-PSMA-617. The median follow-up was 20.9 months. ^{177}Lu-PSMA-617 plus standard care significantly prolonged imaging-based PFS compared to standard care alone (median, 8.7 vs. 3.4 months; hazard ratio [HR] for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P1.

All key secondary endpoints, including objective response, disease control, and time to symptomatic skeletal events, significantly favored the ^{177}Lu-PSMA-617 group. The incidence of grade 3 or higher adverse events was higher with ^{177}Lu-PSMA-617 (52.7% vs. 38.0%), but this did not adversely affect the patients' quality of life 1.

The PSMAfore Trial: ^{177}Lu-PSMA-617 in Earlier-Line Therapy

Building on the VISION trial's success, the PSMAfore trial investigated the efficacy of ^{177}Lu-PSMA-617 in an earlier treatment setting: taxane-naive patients with mCRPC who had progressed once on a previous ARPI. This phase 3, randomized, controlled trial enrolled 468 eligible patients across Europe and North America 2.

Patients were randomly allocated (1:1) to receive open-label intravenous ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for six cycles) or a change of ARPI (to abiraterone or enzalutamide). Crossover from the ARPI change group to ^{177}Lu-PSMA-617 was permitted after centrally confirmed radiographic progression. The primary endpoint was radiographic progression-free survival (rPFS) 2.

Key Findings from PSMAfore

In the PSMAfore trial, ^{177}Lu-PSMA-617 significantly prolonged rPFS compared to a change in ARPI. In the primary analysis, the median rPFS was 9.30 months (95% CI 6.77-not estimable) in the ^{177}Lu-PSMA-617 group versus 5.55 months (4.04-5.95) in the ARPI change group (HR 0.41; 95% CI 0.29-0.56; P2.

The safety profile was favorable for ^{177}Lu-PSMA-617 in this earlier line. The incidence of grade 3-5 adverse events was lower in the ^{177}Lu-PSMA-617 group (36% of patients) compared to the ARPI change group (48% of patients). Notably, none of the four grade 5 events in the ^{177}Lu-PSMA-617 group were treatment-related 2.

Clinical Implications and Future Directions

The VISION and PSMAfore trials collectively demonstrate that ^{177}Lu-PSMA-617 offers significant clinical benefits for patients with PSMA-positive mCRPC, both in pre- and post-taxane settings. The VISION trial established its role in heavily pretreated patients, showing improvements in both imaging-based PFS and OS. The PSMAfore trial extends this evidence, suggesting that ^{177}Lu-PSMA-617 can be an effective treatment alternative for taxane-naive patients who have progressed on a prior ARPI, offering superior rPFS with a favorable safety profile compared to switching to another ARPI 1,2.

Why this matters for clinical practice today

These findings provide crucial guidance for clinicians managing mCRPC. The data from PSMAfore suggest that ^{177}Lu-PSMA-617 could be considered earlier in the treatment paradigm, potentially before taxane-based chemotherapy, for appropriate PSMA-positive patients who have progressed on one ARPI. This offers an additional, effective therapeutic option that can delay progression and potentially improve patient outcomes. The decision on sequencing should be individualized, taking into account patient comorbidities, prior treatments, PSMA expression, and shared decision-making. The favorable safety profile observed in the taxane-naive setting further supports its potential for earlier integration into treatment plans.

Limitations and Next Steps

While both trials provide robust evidence, certain limitations should be considered. The VISION trial was open-label, which could introduce some bias, although primary endpoints were objectively assessed. The PSMAfore trial allowed for crossover from the ARPI change group to ^{177}Lu-PSMA-617, which may confound the long-term overall survival analysis for the ARPI change arm. Further research is needed to fully understand the long-term overall survival benefit in the taxane-naive setting and to identify specific patient subgroups who might benefit most from earlier ^{177}Lu-PSMA-617 administration 1,2. Ongoing studies will continue to refine the optimal integration of radioligand therapies into the evolving treatment landscape for mCRPC.

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