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Treatment Decisions in mCSPC: A Review of Retrospective Real-World Evidence

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Treatment Decisions in mCSPC: A Review of Retrospective Real-World Evidence," is sponsored by Johnson & Johnson. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to ReachMD. I'm your host Dr. Jennifer Caudle, and today, we'll be exploring how findings from a randomized clinical trial and real-world evidence studies are shaping our approach to treating metastatic castration-sensitive prostate cancer, or mCSPC. Joining me in this discussion is Dr. Gregory McMahon. He's a urologist in Wynnewood, Pennsylvania.

Dr. McMahon, welcome to the program.

Dr. McMahon:
Thank you for having me!

Dr. Caudle:
Of course. So, for some background, Dr. McMahon, when you're thinking about your treatment strategy for a patient with newly diagnosed mCSPC, what factors inform your decision making?

Dr. McMahon:
I make sure to consider the extent of disease burden along with patient-specific factors, like age, overall health, and comorbidities. But ultimately, when it comes to choosing a treatment approach, I tend to rely on guideline recommendations and go with what the data shows.

Combination treatments that include androgen receptor pathway inhibitors, or ARPIs, and androgen deprivation therapies, or ADTs, are now a first-line approach for patients with mCSPC.[1]

For example, apalutamide plus ADT is classified as a National Comprehensive Cancer Network® (NCCN®) Category 1 preferred treatment option for patients with high-volume and low-volume mCSPC. Category 1 recommendations are based on high-level evidence, resulting in a uniform NCCN consensus that the intervention is appropriate. And preferred interventions are based on superior efficacy, safety, and evidence.

Other NCCN Category 1 options include abiraterone and enzalutamide, and darolutamide is an NCCN Category 2A preferred option for high-volume and 2B for low-volume mCSPC because it has not demonstrated overall survival benefit.[1]

Dr. Caudle:
Well, let's take a closer look at the data supporting ERLEADA plus ADT as a preferred treatment option for mCSPC. Can you walk us through the TITAN trial and what it found?

Dr. McMahon:
Absolutely. So, TITAN was a phase 3, multicenter, double-blinded randomized trial that recruited 1,052 patients with newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. 525 patients received 240 milligrams of ERLEADA plus ADT, and 527 patients received placebo plus ADT. The dual primary endpoints were overall survival and radiographic progression-free survival, or rPFS. And prostate-specific antigen, or PSA, progression was an exploratory endpoint.[2-5]

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Although I also want to point out the variety of clinical characteristics represented in this trial. 63% of patients had high-volume disease, 81% had been diagnosed de novo, 12% had visceral metastases, and 11% had received prior docetaxel, and 67% had a Gleason score of eight or more.[2-4]

Now, if we look at the findings, starting with overall survival, ERLEADA plus ADT reduced the risk of death by 35% at the final analysis after a median follow-up of almost four years. That translates to a hazard ratio of 0.65, with a confidence interval ranging from 0.53 to 0.79. The placebo plus ADT group had a median overall survival of 52.2 months, while median overall survival was not reached in the ERLEADA plus ADT group.[2,6,7]

The primary analysis also demonstrated a significant improvement in overall survival, with a hazard ratio of 0.67 with a confidence interval from 0.51 to 0.89, and that's consistent with the benefit observed at the final analysis.[2,6]

Dr. Caudle:
And what should we know about ERLEADA's safety and tolerability?

Dr. McMahon:
ERLEADA has an established safety profile. In fact, the incidence of serious adverse reactions with ERLEADA plus ADT were similar to ADT alone, with a discontinuation rate of only 8% and no listed contraindications.[2]

Most common adverse reactions that occurred in 10% or more of patients treated with ERLEADA plus ADT included rash in 28%, hot flush in 23%, hypertension in 18%, arthralgia in 17%, and pruritus in 11%. Rates of more severe, Grade 3 or grade 4 events were lower than 10%, with the most common being hypertension.[2]

Treatment-emergent cognitive deficits, including memory impairment, amnesia, cognitive disorders, occurred in 2.7% of patients. And disturbance in attention occurred in 0.2%; however, that occurrence was identical between ERLEADA plus ADT and ADT alone.[8]

Dr. Caudle:
For those just tuning in, you're listening to ReachMD. I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Gregroy McMahon about current evidence on androgen receptor pathway inhibitors in the treatment of metastatic castration-sensitive prostate cancer.

Now, Dr. McMahon, I'd like to turn to the real-world evidence comparing ERLEADA with other ARPIs. What do those studies show us, and how can the findings help us differentiate between these options in everyday practice?

Dr. McMahon:
That's a great question. Real-world evidence studies are becoming more relevant in clinical decision-making because the data reflects what's happening in everyday practice. So having real-world evidence in addition to randomized controlled trials can provide a more complete picture.

And currently, ERLEADA is the only ARPI with overall survival results from a randomized controlled trial versus ADT alone and three retrospective real-world head-to-head analyses versus enzalutamide, generic abiraterone, and darolutamide without docetaxel.

The real-world evidence, head-to-head analysis examining overall survival through 24 months with ERLEADA compared with darolutamide in routine clinical practice in patients with mCSPC specifically excluded patients who received docetaxel to allow for appropriate comparison.[9,10]

Patients were identified using the Precision Point Specialty data and administrative claims from the Komodo Research Database, allowing them to reliably confirm diagnosis, treatment exposure, longitudinal follow-up, and survival.[9,10] In total, 1,747 patients met all prespecified eligibility criteria. 1,460 patients were treated with ERLEADA and 287 patients were treated with darolutamide.[9,10]

Unequal cohort sizes are common in observational real-world studies because they reflect actual treatment uptake in routine clinical practice, and unequal cohort-size differences do not undermine the validity when an analysis prespecifies.

Importantly, the index date was defined as the first paid claim or dispensation on or after August 5th, 2022. This ensured that both treatment groups were evaluated during the same time period, following darolutamide's approval in the mCSPC setting. And by doing this, the analysis helps reduce potential bias related to differences in drug availability or shifts in standards of care over time.[9,10]

From a methodological perspective, the analysis was designed upfront to align with established guidance for real-world evidence. Key elements—like inclusion and exclusion criteria, sample size assumptions, analytic methods, and the primary endpoint of overall survival—were all defined in advance. Power calculations were performed to determine the minimum sample size required to detect true, meaningful differences.

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And to further strengthen the validity of the findings, advanced propensity-based weighting methods were used to balance baseline characteristics between the treatment groups and minimize confounding.[9]

It's important to note that this analysis was not designed to assess differences in safety between cohorts. There have been no prospective head-to-head trials comparing the safety or efficacy of ERLEADA to enzalutamide, abiraterone acetate, or darolutamide. These head-to-head analyses intended to evaluate and compare the effects of treatments on overall survival.[9,10] And per established guidance, Johnson & Johnson is required to report these results regardless of outcome.

Lastly, darolutamide was used off label prior to U.S. Food and Drug Administration, or FDA, approval for mCSPC without docetaxel on June 3, 2025.

As with all real-world evidence studies, it's important to note the limitations. Because this analysis relies on clinical records and large databases, there's a possibility of miscoding or missing information, even though efforts are made to balance the patient populations.[9,10]

While comparison with U.S. Centers for Disease Control and Prevention estimates suggests that the Komodo Research Database captures over 90% of oncology-related deaths[11], it's possible that it may not include all of them.[9,10]

Additionally, certain treatments or clinical details—like PSA testing or the use of therapies such as docetaxel outside of the participating clinical practices—may not be fully captured in the data, which is a known and inherent limitation of real-world data sources.[12]

The analysis can adjust for known factors, but there may still be unknown variables influencing the results.[9,10] And studies for longer follow-up in these patients may be needed to estimate the magnitude of therapeutic effect of these medications.[9,10]

All of these limitations apply equally to both the ERLEADA and darolutamide treatment arms.

So, in this head-to-head comparison, a 51% reduced risk of death through 24 months compared with darolutamide without docetaxel. The hazard ratio was 0.49, and the 95% confidence interval ranged from 0.30 to 0.83.[9,10]

In addition to randomized controlled trials, these real-world studies are important because they provide information that can help inform our approach to patient care.

Dr. Caudle:
And if we look beyond overall survival and focus on dosing and administration, how does ERLEADA compare to other ARPIs, especially for patients managing chronic therapy alongside ADT?

Dr. McMahon:
Great question. We know adherence can be a challenge with oral therapies. A recent descriptive analysis based on an online US survey of 100 adult patients with metastatic prostate cancer showed that 63% of patients view forgetting to take oral medication as a barrier to oral treatment, and 1 in 5 patients have difficulty swallowing pills.[13] On top of that, food restrictions can add another layer of difficulty.[14]

So, considering the planning and burden that oral therapies may cause, it's not a surprise that 91% of patients prefer a single daily dose over other treatment options.[13]

ERLEADA is a once-daily medication option that can be taken with or without food, and for patients who have trouble swallowing, it can be dissolved in water, applesauce, orange juice, or even administered through a feeding tube.[2,15,16] ERLEADA also has approximately 100% bioavailability and doesn't require concomitant corticosteroids, and its approximately 3-day half-life at steady state supports consistent drug exposure over time.[2,15,16]

And when we think about other ARPIs, there are more restrictions to consider, like multiple tablets per dose, strict food requirements, variable absorption, or the need for steroids.[2,17-19]

All of that can add complexity for patients and providers, especially when we're thinking about long-term therapy. And in my experience, making a patient's therapy as simple as possible is the best way to increase treatment adherence.

Dr. Caudle:
Well, that's a great way to round out our discussion today. And I'd like to thank my guest, Dr. Gregory McMahon, for sharing his perspective on clinical evidence and patient-centered considerations in mCSPC care.

Dr. McMahon, it was great speaking with you today.

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Dr. McMahon:
Thank you so much for having me!

Dr. Caudle:
Of course, and for ReachMD, I'm your host, Dr. Jennifer Caudle. Please stay tuned to hear some important safety information.

Announcer:
INDICATION

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)

WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Three patients treated with ERLEADA died from an ischemic cardiovascular event, one patient treated with ERLEADA died from sudden cardiac death, and one patient treated with ERLEADA died from cardio-respiratory arrest. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the TITAN study.

In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. One patient treated with ERLEADA died from a cerebrovascular accident.

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls occurred in patients receiving ERLEADA with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Severe Cutaneous Adverse Reactions — Fatal and life-threatening cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) occurred in patients receiving ERLEADA *[see Adverse Reactions (6.2)]*.

Monitor patients for the development of SCARs. Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy). If a SCAR is suspected, interrupt ERLEADA until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other Grade 4 skin reactions, permanently discontinue ERLEADA *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis — Fatal and life-threatening interstitial lung disease (ILD) or pneumonitis can occur in patients treated with ERLEADA.

Post-marketing cases of ILD/pneumonitis, including fatal cases, occurred in patients treated with ERLEADA. In the TITAN study, 1.1% of patients treated with ERLEADA experienced ILD/pneumonitis *[see Adverse Reactions (6.1, 6.2)]*.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold ERLEADA if ILD/pneumonitis is suspected. Permanently discontinue ERLEADA in patients with severe ILD/pneumonitis or if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.2)]*.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals

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and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA *[see Use in Specific Populations (8.1, 8.3)]*.

Interference with Immunoassay Measurement of Digoxin — ERLEADA can interfere with certain digoxin immunoassays (e.g., Chemiluminescent Microparticle Immunoassays), resulting in falsely elevated digoxin plasma concentration results. Notify the laboratory conducting the digoxin plasma concentration assay to use an appropriate method in patients receiving ERLEADA and digoxin *[see Drug Interactions (7.3)]*.

ADVERSE REACTIONS

In the TITAN study, the most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA-treated patients (≥2% over placebo) were arthralgia, rash, pruritus, hot flush, and hypertension.

Laboratory Abnormalities — All Grades (Grade 3-4)

- **Hematology** — In the TITAN study: white blood cell decreased ERLEADA 27% (0.4%), placebo 19% (0.6%).
- **Chemistry** — In the TITAN study: hypertriglyceridemia ERLEADA 17% (2.5%), placebo 12% (2.3%).
- **Rash** — Rash was most commonly described as macular or maculopapular. In the TITAN study, adverse reactions of rash were 28% with ERLEADA vs 9% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA treatment (6%) vs placebo (0.6%).

Hypothyroidism — In the TITAN study, hypothyroidism was reported for 3.6% of patients treated with ERLEADA and 0.6% of patients treated with placebo.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Reduce the ERLEADA dose as recommended for adverse reactions *[see Dosage and Administration (2.2)]*. Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide).

Effect of ERLEADA on Other Drugs

Substrates of CYP3A4, CYP2C9, CYP2C19, P-gp, BCRP, or OATP1B1

Refer to the Prescribing Information for these substrates. Consider alternative agents when possible or evaluate for loss of activity of the substrate if concomitant use cannot be avoided.

Apalutamide is a strong inducer of CYP3A4 and CYP2C19, a weak inducer of CYP2C9, and an inducer of P-gp, BCRP, and OATP1B1. Apalutamide decreases exposure of substrates of CYP3A4, CYP2C19, CYP2C9, P-gp, BCRP, or OATP1B1, which may decrease the effectiveness of these substrates.

USE IN SPECIFIC POPULATIONS

The recommended ERLEADA dosage in patients with severe hepatic impairment (Child-Pugh C) is lower than the recommended dosage in patients with normal hepatic function. No dosage modification is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Please see full Prescribing Information for ERLEADA.

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Announcer:
This medical industry feature was sponsored by Johnson & Johnson. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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