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Review

Darolutamide: A New Hope in the Battle Against Prostate Cancer Plain Summary

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Abstract

Prostate cancer is the second most prevalent cancer among men globally and represents a significant global health concern. According to GLOBOCAN 2022 data, there were 1,467,854 new cases and 397,430 deaths from prostate cancer worldwide. In Türkiye, 17,274 new cases were diagnosed, with approximately 5,428 deaths reported in 2022. Prostate cancer is typically diagnosed in older age groups, with most patients presenting at localized or locally advanced stages, while a smaller proportion present with de novo metastatic disease. The five-year survival rate for localized prostate cancer is over 98%, whereas it drops to around 30% for metastatic disease.

Darolutamide has emerged as a promising treatment option for non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic hormone-sensitive prostate cancer (mHSPC). Approved by the FDA in 2019 for nmCRPC and in 2022 for use in combination with docetaxel for mHSPC, Darolutamide has demonstrated significant efficacy. The ARAMIS trial revealed that Darolutamide significantly extended metastasis-free survival (MFS) to 40.4 months compared to 18.4 months with placebo, representing a 59% reduction in the risk of metastasis or death. Similarly, the ARASENS trial showed that Darolutamide improved overall survival (OS) by 32.5% and delayed the progression to castration-resistant prostate cancer (CRPC) in mHSPC patients.

Darolutamide is noted for its favorable safety profile, particularly regarding central nervous system (CNS) adverse events, due to its minimal CNS penetration. This distinguishes it from other anti-androgens, which may have higher risks of cognitive and neurological side effects. The recommended dosage is 600 mg twice daily, with potential adjustments for severe hepatic or renal impairment. Understanding Darolutamide's administration and drug interactions is crucial for optimizing treatment outcomes in prostate cancer patients.

Keywords: Castration-sensitive, Darolutamide, Metastasis, Overall survival, Prostate cancer

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Prostate cancer is the second most common cancer among men worldwide and represents a significant global health issue. According to GLOBOCAN 2022 data, there were 1,467,854 new cases of prostate cancer and 397,430 deaths globally.[1] In Türkiye, 17,274 new cases of prostate cancer were diagnosed, and approximately 5,428 deaths were reported in 2022.[2]

Prostate cancer is generally diagnosed in older age groups with a median age of 67. Most patients are diagnosed at a localized or locally advanced stage, while a smaller proportion present with de novo metastatic disease.[3] Survival rates vary significantly based on the stage at diagnosis. Pa-

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tients with localized prostate cancer have a five-year survival rate of over 98%, while this rate drops to around 30% for those with metastatic disease.[4]

Patients with non-metastatic castration-resistant prostate cancer (nmCRPC) have a relatively short metastasis-free survival (MFS) period and are at high risk of progressing to metastatic disease if left untreated.[5] In nmCRPC, novel anti-androgens such as Darolutamide, Enzalutamide, and Apalutamide are effective treatment options that extend MFS.[5-7]

In the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC), therapies include androgen deprivation therapy (ADT) combined with chemotherapy (docetaxel), abiraterone, enzalutamide, and apalutamide. Darolutamide has also shown promising results in mHSPC treatment and has the potential to improve quality of life in these patients.[8]

Darolutamide (Nubeqa) was approved by the FDA in 2019 for use in patients with nmCRPC[9] and in combination with docetaxel for adult patients with mHSPC in 2022.[10] This review aims to provide a detailed examination of the pharmacological properties (Table 1), clinical trial data, and the role of Darolutamide in the treatment of prostate cancer.

Table 1. Pharmacological Properties of Darolutamide

Pharmacodynamic Properties	
Chemical Structure	✓ Darolutamide (Nubeqa) is a non-steroidal anti-androgen with the chemical formula C19H19ClN6O2.[11]
	✓ The molecular structure of Darolutamide consists of a pyridine ring, a chlorophenyl group, and a benzamide moiety, contributing to its high affinity and specificity for the androgen receptor.[11]
Mechanism of Action	✓ Darolutamide acts by binding to the androgen receptor (AR) with high affinity, preventing androgens such as testosterone and dihydrotestosterone from activating the AR.[13]
	✓ This inhibition blocks the AR's interaction with DNA, thereby preventing transcription of androgen-responsive genes that are crucial for the growth and survival of prostate cancer cells.[6]
	✓ Unlike other anti-androgens, Darolutamide's structure minimizes the penetration across the blood-brain barrier, reducing the incidence of central nervous system (CNS) side effects.[14]
Pharmacokinetic Properties	
Absorption and Distribution	✓ Darolutamide is rapidly absorbed after oral administration, with peak plasma concentrations (Cmax) typically reached within 1 to 2 hours.[15]
	✓ The drug is highly protein-bound (~92%), which influences its distribution within the body.[16]
Cmax and AUC	✓ The Cmax of Darolutamide ranges between 4 to 7 µg/mL at steady state after a single dose of 600 mg twice daily.[16]
	✓ The area under the curve (AUC) reflects the total drug exposure over time and for Darolutamide, the AUC is dose-proportional across the therapeutic dosing range.[16]
Half-Life	✓ Darolutamide has a relatively short half-life of approximately 20 hours, which reduces the risk of drug accumulation and allows for steady-state levels to be achieved quickly.[16]
Metabolism and Excretion	✓ Darolutamide is extensively metabolized in the liver, primarily by the cytochrome P450 enzyme CYP3A4 and the enzyme UGT1A9.[17]
	✓ The primary route of excretion is through feces (63%), with a smaller proportion excreted via urine (32%).[17]
Blood-Brain Barrier Penetration	✓ Darolutamide exhibits minimal penetration across the blood-brain barrier due to its chemical structure, resulting in a lower incidence of CNS-related side effects such as seizures and cognitive impairment.[14]
Drug-Drug Interactions	✓ Darolutamide has a lower potential for drug-drug interactions compared to Enzalutamide and Apalutamide, as it does not significantly induce or inhibit major CYP enzymes involved in drug metabolism.[18]
	✓ It can be co-administered with various other medications without significant alterations in its pharmacokinetic profile.[18]
Special Populations	✓ Age: Pharmacokinetic studies indicate no significant differences in Darolutamide exposure between younger and older adults, suggesting age does not necessitate dosage adjustments.[16]
	✓ Race: No clinically meaningful differences in pharmacokinetics have been observed among different racial groups.[16]
	✓ Hepatic Impairment: Patients with mild to moderate hepatic impairment show increased AUC and Cmax, but no dose adjustment is recommended. However, caution is advised in severe hepatic impairment due to limited data.[15]
	✓ Renal Impairment: In patients with severe renal impairment, AUC and Cmax are significantly increased, indicating the need for dose adjustments.[19]

Pharmacological Properties

Comparison of Darolutamide with Other Anti-Androgens

Darolutamide functions as a competitive inhibitor of androgens by preventing their binding to androgen receptors (AR), thereby obstructing AR nuclear translocation and subsequent AR-mediated transcription. This mechanism results in reduced proliferation of prostate cancer cells and a decrease in tumor volume.[9, 10] Additionally, the principal metabolite of darolutamide, keto-darolutamide, exhibits pharmacological properties comparable to those of the parent compound.[9-11] Notably, darolutamide demonstrates a higher binding affinity for the AR receptor compared to other androgen receptor antagonists, such as apalutamide and enzalutamide.[12] The biochemical structures of Darolutamide and the other 2 anti-androgens Apalutamide and Enzalutamide are shown in Figure 1.

By detailing these pharmacodynamic and pharmacokinetic properties, we highlight Darolutamide's unique profile and its potential advantages over other anti-androgens in the treatment of prostate cancer.

Clinical Trials of Darolutamide

Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

Definition and Clinical Significance

Non-metastatic castration-resistant prostate cancer (nmCRPC) is characterized by a rising prostate-specific antigen (PSA) level despite androgen deprivation therapy (ADT) and the absence of detectable metastatic disease on imaging. This condition represents a critical therapeutic challenge, as patients are at high risk for developing metastatic disease, which is associated with significant morbidity and mortality.[20] The primary clinical goal in nmCRPC is to delay the onset of metastasis and improve overall survival while maintaining quality of life.[21]

Treatment Options

The management of nmCRPC has evolved significantly with the introduction of novel anti-androgen therapies. Before the advent of these treatments, options were limited, primarily focusing on continued ADT and surveillance. The approval of novel androgen receptor inhibitors (ARIs) such as Darolutamide, Enzalutamide, and Apalutamide has transformed the therapeutic landscape.[20] These agents have been shown to significantly prolong metastasis-free survival (MFS) and, in some cases, overall survival (OS).[20, 21]

Darolutamide in nmCRPC

The ARAMIS study, a pivotal phase III study, evaluated the efficacy and safety of Darolutamide in men with nmCRPC. Patient characteristics and clinical study design are shown in Figure 2.[6] The trial enrolled 1,509 patients with rapidly rising PSA levels despite ADT, with a PSA doubling time of 10 months or less. Patients were randomized to receive either Darolutamide (600 mg twice daily) or placebo, in addition to continued ADT.

Efficacy Results

Metastasis-Free Survival (MFS): The primary endpoint of the ARAMIS trial was MFS. Darolutamide significantly improved median MFS to 40.4 months compared to 18.4 months with placebo (HR 0.41, 95% CI 0.34-0.50; p<0.001). This represents a 59% reduction in the risk of metastasis or death.

Overall Survival (OS): Although the study was not initially powered to detect an OS benefit, subsequent analyses showed a favorable trend toward improved OS with Darolutamide.[22] The efficacy results from ARAMIS are summarized in Figure 3.

Time to Pain Progression: Darolutamide significantly delayed the median time to pain progression compared to placebo (HR 0.65; 95% CI 0.53-0.79; p<0.001).

Safety Profile

Darolutamide was well-tolerated with a safety profile comparable to placebo. The incidence of adverse events

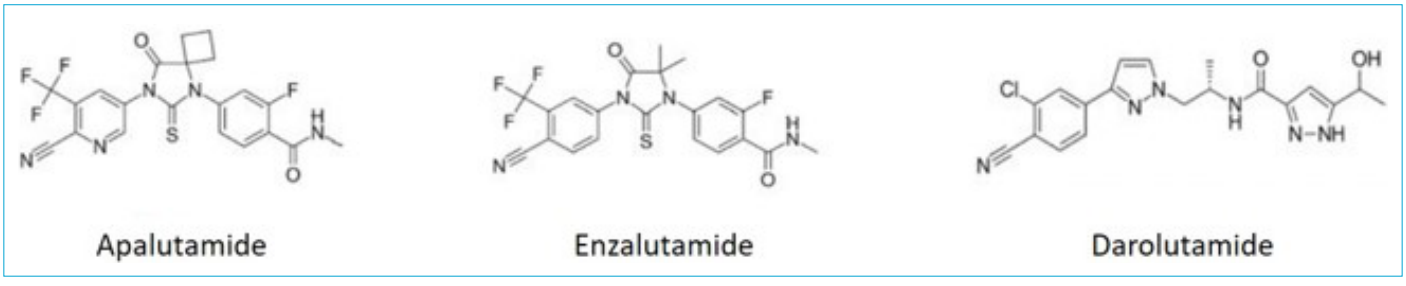

Figure 1. 2D structures of apalutamide and enzalutamide compared to darolutamide.

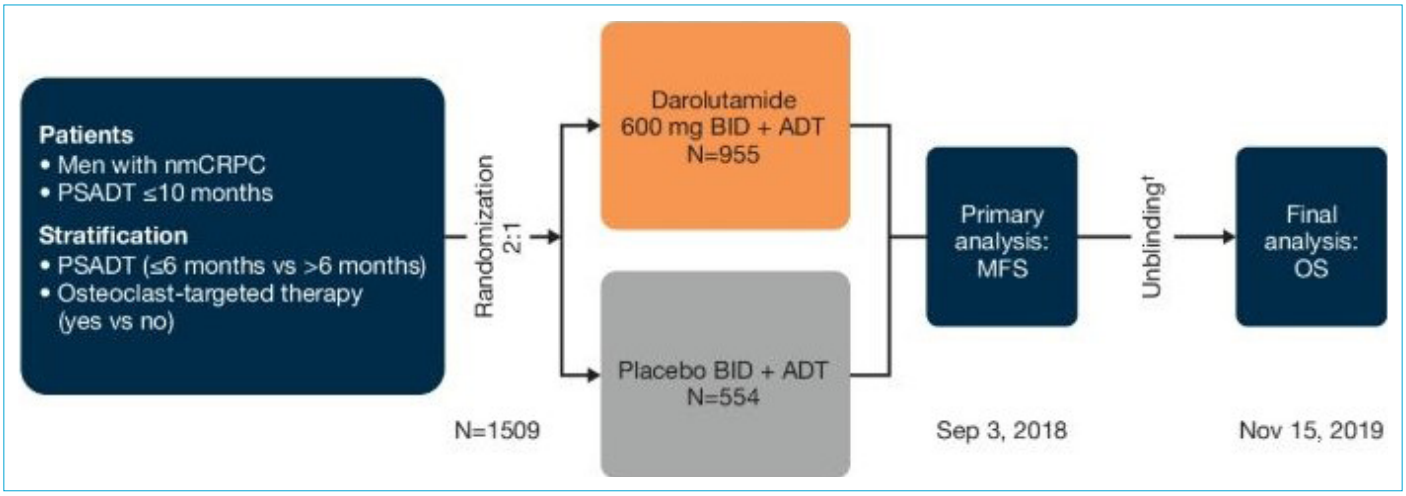

Figure 2. Trial design of the randomized, double-blind, multinational phase III ARAMIS trial in adults with non-metastatic castration-resistant prostate cancer.

ADT: androgen deprivation therapy; BID: twice daily; MFS: metastasis-free survival; nmCRPC: non-metastatic castration-resistant prostate cancer; OS: overall survival; PSADT: prosatate-specific antigen doubling time.

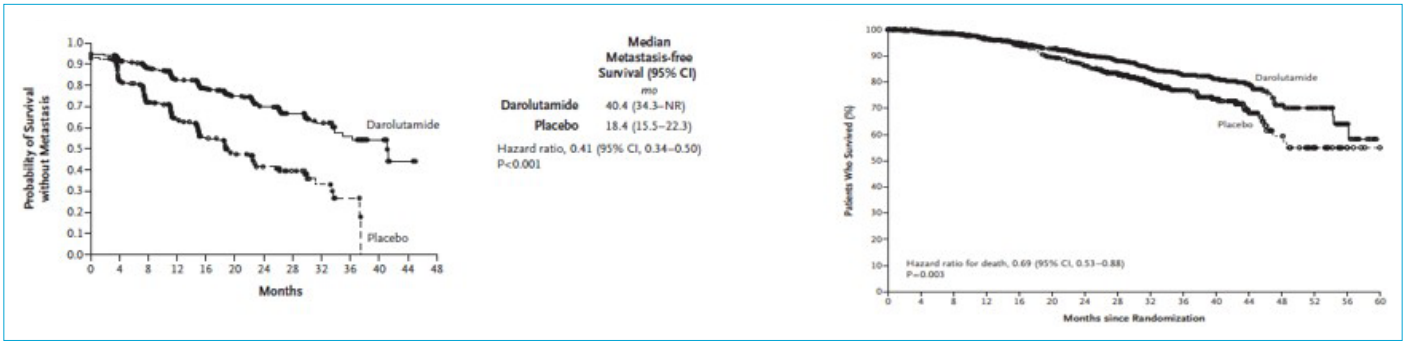

Figure 3. Kaplan-Meier Curve **(a)** Metastasis Free Survival, **(b)** Overall Survival; Intent-To-Treat nmCRPC population (ARAMIS).

(AEs) was similar between the Darolutamide and placebo groups, with fatigue, hypertension, and hot flushes being the most common.[6, 14]

Importantly, the incidence of CNS-related AEs, such as seizures, was low, reflecting Darolutamide's minimal CNS penetration.[6]

Comparison with Other Anti-Androgens

Enzalutamide

PROSPER Trial: The PROSPER trial evaluated Enzalutamide in nmCRPC patients with a similar PSA doubling time criterion.[7] Enzalutamide significantly improved MFS to 36.6 months compared to 14.7 months with placebo (HR 0.29, 95% CI 0.24-0.35; p<0.001). The OS benefit was also evident, with a 27% reduction in the risk of death (HR 0.73; 95% CI 0.61-0.89; p=0.001).

Safety: Enzalutamide was associated with a higher incidence of CNS-related AEs, including fatigue, cognitive impairment, and seizures, likely due to its higher CNS penetration.[7, 14]

Apalutamide

SPARTAN Trial: The SPARTAN trial investigated Apalutamide in nmCRPC patients with similar inclusion criteria.[7] Apalutamide extended MFS to 40.5 months compared to 16.2 months with placebo (HR 0.28, 95% CI 0.23-0.35; p<0.001).[18] The trial also demonstrated a significant OS benefit (HR 0.78; 95% CI 0.64-0.96; p=0.016).[5]

Safety: Apalutamide's safety profile included a higher incidence of rash, hypothyroidism, and falls, along with CNS-related AEs such as seizures.[5, 14]

Comparative Analysis

Efficacy

Darolutamide, Enzalutamide, and Apalutamide all significantly improve MFS in nmCRPC patients. However, Darolutamide's advantage lies in its lower incidence of CNS-related AEs, making it a preferable option for patients concerned about cognitive and neurological side effects.[6, 14, 20-22]

Safety

The unique pharmacokinetic properties of Darolutamide, particularly its low CNS penetration, contribute to its favorable safety profile, distinguishing it from Enzalutamide and Apalutamide.[6, 14, 20-22]

Metastatic Prostate Cancer (mPC)

Definition and Clinical Significance

Metastatic prostate cancer (mPC) can be categorized into metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC). mHSPC is an advanced form of prostate cancer, defined by the presence of metastatic disease and continued responsiveness to hormone therapy,[23] while mCRPC refers to disease progression despite castrate levels of testosterone.[24] The management of mPC aims to prolong survival, alleviate symptoms, and maintain quality of life.

Treatment Options for mHSPC

For mHSPC, treatment strategies include ADT combined with docetaxel,[25] abiraterone,[26] enzalutamide,[27] or apalutamide,[28] reflecting the shift towards more intensive upfront therapy. In mCRPC, treatment options are broader, including novel hormonal agents (enzalutamide,[29] abiraterone [29]), chemotherapies (docetaxel,[30] cabazitaxel [31]), immunotherapy (sipuleucel-T [32]), and radiopharmaceuticals (radium-223 [33], Lutetium-177 [34]).

Darolutamide in mPC

The ARASENS trial, a phase III study, evaluated the efficacy and safety of Darolutamide in combination with ADT and docetaxel in patients with mHSPC. Patient characteristics and clinical study design are shown in Figure 4.[8] This trial included 1,306 patients with newly diagnosed mHSPC who were randomized to receive either Darolutamide (600 mg twice daily) or placebo, in addition to ADT and docetaxel.

Efficacy Results

- **Overall Survival (OS):** The primary endpoint of the ARASENS trial was OS. Darolutamide significantly improved OS, reducing the risk of death by 32.5% compared to the placebo group (HR 0.68, 95% CI 0.57-0.80; p<0.001).[8] (Fig. 5).
- **Time to Castration-Resistant Prostate Cancer (CRPC):** Darolutamide significantly delayed the progression to CRPC (HR 0.61, 95% CI 0.52-0.72; p<0.001).
- **Time to Pain Progression:** Darolutamide also delayed the median time to pain progression compared to placebo (HR 0.79; 95% CI 0.66-0.95; p=0.012).

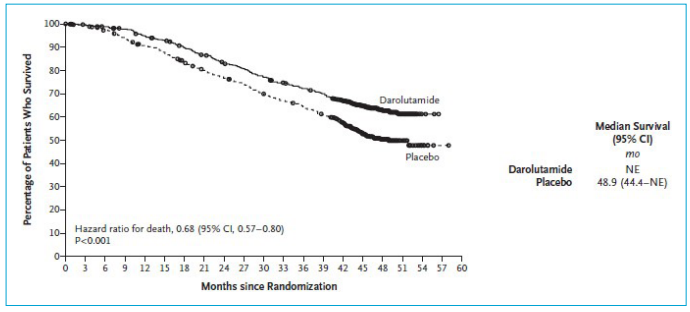

Figure 5. Kaplan-Meier curves of Overall Survival; mHSPC population (ARASENS).

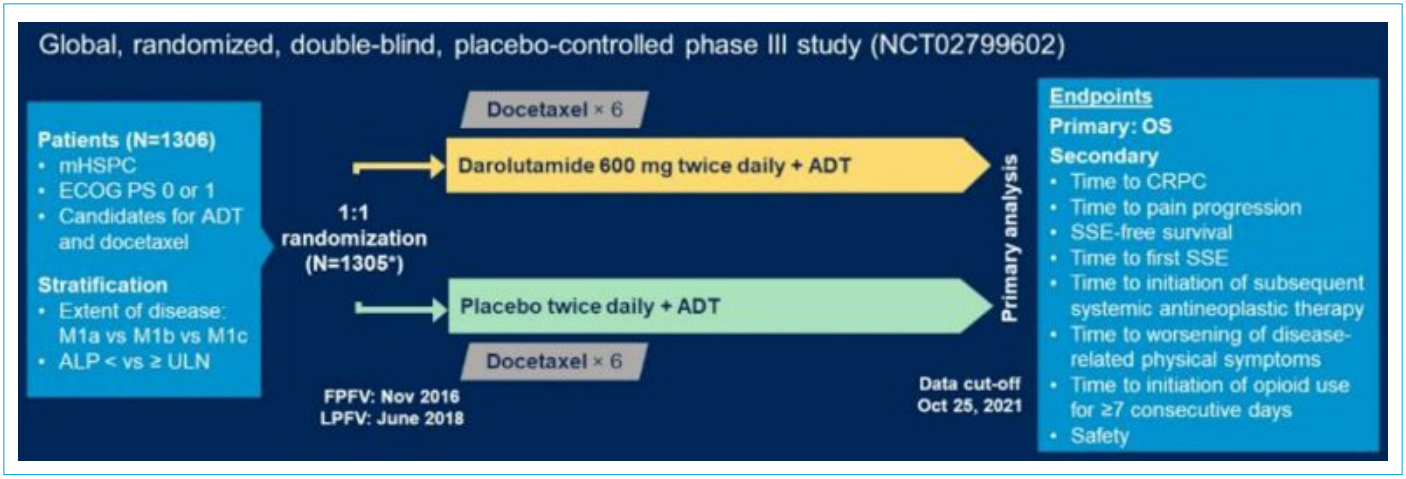

Figure 4. Trial design of the randomized, double-blind, multinational phase III ARASENS trial in adults with metastatic hormone-sensitive prostate cancer.

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status Scale; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; SSE: Symptomatic skeletal events.

Safety Profile

- Darolutamide was well-tolerated, with a safety profile similar to that of the placebo group when combined with ADT and docetaxel. The most common adverse events were fatigue, hypertension, and nausea.[8]
- The incidence of CNS-related AEs was low, supporting the favorable safety profile observed in the ARAMIS trial.[22]

Comparison with Other Anti-Androgens

Enzalutamide

- **ARCHES Trial:** The ARCHES trial evaluated Enzalutamide in mHSPC patients, demonstrating significant improvements in radiographic progression-free survival (rPFS) and OS.[27] The ARCHES trial showed a 34% reduction in the risk of death with Enzalutamide (HR 0.66, 95% CI 0.53-0.81; p<.001).[26]
- **Safety:** Enzalutamide was associated with a higher incidence of fatigue, hypertension, and CNS-related AEs.[27]

Apalutamide

- **TITAN Trial:** The TITAN trial assessed Apalutamide in mHSPC patients, demonstrating significant improvements in OS and rPFS.[28] The trial reported a 33% reduction in the risk of death with Apalutamide (HR 0.67, 95% CI 0.51-0.89; p=0.005).[28]
- **Safety:** Apalutamide's safety profile included a higher incidence of rash, hypothyroidism, and CNS-related AEs such as seizures.[28]

Comparative Analysis

Efficacy: Darolutamide, Enzalutamide, and Apalutamide all demonstrate significant efficacy in prolonging OS and delaying disease progression in mHSPC patients. Darolutamide's distinct advantage is its lower incidence of CNS-related AEs, making it a safer option for patients at risk of neurological complications.[8, 14]

Safety: The favorable safety profile of Darolutamide, with minimal CNS penetration and lower rates of associated AEs, makes it a unique and valuable addition to the therapeutic arsenal for mHSPC.[14]

Treatment Options for mCRPC

A number of phase 1/2 studies have been conducted on darolutamide in patients with mCRPC. The characteristics of the patients included in these studies, along with the study results, are presented in the following sections.

The ARADES trial, a Phase 1/2 study, was designed to evaluate the safety, pharmacokinetics, and activity of ODM-201 (Darolutamide) in men with progressive metastatic castration-resistant prostate cancer (mCRPC).[35] This study included men who had achieved castrate levels of testosterone and maintained an ECOG performance status of 0-1. In the Phase 1 part, participants were administered oral ODM-201, starting with a daily dose of 200 mg, which was escalated sequentially to 400 mg, 600 mg, 1000 mg, 1400 mg, and ultimately 1800 mg. The Phase 2 component involved centrally randomized patients, who were stratified based on prior chemotherapy and previous treatment with CYP17 inhibitors, to receive one of three fixed daily doses of ODM-201: 200 mg, 400 mg, or 1400 mg. The primary endpoint for Phase 1 was the assessment of safety and tolerability, whereas Phase 2 aimed to measure the proportion of patients exhibiting a PSA response, defined as a 50% or greater reduction in serum PSA levels at week 12. The results demonstrated that ODM-201 monotherapy effectively suppressed disease progression and presented a favorable safety profile, thus providing a rationale for further clinical investigation into the efficacy of ODM-201 in managing castration-resistant prostate cancer.

The ARAFOR trial, an open-label Phase 1 study, aimed to evaluate the pharmacokinetics, antitumor activity, and safety of ODM-201 in chemotherapy-naive men with metastatic castration-resistant prostate cancer (mCRPC).[36] This study specifically targeted chemotherapy-naive patients with mCRPC. The primary objectives included assessing the pharmacokinetics of ODM-201 tablet formulations, as well as evaluating their long-term safety, tolerability, and preliminary anti-tumor activity. The endpoints for the study encompassed the pharmacokinetics, safety, and tolerability of ODM-201 until disease progression or the occurrence of an intolerable adverse event. Additionally, antitumor activity was measured by changes in prostate-specific antigen (PSA) levels and through imaging assessments. The results indicated that the tablet formulation of ODM-201 demonstrated pharmacokinetics comparable to the capsule form. Furthermore, a 600-mg twice-daily dose of ODM-201 was shown to provide anticancer activity and was well tolerated among the chemotherapy-naive men with mCRPC.

The SAKK 08/16 trial, a Phase 2 study, aimed to evaluate the efficacy and safety of darolutamide maintenance therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) who exhibited nonprogressive disease following taxane chemotherapy.[37] The patient population comprised individuals who had previously received androgen-receptor pathway inhibitors (ARPIs) and subsequently demonstrated nonprogressive disease while on a taxane regimen. Participants were randomly assigned to receive either darolutamide at a dose of 600 mg twice daily or a placebo administered twice daily. The primary endpoint of the study was

radiographic progression-free survival (rPFS) at 12 weeks, while secondary endpoints included rPFS, event-free survival, overall survival (OS), the prostate-specific antigen (PSA) 50% response rate, and the incidence of adverse events. The trial successfully met its primary endpoint, demonstrating that darolutamide maintenance following prior taxane chemotherapy and at least one ARPI led to a statistically significant but clinically modest prolongation in rPFS with favorable tolerability.[37] The median OS with darolutamide maintenance appeared promising. If these results are validated in a larger study, maintenance treatment with darolutamide could represent a novel and effective strategy for managing patients with mCRPC, particularly those who have responded well to previous ARPI therapy.

Ongoing Clinical Trials of Darolutamide

Darolutamide is currently being evaluated in several clinical trials (11 Not yet recruiting and 43 Recruiting) to determine its efficacy and safety in various stages of prostate cancer. These trials are crucial in expanding the therapeutic applications of Darolutamide and further understanding its benefits across different patient populations. Of these studies, the one that is closest to being finalised is ARANOTE, a phase 3 study.

The ARANOTE trial, a Phase 3 study, is designed to evaluate the efficacy and safety of adding darolutamide to standard androgen deprivation therapy (ADT) compared to ADT alone in men with metastatic hormone-sensitive prostate cancer (mHSPC).[38] The study population consists of men diagnosed with mHSPC. The primary endpoint of the trial is radiological progression-free survival (rPFS), while secondary endpoints include overall survival (OS), time to development of castration-resistant prostate cancer (CRPC), time to PSA progression, and the occurrence of adverse events. This study is planned to enroll 662 patients, with an estimated completion date of September 26, 2025.

Tolerability of Darolutamide

Darolutamide has been demonstrated to have a favorable tolerability profile, which is crucial for long-term treatment adherence and patient quality of life. The safety and tolerability of Darolutamide have been extensively studied in clinical trials, highlighting its advantages over other anti-androgens.

Safety Profile

Central Nervous System (CNS) Effects:

Darolutamide significantly reduces the risk of CNS-related adverse events (AEs) such as seizures, cognitive impairment and fatigue, as it has minimal penetration across the blood-brain barrier and also does not reduce cerebral blood flow.[6, 39]

In the ARAMIS trial, the incidence of CNS-related AEs was similar between the Darolutamide and placebo groups, demonstrating a lower risk compared to other anti-androgens like Enzalutamide and Apalutamide.[6]

Cardiovascular Effects

Darolutamide has shown a low incidence of cardiovascular AEs. The ARAMIS trial reported similar rates of hypertension and other cardiovascular events in both the Darolutamide and placebo groups.[6]

This makes Darolutamide a suitable option for patients with pre-existing cardiovascular conditions who may be at higher risk when treated with other anti-androgens.

Hepatic and Renal Safety

Darolutamide is primarily metabolized by the liver, and clinical trials have indicated a low risk of hepatotoxicity. The ARAMIS trial reported low rates of liver enzyme elevations and no significant hepatotoxic events.[6]

Renal safety has also been confirmed, with no significant changes in renal function parameters observed during treatment.[6]

General Adverse Events

The most common AEs associated with Darolutamide include fatigue, arthralgia, and rash, but these are generally mild and manageable.[6]

In the ARAMIS trial, serious AEs were less frequent in the Darolutamide group compared to placebo, further emphasizing its tolerability.[6]

Comparative Tolerability

Enzalutamide

Higher incidence of fatigue, hypertension, and CNS-related AEs.[7]

PROSPER trial showed significant CNS toxicity, limiting its use in patients with higher risk of seizures or cognitive decline.[7]

Apalutamide

Associated with rash, hypothyroidism, and a higher incidence of CNS-related AEs.[5]

SPARTAN trial reported similar findings, with increased rates of skin reactions and falls.[5]

In conclusion, the favorable tolerability profile of Darolutamide, especially regarding CNS-related AEs, cardiovascular safety, and overall AE management, makes it a preferred option for long-term therapy in prostate cancer patients. This profile supports better treatment adherence and improved patient quality of life.

Dosage and Administration of Darolutamide

Proper dosage and administration are crucial for maximizing efficacy and minimizing adverse effects.

Recommended Dosage

Standard Dosage

The recommended dosage of Darolutamide for adult patients is 600 mg (two 300 mg tablets) taken orally twice daily, approximately 12 hours apart.[6]

Darolutamide should be taken with food to enhance absorption.[6]

Dose Adjustments

- **Hepatic Impairment:** No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh class A). However, caution is advised for patients with moderate impairment (Child-Pugh class B) and advised to reduce the dose to 300 mg twice daily and for severe hepatic impairment (Child-Pugh class C) no dosage adjustments provided in the manufacturer's labeling due to limited data.[6, 8]
- **Renal Impairment:** No dosage adjustment is required for patients with mild (eGFR 30 to 89 mL/minute/1.73 m^2) renal impairment. For patients with moderate (eGFR 15 to 29 mL/minute/1.73 m^2, and not receiving hemodialysis) advised to reduce the dose to 300 mg twice Daily and close monitoring is recommended. For severe renal impairment (creatinine clearance <15 mL/min/1.73 m^2), no dosage adjustments provided in the manufacturer's labeling due to limited data.[6, 8]
- **Dosing:** Adjustment for Toxicity: In the event that a Grade 3 or higher toxicity (or an intolerable adverse reaction) is encountered, the following course of action shall be pursued:
  - It is recommended that darolutamide be withheld or the dose reduced to 300 mg twice daily until the symptoms improve. Once the adverse reaction has returned to the baseline level, the therapy may then be resumed at 600 mg twice daily. It is not recommended to reduce the dose to below 300 mg twice daily.[6, 8]
  - In the event of grade 3 or 4 ischaemic heart disease, darolutamide should be discontinued.[6, 8]
  - In the event of a seizure, darolutamide should be discontinued in patients who develop a seizure during treatment.[6, 8]
  - In the event of delayed, interrupted, or discontinued docetaxel, darolutamide may be continued in patients with metastatic hormone-sensitive prostate cancer.[8]

Administration Guidelines

Food Interaction

Darolutamide should be taken with food to ensure optimal absorption and bioavailability. It is recommended to take it with a meal or a snack.[8]

Missed Dose

If a dose is missed, it should be taken as soon as possible on the same day. Patients should not take two doses at the same time to make up for a missed dose (8).

Drug Interactions

Darolutamide is a substrate of CYP3A4 and P-gp. Concurrent use of strong CYP3A4 inducers or inhibitors may alter its plasma concentration. Caution and dose adjustments may be required when used with such medications.[18]

It is recommended to monitor for potential drug interactions and adjust Darolutamide dosage as necessary.[18]

Special Populations

Elderly Patients

No overall differences in safety or efficacy have been observed between elderly and younger patients. Therefore, no specific dose adjustments are recommended for elderly patients.[6, 8]

Race and Ethnicity

Clinical studies have not indicated significant differences in Darolutamide pharmacokinetics or response across different racial and ethnic groups. Thus, standard dosing is applicable regardless of race or ethnicity.[6, 8]

In conclusion, the standard dosage of Darolutamide is 600 mg taken orally twice daily with food. Dose adjustments may be necessary for patients with severe renal or hepatic impairment. Understanding the proper administration and potential drug interactions of Darolutamide is essential for optimizing treatment outcomes in prostate cancer patients.

Discussion

The role of darolutamide in the treatment of prostate cancer is clearly delineated by its pharmacological properties and the results of clinical trials. In the treatment of castration-resistant prostate cancer (nmCRPC), The ARAMIS trial demonstrated that Darolutamide significantly improves MFS in nmCRPC patients, achieving a 59% reduction in the risk of metastasis or death compared to placebo. This substantial benefit is particularly noteworthy given the limited treatment options historically available for nmCRPC, which

predominantly involved continued androgen deprivation therapy (ADT) and surveillance. The extension of MFS not only provides a tangible clinical benefit but also potentially enhances patients' quality of life by delaying disease progression and the associated complications. And also, darolutamide offers significant benefits in terms of metastasis-free survival (MFS) with a favourable safety profile, particularly in comparison to other androgen receptor inhibitors (ARIs), where central nervous system (CNS) adverse events (AEs) are minimal.[6] In mHSPC, the ARASENS trial highlighted Darolutamide's ability to improve OS by 32.5% and delay progression to castration-resistant prostate cancer (CRPC). This positions Darolutamide as a valuable addition to the therapeutic arsenal for mHSPC, where treatment strategies have shifted towards more intensive upfront therapies, including the combination of ADT with docetaxel and novel anti-androgens.[8]

A notable advantage of Darolutamide over other anti-androgens, such as Enzalutamide and Apalutamide, is its favorable safety profile. The reduced incidence of central nervous system (CNS)-related adverse events (AEs) reflects Darolutamide's minimal CNS penetration, which is beneficial for patients at higher risk for cognitive and neurological side effects. This safety profile is particularly important for long-term therapy and patient adherence, as it mitigates some of the common concerns associated with other treatments.

Further head-to-head trials with other androgen receptor inhibitors (ARIs) will contribute to a deeper understanding of darolutamide's role in prostate cancer treatment, potentially reinforcing its position as a preferred option due to its distinctive pharmacokinetic properties and lower incidence of adverse effects.

Conclusion

Darolutamide emerges as a promising therapeutic option in the management of prostate cancer, offering significant improvements in both efficacy and safety profiles. For patients with nmCRPC, Darolutamide extends metastasis-free survival and potentially enhances quality of life by delaying disease progression. In mHSPC, it provides a considerable benefit in overall survival and progression-free survival, supporting its integration into current treatment regimens.

The distinct advantage of Darolutamide lies in its lower incidence of CNS-related adverse events compared to other anti-androgens, making it a preferable option for patients with concerns about cognitive or neurological side effects. Its safety profile, coupled with effective disease management, underscores Darolutamide's role as a valuable addition to prostate cancer therapies.

Further research and long-term studies will be essential to fully elucidate Darolutamide's benefits and optimize its use in various prostate cancer settings. However, current evidence supports its role in improving patient outcomes and provides a hopeful prospect for those battling advanced stages of prostate cancer.

Disclosures

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