Is There an Optimal Sequential Order to Androgen Receptor Axis Therapeutics?

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Abstract: The hormonal therapeutic landscape in prostate cancer has expanded greatly over the last few decades with the advent of abiraterone acetate and second-generation antiandrogens such as enzalutamide, darolutamide, and apalutamide. These agents are superior to first-generation antiandrogens because they are more effective at blocking the androgen receptor signaling pathway and can overcome many of the resistance mechanisms that limited first-generation antiandrogens. With the growing number of available treatments, questions have arisen regarding patient-specific factors influencing medication selection, stage-specific use, and strategies for combination therapy and sequencing. This manuscript is intended to provide a comprehensive review of the landmark clinical trials that led to the US Food and Drug Administration approval of abiraterone and second-generation antiandrogens in various settings of prostate cancer, along with real-world off-label prescribing practices. Additionally, the article offers insight into the optimal sequencing of antiandrogens based on current data.

Introduction

The sequencing of hormonal therapy for prostate cancer is complex. First, numerous androgen receptor signaling inhibitors (ARSIs) exist, and limited head-to-head data are available to guide us on which are the most effective and best tolerated. Second, these ARSIs are approved for various settings of prostate cancer. For example, abiraterone acetate is approved for metastatic prostate cancer but not for nonmetastatic castration-resistant disease. Third, each agent has a unique toxicity profile that prescribers must understand if they are to reconcile their choice of treatment with their patients' physical and mental health conditions. Fourth, we know from prospective and retrospective data that when these therapies are sequenced, the first ARSI proves significantly more effective than the second. An optimal sequence of ARSIs may exist that optimizes each activity.

In this article, we provide a concise overview of the mechanisms of action and resistance of the 4 hormonal agents for prostate cancer approved by the US Food and Drug Administration (FDA). We then examine their clinical applications across different prostate cancer settings, as supported by landmark clinical trials, and highlight both their efficacy and their associated toxicities. Finally, we explore data on treatment sequencing and discuss real-world evidence, with a focus on outcomes within the veteran population.

ARSI Mechanisms of Action

Enzalutamide (Xtandi, Astellas), apalutamide (Erleada, Janssen), and darolutamide (Nubeqa, Bayer HealthCare) are the 3 second-generation androgen receptor (AR) antagonists. These agents block the binding of androgens to the AR, prevent migration of the AR complex into the nucleus, and inhibit binding to the DNA of the cancer cell. Unlike the first-generation nonsteroidal antiandrogens—bicalutamide, flutamide, and nilutamide—these medications have no partial androgen agonist activity and inhibit AR translocation to the nucleus; they also have higher binding affinities. The fourth agent, abiraterone, is a cytochrome P450 17 (CYP17) inhibitor that decreases circulating androgens by blocking the conversion of mineralocorticoids to glucocorticoids to androgens in the adrenal gland.

ARSI Mechanisms of Resistance

It quickly became apparent that first-generation antiandrogens had 2 primary weaknesses. First, they were vulnerable to a variety of resistance mechanisms, including AR amplification, point mutations, and AR splice variants. Second, in the presence of excess androgens, these medications switched to agonist behavior, further exacerbating antiandrogen resistance. Although second-generation antiandrogens are susceptible to many of the same resistance mechanisms, they have been shown to have a lower incidence of selective AR mutations and are much less prone to agonist switch.

ARSI Unique Adverse Events

As previously described, owing to the limited number of head-to-head superiority comparisons among various antiandrogens, prescribers should consider the unique adverse event (AE) profile of each ARSI when making their medication recommendation (Table 1). Abiraterone is most frequently associated with effects related to excess mineralocorticoid activity, along with hepatocellular injury. The effects of excess mineralocorticoid activity (hypertension, hypokalemia, and fluid retention) are minimized by coadministering prednisone). Previous trials have shown a signal for increased cardiovascular events (heart failure and arrhythmias) in a comparison of abiraterone with placebo. At the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting, Dr Alan Bryce presented a real-world comparative causal inference study that evaluated cardiovascular risk in chemotherapy-naive patients aged 65 years or older with metastatic castration-resistant prostate cancer (mCRPC) who received initial therapy with either abiraterone or enzalutamide. The analysis revealed a statistically significantly greater risk for major adverse cardiovascular events (MACEs) in patients on abiraterone than in patients on enzalutamide irrespective of cardiovascular history, with a hazard ratio (HR) of 1.12 (95% CI, 1.02-1.24).[1] Although the study was limited to the mCRPC population, the prior signal of excess cardiovascular risk with abiraterone raises considerable concern over whether the overall survival (OS) benefits would extend to older patients, especially those with preexisting cardiovascular disease. Additional unique AEs include the rare but well-documented risk of seizures with enzalutamide, and to a lesser extent with apalutamide. Therefore, enzalutamide should be administered with caution to patients with a history of seizures or other predisposing features that lower the seizure threshold. Notably, the minimal central nervous system penetration of darolutamide theoretically suggests a lower risk for seizures and neurologic effects such as dizziness, fatigue, and falls.

Nonmetastatic Hormone-Sensitive Prostate Cancer

As of this writing, only enzalutamide is FDA-approved for the treatment of nonmetastatic hormone-sensitive prostate cancer (nmHSPC); it is specifically indicated for high-risk patients with biochemical relapse. For the sake of comprehension and to reflect real-world practices, we also review robust data from the STAMPEDE trial that have led to the off-label prescribing of abiraterone for high-risk patients with locoregional disease, as well as data from the PRESTO trial that reinforce the role of treatment intensification with apalutamide in patients with nmHSPC at high risk of biochemical recurrence.

Enzalutamide

EMBARK was a phase 3 trial that investigated the role of treatment intensification with enzalutamide in patients with nmHSPC who had high-risk biochemical recurrence after local therapy (prostatectomy and/or radiation therapy). High risk was defined as a prostate-specific antigen (PSA) doubling time of 9 months or less and a PSA level of

Table 1. Review of ARSIs and Abiraterone Acetate With Their Indications, Based on Landmark Clinical Trials

Medication	nmHSPC	nmCRPC	mHSPC	mCRPC	Special toxicities	Special considerations*
Enzalutamide	EMBARK[2]	PROSPER[7]	ARCHES[14]	AFFIRM,[29] PREVAIL[22]	Seizures, posterior reversible encephalopathy syndrome, falls and fractures, hypersensitivity reactions, ischemic heart disease	Has not been studied in patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease
Apalutamide		SPARTAN[9]	TITAN[17]		Seizures, falls and fractures, ischemic cardiovascular events, cerebrovascular events, ILD/pneumonitis, SJS/TEN, DRESS	
Darolutamide		ARAMIS[11]	ARASENS[19]		Ischemic heart disease, seizures	Dose reduction with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) not on hemodialysis and moderate hepatic impairment (Child-Pugh class B).
Abiraterone acetate	STAMPEDE[3]		LATITUDE[12]	STAMPEDE,[3] COU-AA-301,[26] COU-AA-302[21]	HTN, hypokalemia, fluid retention, hepatotoxicity, cardiovascular events	Dose modification for hepatic impairment (Child-Pugh class B), contraindicated in Child-Pugh class C

*Numerous drug-drug interactions based on cytochrome P450 inducers/inhibitors require review before administration.

ARSI, androgen receptor signaling inhibitor; CrCL, creatinine clearance; DRESS, drug reaction with eosinophilia and systemic symptoms; eGFR, estimated glomerular filtration rate; HTN, hypertension; ILD, interstitial lung disease; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; nmHSPC, nonmetastatic hormone-sensitive prostate cancer; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

at least 2 ng/mL above nadir after radiation therapy or at least 1 ng/mL after radical prostatectomy with or without postoperative radiation therapy. Notably, a serum testosterone level of at least 150 ng/dL was an inclusion requirement. Additionally, notable exclusion criteria included any prior hormonal therapy unless it had been done in a neoadjuvant or adjuvant setting relative to radiation therapy or done as a short course (<6 months) owing to rising PSA levels at least 9 months before randomization.[2]

EMBARK then randomized 1068 patients in a 1:1:1 ratio to receive enzalutamide plus leuprolide (combination group, double-blind), placebo plus leuprolide (leuprolide group, double-blind), or enzalutamide monotherapy (monotherapy group, open-label). The primary endpoint of 5-year metastasis-free survival was found to be 87.3% in the combination group and 71.4% in the leuprolide group. The secondary endpoint of 5-year metastasis-free survival was found to be 80% in the monotherapy group. Notably, treatment was discontinued owing to adverse effects in 20.7% of patients in the combination group, 10.2% in the leuprolide group, and 17.8% in the monotherapy group. Fatigue and hypertension were the most common grade 3/4 AEs, and seizures, a known risk of enzalutamide, occurred in 1.1% of the combination group, 0% of the leuprolide group, and 0.8% of the monotherapy group.[2]

Overall survival data are still immature. When the results become available, it will be important to interpret them in the context of how many patients in the leuprolide arm received postprotocol access to enzalutamide. Nevertheless, the results of EMBARK on the efficacy and safety profile of enzalutamide were consistent with data from previous phase 3 trials in the settings of nonmetastatic castration-resistant prostate cancer (nmCRPC), metastatic hormone-sensitive prostate cancer (mHSPC), and mCRPC, leading to FDA approval in November 2023.

Abiraterone

STAMPEDE was a multiarm and multistage platform-designed study that tested if the addition of treatments such as abiraterone to androgen deprivation therapy (ADT) led to survival benefit in the first-line setting. Although the trial enrolled 1917 patients, this section focuses on the 48% of patients with "high-risk" locally advanced nonmetastatic disease (20% node-positive or node-indeterminate and 28% node-negative), of whom 95% had newly diagnosed disease. Notably, "high-risk" in the trial was defined differently than in the National Comprehensive Cancer Network guidelines, and the definition included the following criteria:

- Any regional node involvement (N1 disease), whether in the setting of newly diagnosed or relapsed disease
- Meeting at least 2 of 3 criteria: T3 or T4 staging, Gleason sum score of 8 to 10, and PSA level of ≥40 ng/mL
- Relapse with high-risk features: ≤12 months of total ADT with an interval of ≥12 months without treatment and a PSA concentration of ≥4 ng/mL with a doubling time of <6 months, or a PSA concentration of ≥20 ng/mL

Overall, 914 patients were randomized in a 1:1 ratio in an open-label fashion to either abiraterone/prednisolone plus ADT (abiraterone group) or ADT alone (control group). The primary endpoint of OS for patients with nonmetastatic disease was not calculable at the time of analysis owing to data immaturity; however, a significant survival advantage was observed in the pooled combination group consisting of patients with both metastatic and nonmetastatic disease, with a 3-year survival rate of 83% in the abiraterone group vs 76% in the control group (HR, 0.63; 95% CI, 0.52-0.76).[3] A later meta-analysis with 6-year follow-up data, mentioned below, revealed a metastasis-free survival HR of 0.54 (95% CI, 0.43-0.68) and an OS HR of 0.63 (95% CI, 0.48-0.82) in favor of the abiraterone group.[4]

A subsequent arm of the STAMPEDE trial investigated the potentially marginal benefit of adding enzalutamide to abiraterone. In the abiraterone-and-enzalutamide trial, 1060 patients with "high-risk" locally advanced nonmetastatic disease were randomized 1:1 either to abiraterone/prednisolone plus enzalutamide plus ADT (combination group) or to ADT alone (control group).

Both the metastasis-free survival HR of 0.53 (95% CI, 0.39-0.71) and the OS HR of 0.54 (95% CI, 0.39-0.76) favored the combination group over the control group.[4] Clearly, a mortality benefit was noted when enzalutamide added to abiraterone plus ADT was compared with ADT alone; however, indirect cross-trial comparisons with the abiraterone-plus-ADT arm of STAMPEDE resulted in the authors' conclusion that although a small benefit from combining enzalutamide and abiraterone cannot be excluded, the increased toxicity and cost resulting from adding enzalutamide is not currently justified for this population.

The STAMPEDE trial group conducted a comprehensive meta-analysis incorporating data from the patients with high-risk locoregional disease in the 2 aforementioned trials. The primary endpoint of metastasis-free survival, a validated surrogate for OS in localized prostate cancer, resulted in an improved 6-year metastasis-free survival rate of 82% in the combination therapy groups vs 69% in the control groups, along with improved OS (HR, 0.60) and prostate cancer–specific survival (HR, 0.49), with acknowledgment that the medians were not reached by the 6-year analysis.[4,5]

Apalutamide

PRESTO was a phase 3 trial that investigated the role of treatment intensification with apalutamide in patients with nmHSPC who had high-risk biochemical recurrence after local therapy (prostatectomy and adjuvant or salvage radiation). High-risk was defined as a PSA doubling time of no more than 9 months and a PSA level of at least 0.5 ng/mL above the nadir after local therapy. A serum testosterone level of at least 150 ng/dL was an inclusion requirement. Additionally, notable exclusion criteria included any prior hormonal therapy unless it had been done in a neoadjuvant or adjuvant setting relative to radiation therapy, with the last dose administered at least 9 months before randomization.[6]

PRESTO then randomized 503 patients in a 1:1:1 ratio to receive apalutamide plus abiraterone/prednisone plus ADT (combination A group), apalutamide plus ADT (combination B group), or ADT alone (control group) for a total treatment duration of 52 weeks. The primary endpoint of median PSA progression-free survival (PSA PFS) was found to be 26 months in the combination A group and 20 months in the control group, with an HR of 0.48 (95% CI, 0.32-0.71). Likewise, the median PSA PFS was found to be 24.9 months in the combination B group and 20.3 months in the control group, with an

HR of 0.52 (95% CI, 0.35-0.77). It is important to note that this study was not powered to compare the 2 combination groups directly, although it does not appear that the addition of abiraterone/prednisone to apalutamide is substantially superior to apalutamide and ADT; however, metastasis-free survival data are still immature. Notably, serious AEs (hypertension 1%, dyspnea 0.6%, falls 0.6%) occurred in 8% of patients in the control group, 9% in the combination B group, and 17% in the combination A group, with treatment discontinuation in none of the control group, 2% of the combination B group, and 3% of the combination A group.[6] A few key differences between PRESTO and EMBARK include the longer cumulative duration of treatment exposure in the patients enrolled in EMBARK and the lack of a requirement for metabolic imaging (fluciclovine F 18 or prostate-specific membrane antigen positron emission tomography) at the time of screening in PRESTO.

In summary, EMBARK confirms a metastasis-free survival benefit for patients with nmHSPC who have high-risk biochemical recurrence after local therapy with enzalutamide treatment intensification. PRESTO reports a median PSA PFS benefit with intensification of androgen blockage with apalutamide, but real-world applicability is limited owing to the immaturity of metastasis-free survival or OS data. STAMPEDE confirms metastasis-free and OS benefit with the addition of abiraterone to ADT in patients with "high-risk" locally advanced nonmetastatic disease. Of note, it is unclear if the benefit of abiraterone is larger when it is given upfront with ADT as opposed to being added at the time of further progression on ADT.

Nonmetastatic Castration-Resistant Prostate Cancer

In this section, we summarize the pivotal trials that led to the FDA approval of enzalutamide, apalutamide, and darolutamide for patients with nmCRPC and a PSA doubling time of 10 months or less. As in nmHSPC, abiraterone has not been FDA-approved in this disease space but is commonly prescribed off label. Unfortunately, no direct head-to-head comparisons between these agents are available, nor guidelines that indicate a preference for one treatment over another.

Enzalutamide

PROSPER was a double-blind, placebo-controlled phase 3 trial that investigated intensification of treatment with enzalutamide in patients who had nmCRPC with a minimum of 3 rising PSA levels taken at least one week apart, a baseline PSA level of at least 2 ng/mL, and a PSA doubling time of 10 months or less. Notable exclusion criteria included any prior use of abiraterone or enzalutamide, and any first-generation AR antagonist must have been discontinued at least 4 weeks earlier.[7]

PROSPER randomized 1401 patients in a 2:1 ratio to receive either enzalutamide (the enzalutamide arm) or placebo (the placebo arm), all while continuing prior ADT. Of note, the median PSA doubling time was 3.8 months in the enzalutamide arm and 3.6 months in the placebo arm. The primary endpoint of median metastasis-free survival was found to be 36.6 months in the enzalutamide arm and 14.7 months in the placebo arm (HR, 0.29; 95% CI, 0.24-0.35).[7] As prespecified in the protocol, after completion of the primary analysis, patients were followed in an unblinded manner for a final analysis of secondary endpoints that included OS and safety. The final 2020 trial data revealed a median OS of 67 months in the enzalutamide arm and of 56.3 months in the placebo arm (HR, 0.73; 95% CI, 0.61-0.89). No significant differences between the rates of grade 3/4 AEs were found in the 2 arms, with the most common AEs being fatigue and musculoskeletal events. However, in the enzalutamide arm, AEs of special interest, such as 3 cases of seizures, were increased, as were exposure-adjusted rates of fractures, falls, and hypertension.[8]

Apalutamide

Apalutamide was evaluated in the SPARTAN trial, which was a double-blind, placebo-controlled phase 3 study in which 1207 patients with nmCRPC and a PSA doubling time of 10 months or less were randomized in a 2:1 ratio to either apalutamide or placebo, all while continuing prior ADT. Notably, the median PSA doubling time was 4.4 months in the apalutamide arm and 4.5 months in the placebo arm. The primary endpoint of median metastasis-free survival was found to be 40.5 months in the apalutamide arm and 16.2 months in the placebo arm (HR, 0.28; 95% CI, 0.23-0.35).[9] Again, as prespecified in the protocol, after completion of the primary analysis, patients were followed in an unblinded manner for a final analysis of secondary endpoints including OS and safety. The final 2021 trial data revealed a median OS of 73.9 months in the apalutamide arm and of 59.9 months in the placebo arm (HR, 0.78; 95% CI, 0.64-0.96).[10]

Darolutamide

Darolutamide was evaluated in the ARAMIS trial, which was a double-blind, placebo-controlled phase 3 study in which 1509 patients with nmCRPC and a PSA doubling time of 10 months or less were randomized in a 2:1 ratio to either darolutamide or placebo, all while continuing prior ADT. The median PSA doubling time was 4.4 months in the darolutamide arm and 4.7 months in the placebo arm. The primary endpoint of median metastasis-free survival was found to be 40.4 months in the

darolutamide arm and 18.4 months in the placebo arm (HR, 0.41; 95% CI, 0.34-0.50).[11] Again, patients were followed in an unblinded manner after the primary analysis for a final analysis of secondary endpoints including OS and safety. Although the median OS had not been reached in either arm at the time of the 2020 final analysis, the analysis favored the darolutamide arm (HR, 0.69; 95% CI, 0.53-0.88). No significant differences between the rates of grade 3/4 AEs were found in the 2 arms; the most common AEs were fatigue and hypertension.

Metastatic Hormone-Sensitive Prostate Cancer

In this section, we summarize the pivotal trials that led to the FDA approval of abiraterone, enzalutamide, apalutamide, and darolutamide for patients with mHSPC. Importantly, unlike enzalutamide and apalutamide, darolutamide was approved only in combination with docetaxel because ARASENS mandated that both the darolutamide arm and the placebo arm receive 6 cycles of docetaxel concurrently. Of note, the trials included patients with either de novo metastatic disease or recurrence after prior local therapy. Both ARCHES and TITAN permitted patients to have received up to 6 cycles of prior docetaxel.

Abiraterone

In LATITUDE, 1199 patients with newly diagnosed mHSPC were randomized in a 1:1 ratio to either abiraterone/prednisone plus ADT or placebo plus ADT. Patients were excluded if they had received prior chemotherapy. The primary endpoint of OS was 53.3 months in the abiraterone/prednisone group and 36.5 months in the placebo group (HR, 0.66; 95% CI, 0.56-0.78) in the 2018 final analysis.[12,13]

Enzalutamide

Enzalutamide was evaluated in the ARCHES trial, a double-blind, placebo-controlled phase 3 study in which 1150 patients with mHSPC were randomized in a 1:1 ratio to either enzalutamide or placebo, all while continuing prior ADT. The primary endpoint of radiographic PFS (rPFS) was found to be 49.8 months in the enzalutamide arm and 38.9 months in the placebo arm (HR, 0.63; 95% CI, 0.52-0.76).[14] Although the median OS was not reached in either arm at the time of the 2021 final analysis, the analysis favored the enzalutamide arm (HR, 0.66; 95% CI, 0.53-0.81).[15] The 5-year follow-up data on OS were presented at the 2025 ASCO Annual Meeting, and the enzalutamide arm continued to demonstrate a significant survival benefit (HR, 0.70; 95% CI, 0.58-0.85).[16] Fatigue, falls, and fractures, along with the incidence of grade 3/4 treatment-emergent AEs (TEAEs), were all more common in the enzalutamide arm.

Apalutamide

Apalutamide was evaluated in the TITAN trial, which was a double-blind, placebo-controlled phase 3 study in which 1052 patients with mHSPC were randomized in a 1:1 ratio to either apalutamide or placebo, all while continuing prior ADT. For the first primary endpoint of rPFS, the analysis favored the apalutamide arm, with the median not reached (HR, 0.48; 95% CI, 0.39-0.60).[17] The second primary endpoint of OS in the 2021 final analysis also favored the apalutamide arm (HR, 0.65; 95% CI, 0.53-0.79), with the median not reached in the apalutamide arm. The most common TRAEs related to apalutamide were rash and fatigue.[18]

Darolutamide

Darolutamide was evaluated in the ARASENS trial, which was a double-blind, placebo-controlled phase 3 study in which 1306 patients with mHSPC were randomized in a 1:1 ratio to either darolutamide or placebo, all notably in combination with ADT and 6 cycles of docetaxel. The primary endpoint was OS. Although the primary endpoint was not reached in the darolutamide arm, the analysis favored the darolutamide arm (HR, 0.68; 95% CI, 0.57-0.80).[19]

All the aforementioned trials found a preserved benefit in the prespecified subgroups of patients with or without prior docetaxel chemotherapy, as well as in those with low- or high-volume metastatic disease.[20] A common critique is that all these trials either failed to report the percentage or had a very low percentage of patients in the control arms receiving standard-of-care therapy after progression.

Metastatic Castration-Resistant Prostate Cancer

Therapy for Newly Diagnosed Metastatic Disease

Abiraterone. Given the establishment of the mortality benefit of abiraterone in both mHSPC and mCRPC, the STAMPEDE trial provided additional evidence of its efficacy in newly diagnosed metastatic prostate cancer. The abiraterone arm of the trial included patients who had metastatic, node-positive, high-risk locally advanced, and previously treated (radical surgery or radiotherapy) disease with relapsing high-risk features. Despite the heterogeneity of the inclusion criteria, 941 of the 1917 patients had newly diagnosed metastatic prostate cancer and 61 of the 1917 patients had previously treated metastatic disease. These patients were randomized in a 1:1 ratio in an open-label fashion to either abiraterone/prednisolone

plus ADT (abiraterone group) or ADT alone (control group).[3]

Within the prespecified subgroup analysis of all 1002 patients with metastatic disease, an OS benefit was found for the abiraterone group vs the control group (HR, 0.61; 95% CI, 0.49-0.75).[3] The 2023 final results of the trial revealed a median OS of 76.6 months in the abiraterone group vs 45.7 months in the control group.[4] Additionally, secondary endpoints of 3-year PFS and 3-year percentage of patients without symptomatic skeletal events all favored the abiraterone group.

Enzalutamide. A subsequent arm of the STAMPEDE trial investigated the potential marginal benefit of adding enzalutamide to abiraterone. In the abiraterone-and-enzalutamide trial, 916 patients with metastatic disease were randomized in a 1:1 ratio to either standard of care plus abiraterone/prednisolone plus enzalutamide (combination group) or standard of care alone. In the group with standard-of-care therapy, 100% of participants received either luteinizing hormone-releasing hormone agonists or antagonists, and approximately 9% of patients were planned to receive docetaxel.[4]

The median OS was 73.1 months in the combination group vs 51.8 months in the standard-of-care group, showing a clear mortality benefit with combination therapy vs ADT alone.[4] Cleverly, however, the trialists performed an indirect cross-trial comparison between the abiraterone arm and the abiraterone/enzalutamide arm of the multiarm STAMPEDE trial. This fixed-effects meta-analysis revealed no difference in OS when enzalutamide was added to abiraterone while rates of grade 3 to 5 AEs increased. As a result, combining enzalutamide with abiraterone and ADT is not recommended in the first-line treatment of newly diagnosed metastatic prostate cancer.

Therapy for Chemotherapy-Naive Metastatic Disease

Abiraterone. After the success of COU-AA-301 in establishing the efficacy of abiraterone in mCRPC that has progressed after docetaxel, the group designed COU-AA-302 to investigate the efficacy of abiraterone in chemotherapy-naive patients with mCRPC. COU-AA-302 was a double-blind, placebo-controlled phase 3 study in which 1088 patients with chemotherapy-naive mCRPC were randomized in a 1:1 ratio to either abiraterone/prednisone (abiraterone group) or placebo/prednisone (placebo group), all while continuing any prior ADT. Notably, prior therapy with an antiandrogen was a requirement for inclusion in the trial.[21]

The 2015 final trial data revealed a median OS of 34.7 months in the abiraterone group and 30.3 months in the placebo group, resulting in the FDA approval of abiraterone in 2012 for chemotherapy-naive mCRPC.[21] The COU-AA-302 trial, however, has been subject to several criticisms. It is important to note that before COU-AA-302, docetaxel/prednisone had been approved by the FDA in 2004 for the treatment of mCRPC on the basis of a mortality benefit found in TAX 327 when compared with mitoxantrone. As a result, many criticized the inappropriate control arm of COU-AA-302, in which patients experienced disease progression on prednisone monotherapy when they could have been on active treatment with docetaxel. In fact, when disease progressed in the trial, 57% of the abiraterone group and 61% of the control group started docetaxel as their subsequent therapy. Critics highlight the delay in docetaxel in the control arm and argue that a control arm of investigator's choice would have been more appropriate, as it would have allowed patients who were willing candidates to receive docetaxel, a proven agent, immediately. As such, although COU-AA-302 did establish mortality benefit with abiraterone in chemotherapy-naive mCRPC, it did not answer the question of whether abiraterone is superior to docetaxel in the castration-resistant setting.

Enzalutamide. Enzalutamide was first evaluated in patients with chemotherapy-naive mCRPC in the PREVAIL trial, which randomized 1717 patients in a 1:1 ratio to either enzalutamide or placebo. Continued ADT therapy was required in both arms. The final 2020 trial data revealed a median OS of 36 months in the enzalutamide arm vs 31 months in the placebo arm. No significant differences between the rates of grade 3/4 AEs were found in the 2 arms, with the most common AEs being fatigue, selected gastrointestinal events, hypertension, and fractures. Like COU-AA-302, the PREVAIL trial was criticized for inappropriately delaying time to docetaxel for patients in the control arm, who were essentially receiving no active therapy. These observations were evident in the 5-year final trial data, by which time 70% of the enzalutamide arm had experienced disease progression vs 85.8% in the placebo arm. When these patients' disease progressed, 55% of the enzalutamide group and 65% of the control group started docetaxel as their subsequent therapy.[22]

Enzalutamide was then studied in combination with abiraterone/prednisone in 2 trials: ALLIANCE A031201 and PLATO. ALLIANCE A031201 was a more robust study than PLATO, with 1311 vs 251 participants, respectively. ALLIANCE A031201 was a double-blind phase 3 study that randomized patients with chemotherapy-naive mCRPC in a 1:1 ratio to either enzalutamide plus abiraterone/prednisone (combination group) or enzalutamide monotherapy (control group). Median OS was not meaningfully different in the 2 arms, at 34.2 months in the combination group vs 32.7 months in the

Table 2. Review of the Literature Regarding ARSI Sequencing

Study type	Total sample size	Stage	(Sample size) Sequence of treatment	Endpoints	Outcome
Randomized, open-label phase 2 crossover	148	mCRPC	73) AA → Enz (75) Enz → AA	• Time to second PSA progression	• Time to second PSA progression: AA → Enz (19.3 mo) vs Enz → AA (15.2 mo)
Multicenter retrospective[33]	97	Chemotherapy-naive mCRPC	(50) AA → Enz (47) Enz → AA	• cPFS • OS	• cPFS: AA → Enz (11.1 mo) vs Enz → AA (9.04 mo) • No difference in OS
Unicenter retrospective[34]	81	mCRPC	65) AA → Enz (16) Enz → AA	• cPFS • cPSA-PFS • OS	• cPFS: AA → Enz (19.5 mo) vs Enz → AA (13.0 mo) • cPSA-PFS: AA → Enz (17.5 mo) vs Enz → AA (12.3 mo) • No difference in OS
Multicenter retrospective[35]	198	Chemotherapy-naive mCRPC	(113) AA → Enz (85) Enz → AA	• cPSA-PFS • OS	• cPSA-PFS: AA → Enz (455 days) vs Enz → AA (296 days) • No difference in OS
Unicenter retrospective[36]	69	mCRPC	(23) AA → Enz (46) Enz →AA	• cPFS • cPSA-PFS • OS	• cPFS: AA → Enz (median not reached) vs Enz → AA (11 mo) • cPSA-PFS: AA → Enz (9 mo) vs Enz → AA (7 mo) • No difference in OS
Multicenter retrospective[37]	108	Chemotherapy-naive mCRPC	(49) AA → Enz (59) Enz → AA	• cPSA-PFS • OS	• cPSA-PFS: AA → Enz (18.4 mo) vs Enz → AA (12.8 mo) • No difference in OS

AA, abiraterone acetate; ARSI, androgen receptor signaling inhibitor; cPFS, clinical progression-free survival; Enz, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; mo, months; OS, overall survival; PSA, prostate-specific antigen; cPSA-PFS, combined PSA progression-free survival.

control group. These results were concordant with those of PLATO, which also failed to find a significant difference between OS in the combination arm and OS in the control arm.[23]

Most recently, the PRESIDE trial sought to evaluate the efficacy of continuing enzalutamide in patients with chemotherapy-naive mCRPC whose disease had progressed on prior enzalutamide. The PRESIDE trial was a double-blind phase 3 study that randomized 271 patients in a 1:1 ratio to either enzalutamide plus docetaxel/prednisolone (enzalutamide group) or placebo plus docetaxel/prednisolone (placebo group) after patients with progression on enzalutamide monotherapy had been selected following a 12-week run-in period. Median PFS was 9.5 months in the enzalutamide group vs 8.3 months in the placebo group. The most common grade 3/4 TEAEs were neutropenia and asthenia, which occurred at relatively similar rates in the 2 arms. Notably, serious TEAEs were increased in the enzalutamide group (49%) vs the placebo group (39%), and a slightly increased rate of TEAEs (9% in the enzalutamide group vs 7% in the placebo group) led to discontinuation of the study group. As such, the decision to continue enzalutamide in conjunction with docetaxel/prednisolone after progression with prior enzalutamide should not be made without a consideration of the increased rate of adverse effects, along with the lack of OS outcomes.[24]

Apalutamide. Apalutamide was evaluated in the ACIS trial, which was a double-blind, placebo-controlled phase 3 study in which 982 chemotherapy-naive patients with mCRPC were randomized in a 1:1 ratio to either apalutamide plus abiraterone/prednisone (combination group) or placebo plus abiraterone/prednisone (control group), all while continuing prior ADT. The primary endpoint of median rPFS was 24 months in the combination group vs 16.6 months in the control group. The secondary endpoint of median OS was nonsignificant, at 36.2 months in the combination group and 33.7 months in the control group. The overall incidence of TEAEs was similar in the 2 groups. The TEAEs that were more common in the combination group were grade 3 and 4 skin rashes, extremity pain, and hypertension.[25]

Therapy for Metastatic Disease After Docetaxel

Abiraterone. Both abiraterone and enzalutamide have been found to have mortality benefits in patients with mCRPC that has progressed after docetaxel. In fact, the COU-AA-301 trial was the basis for the FDA approval of abiraterone for its first indication in patients with prostate cancer in 2011. COU-AA-301 was a double-blind, placebo-controlled phase 3 study in which 1195 patients were randomized in a 2:1 ratio to either abiraterone/prednisone (abiraterone group) or placebo plus prednisone (placebo group), all while continuing prior ADT. Patients in the trial were required to have received at least one previous cytotoxic chemotherapy regimen containing docetaxel and no more than 2 distinct prior lines of chemotherapy. Baseline characteristics were balanced in the abiraterone and placebo groups. In a post hoc analysis that looked at duration from the last dose of docetaxel to the first dose of study treatment, the previous median duration of docetaxel treatment and the reasons for discontinuation were not significantly different between the 2 groups.[26]

The median survival was 15.8 months in the abiraterone group and 11.2 months in the placebo group. The secondary endpoints of median time to PSA progression, median rPFS, and proportion of patients who had a PSA response were all better in the abiraterone group than in the placebo group. The most common grade 3/4 AEs in the abiraterone group were fatigue, anemia, back pain, and bone pain.[26]

Briefly, it is important to highlight the expanding indications for ARSI combination therapy, such as with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca). The PROpel trial investigated abiraterone plus olaparib in the setting of first-line mCRPC treatment irrespective of homologous recombination repair (HRR) mutation status. PROpel was a double-blind, placebo-controlled phase 3 study in which 796 patients were randomized in a 1:1 ratio to either olaparib plus abiraterone/corticosteroid (prednisone or prednisolone) or placebo plus abiraterone/corticosteroid, all while continuing prior ADT. Key inclusion criteria mandated that patients be treatment-naive at the mCRPC stage, but prior docetaxel as neoadjuvant/adjuvant treatment during localized or mHSPC stages was allowed if no signs of treatment failure had occurred during or immediately following docetaxel. Roughly 24% of the trial patients had received prior docetaxel treatment; this was received in the mHSPC stage in approximately 22.5% of cases. Additionally, 33.6% of patients in the olaparib arm had received prior local treatment with curative intent vs 36.3% in the control arm, and 67.4% in the olaparib arm had negative HRR mutation status vs 67.3% in the control arm.[27]

The primary outcome of median rPFS revealed clinically meaningful benefit of 24.8 months in the olaparib arm vs 16.6 months in the control arm.[27] However, the final prespecified analysis examined the secondary outcome of OS, which was 42.1 months in the olaparib arm vs 34.7 months in the control arm (HR, 0.81; 95% CI, 0.67-1; *P*=.054), resulting in a statistically insignificant result.[28] Nonetheless, hypothesis-generating exploratory post hoc analysis suggested significant median OS benefit in the *BRCA* mutation subgroup. This research plus subsequent trials such as MAGNITUDE, which compared niraparib plus abiraterone vs abiraterone alone and enrolled larger *BRCA1/2*-mutated cohorts, resulted in two 2023 FDA approvals of combination therapy with a PARP inhibitor (olaparib or niraparib) plus abiraterone as first-line treatment of *BRCA*-mutated mCRPC.

Enzalutamide. Enzalutamide was evaluated in the AFFIRM trial, which was a double-blind, placebo-controlled phase 3 study in which 1199 patients were randomly assigned in a 2:1 ratio to either enzalutamide or matched placebo capsules. Patients in the trial were required to have received at least one previous cytotoxic chemotherapy regimen containing docetaxel and no more than 2 distinct prior lines of chemotherapy. The rates of grade 3 to 5 AEs were similar in the enzalutamide and placebo groups, with the most common AEs being fatigue, diarrhea, and hot flashes. Notably, seizures were seen in phase 1 to 3 trials of enzalutamide and were reported in 5 of 800 (0.6%) of the patients receiving enzalutamide in this trial. Therefore, enzalutamide should be administered with caution to patients with a history of seizures or other predisposing features that lower the seizure threshold.[29]

The median survival was 18.4 months in the enzalutamide group vs 13.6 months in the placebo group. All secondary endpoints, including time to PSA progression, rPFS, and time to the first skeletal-related event favored the enzalutamide group vs the placebo group.[29]

The summation of these 2 trials dispelled the previous theory that CRPC was a hormone-refractory disease and instead established that AR signaling contributes to disease progression despite castrate levels of testosterone, previous antiandrogen treatment, and even chemotherapy.

Sequence of Therapy

Both abiraterone and enzalutamide have been found to have an independent mortality benefit in mCRPC; however, no head-to-head randomized control trials have directly evaluated superiority (Table 2). An examination of recent observational data yields the most robust retrospective, multicenter cohort study to date investigating differences in OS and prostate cancer-specific survival (PCS); time to treatment switching or death (TTS); and time to PSA response (TTR) in patients with mCRPC who were initiated on abiraterone vs enzalutamide. This cohort study included 5779 patients with mCRPC in the

US Department of Veterans Affairs between 2014 and 2022. After control for potential confounders via inverse probability of weighted treatment, the data revealed that enzalutamide was associated with "meaningful improvements in short-term outcomes (TTS and TTR) after treatment initiation compared with abiraterone, but these improvements were more subtle in long-term outcomes (OS and PCS)." In terms of OS, at 4 years, patients who had been initiated on enzalutamide had a mean survival time of 24.29 months vs 23.38 months for those initiated on abiraterone. Although this study is limited by its observational design, which includes residual confounders, and by the relatively homogeneous veteran population vs the American population at large, it shows in general mildly favorable outcomes with enzalutamide initiation vs abiraterone initiation.[30]

Unfortunately, the clarity of the retrospective studies is tempered by the results of a multicenter, randomized, open-label phase 2 crossover trial that sought to determine the optimal sequence of therapy with abiraterone and enzalutamide in patients with mCRPC who continued on prior ADT. This trial randomized 202 patients with newly diagnosed mCRPC in a 1:1 ratio to either abiraterone/prednisone or enzalutamide until PSA progression, at which point patients crossed over into the other arm. The primary endpoint, median time to second PSA progression, favored enzalutamide after progression on abiraterone/prednisone (19.3 months) vs abiraterone/prednisone after progression on enzalutamide (15.2 months). In fact, 33% of patients had a response to enzalutamide in the second line, whereas only 4% of patients had a response to abiraterone/prednisone in the second line. In summary, the data favor first-line treatment with abiraterone/prednisone followed by enzalutamide as a second-line treatment owing to longer time to second PSA progression and a potentially higher level of antitumor activity. By extension, adding abiraterone/prednisone as a second-line agent after enzalutamide would not be advised because the activity of abiraterone is minimal in this setting, likely because of resistance mechanisms.[31]

The apparent minimal clinical benefit in sequencing ARSIs led to the CARD trial, which was an open-label phase 3 study that randomized 255 patients with mCRPC who had received prior docetaxel and whose disease had progressed within 12 months on an ARSI to either cabazitaxel (Jevtana, Sanofi-Aventis) or the previously unreceived ARSI (enzalutamide or abiraterone). The primary outcome of median imaging-based PFS revealed a benefit of 8 months in the cabazitaxel arm vs 3.7 months in the ARSI arm. The secondary outcome of median OS was 13.6 months in the cabazitaxel arm vs 11.0 months in the ARSI arm (HR, 0.64; 95% CI, 0.46-0.89).[32] Although the trial was not powered to identify any differences in outcomes according to the sequencing order of the ARSI arm, a post hoc analysis supported the notion of minimal clinical benefit in sequencing ARSIs; the enzalutamide group achieved a median imaging-based PFS of 4.8 months vs 3.4 months in the abiraterone group. Overall, the incidence of serious AEs was similar in the 2 arms. Febrile neutropenia, diarrhea, and peripheral neuropathy were more common with cabazitaxel, whereas renal and cardiac disorders were more common with ARSIs. In summary, although patients may prefer to avoid the chemotoxicity of cabazitaxel, these data suggest that cabazitaxel should be a standard third-line therapy for patients with disease progression on docetaxel and an ARSI.

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