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Apalutamide for the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer

URVI J. PATEL, PharmD, MPH, and SARAH CAULFIELD, PharmD, BCOP

From Emory University Hospital, Atlanta, Georgia; and Winship Cancer Institute, Emory Healthcare, Atlanta, Georgia

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Urvi J. Patel, PharmD, MPH, Emory University Hospital, 1364 Clifton Road NE, B712, Atlanta, GA 30322.
E-mail: urvi.patel@emoryhealthcare.org

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Abstract

Prostate cancer is the fourth leading cause of cancer in the United States. Treatment of this oncologic disease involves a variety of different modalities including surgery, radiation, and systemic therapy. Systemic therapy is used for locally advanced and metastatic disease, and primarily involves hormonal blockade as a mechanism of disease control. Apalutamide is a nonsteroidal androgen receptor inhibitor that binds directly to the androgen receptor ligand binding-domain to prevent androgen receptor translocation. This agent is used in combination with gonadotropin-releasing hormone antagonists to shut down the production of testosterone through the reproductive system. It is the first drug to receive U.S. Food & Drug Administration approval for the treatment of nonmetastatic, castration-resistant prostate cancer. This article reviews the pharmacology of apalutamide along with its current place in therapy and management of associated adverse events.

Prostate cancer is a male-specific oncologic disease that is one of the top four leading causes of cancer in the United States, which is evidenced by an incidence rate of 9.9% of all new cancer cases in 2019 (National Cancer Institute, 2019). It is the most commonly diagnosed cancer in males, with an estimated 174,650 new cases to be diagnosed in 2019 (National Cancer Institute, 2019). The median age of diagnosis for patients within this cancer group is 66 years old, with the vast majority of those individuals being of African American descent (176.7 per 100,000; 73% higher rate than Caucasian males). Despite the high incidence rate of prostate cancer, it has one of the most favorable 5-year survival rates (98%). These rates can be further stratified by the stage of disease at which a patient presents. Individuals with localized and regional diseases have an approximate 100% 5-year survival rate, whereas disease that has spread to distant sites has a much lower 5-year survival rate of 30% (National Cancer Institute, 2019).

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CURRENT TREATMENT MODALITIES

Androgen deprivation therapy (ADT) serves as a mainstay of treatment for prostate cancer in the systemic, recurrent, and metastatic settings. It is a treatment modality that has the goal of inducing castration levels of testosterone (< 50 ng/dL) through surgical or chemical/medical castration. Surgical castration involves the surgical removal of the testes through bilateral orchiectomy, whereas chemical/medical castration involves the use of agents such as gonadotropin-releasing hormone (GnRH) agonists or GnRH antagonists to shut down the production of testosterone through the reproductive system (Sharifi, Gulley, & Dahut, 2010). The National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer (2018) considers these options equally effective; therefore, the decision of therapy can be based on patient preference.

Although ADT is initially effective, castration-resistant disease eventually develops in almost all men with prostate cancer. Additionally, among those men with nonmetastatic castration-resistant prostate cancer (CRPC), a short prostate-specific antigen doubling time (PSADT) is associated with a shorter time to metastases or death (Dai, Heemers, & Sharifi, 2017; Smith et al., 2005). Prostate-specific antigen doubling time serves as a way to predict the likelihood of early clinical progression, as it is a representation of the aggressiveness of the original tumor. It is defined as the time it takes for the serum PSA to double. A short PSADT (defined as 10 months in the SPARTAN trial) represents a higher risk of developing rapid systemic progression (Roberts, Blute, Bergstralh, Slezak, & Zincke, 2001; Smith et al., 2018).

A variety of agents can be used to achieve chemical castration through ADT. These agents include GnRH agonists (goserelin, leuprolide, histrelin, and triptorelin), GnRH antagonists (degarelix), and antiandrogens (nilutamide, bicalutamide, flutamide). Each of these agents is used throughout various phases of prostate cancer, with primary utility in the recurrent, or metastatic settings. The use of these agents allows for initial efficacy, but castration-resistant (testosterone levels < 50 ng/dL with rising PSA) disease eventually develops in most men with prostate cancer, leading to a greater risk for further disease progression to metastases (Dai et al., 2017).

Until recently, patients who achieved castration levels of testosterone but progressive PSA without metastatic disease had few noncytotoxic treatment options. Apalutamide (Erleada) serves as the first U.S. Food & Drug Administration (FDA)–approved second-generation androgen receptor (AR) inhibitor indicated for the treatment of patients with nonmetastatic CRPC. The introduction of this agent to the market allows for a vast expansion of treatment for men with nonmetastatic prostate cancer (Janssen Pharmaceutical Companies, 2018).

PHARMACOLOGY AND MECHANISM OF ACTION

The AR plays a significant role in the development of prostate cancer, as this is the site at which active androgens, such as testosterone and dihydrotestosterone, bind to exert the ultimate action of cellular proliferation and differentiation upon hormonally responsive tissues such as the prostate (Basu & Tindall, 2010). Apalutamide exerts its action by directly inhibiting the AR at the ligand-binding domain. This action allows for the inhibition of AR nuclear translocation, DNA binding, and impedes AR-mediated transcription. Apalutamide's major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR. The inhibitory actions of apalutamide allow for decreased tumor cell proliferation and increased apoptosis, leading to decreased tumor volume (Janssen Pharmaceutical Companies, 2018).

Apalutamide is primarily metabolized by the hepatic enzymes CYP2C8 and CYP3A4 to an active component (N-desmethyl apalutamide) that is a less potent inhibitor of AR (exhibiting only one third of the activity of apalutamide in an in vitro transcriptional reporter assay). Its half-life at steady state is 3 days, and it is mostly excreted through the urine (65%). The drug's time to peak plasma concentration is 2 hours (Janssen Pharmaceutical Companies, 2018).

CLINICAL TRIALS

The SPARTAN trial was a double-blind, placebo-controlled, phase III trial that evaluated the use of apalutamide in patients with nonmetastatic CRPC

and a prostate-specific antigen doubling time of 10 months or less. This study randomized 1,207 men with a median age of 74 who had histologically or cytologically confirmed nonmetastatic, high-risk, and castration-resistant adenocarcinoma of the prostate (PSA doubling time of 10 months or less during continuous administration of ADT [bilateral orchiectomy or treatment with GnRH agonists or antagonists]). Patients were required to have no local or regional nodal disease or have malignant pelvic lymph nodes that measured less than two centimeters. Patients in this study were stratified on the basis of PSA doubling time, use of bone-sparing agents, and classification of local or regional nodal disease in a 2:1 fashion to receive either apalutamide (240 mg by mouth daily) or matched placebo (806 to the apalutamide group and 401 to the placebo group). Androgen deprivation therapy was continued throughout the trial. Detection of distant metastases deemed the patient eligible to transition treatment to abiraterone acetate plus prednisone (Smith et al., 2018).

The primary endpoint for the SPARTAN study was metastasis-free survival (MFS), with an MFS of 40.5 months in the apalutamide group and 16.2 months in the placebo group (95% confidence interval = 0.23–0.35; $p < .001$). The secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy. Apalutamide was shown to have statistically significantly improved results compared to placebo for all secondary endpoints (Table 1). Based on the results of this study, it can be stated that apalutamide is a safe and effective therapeutic option in men with nonmetastatic CRPC in terms of improved MFS and symptomatic progression (Smith et al., 2018).

ADVERSE EVENTS

Apalutamide had to be discontinued in 85 patients (10.6%) due to an adverse event. Grade 3 and 4 toxicities were observed in 45.1% of the patients in the apalutamide group and in 34.2% of those in the placebo group. The rate of serious events was similar between the two groups (24.8% in the apalutamide group and 23.1% in the placebo group). Ten patients in the apalutamide group experienced adverse events that led to death. These adverse events included acute myocardial infarction, cardiorespiratory arrest, cerebral hemorrhage, multiple organ dysfunction, and pneumonia (Smith et al., 2018).

The major adverse events associated with this regimen include rash, hypothyroidism, and fracture. Additional adverse events that were found to be higher in the apalutamide group than the placebo group included fatigue, falls, and seizure. Additional adverse event information can be found in Table 2 (Smith et al., 2018).

CURRENT PLACE IN THERAPY

Apalutamide is the first non-hormonal agent to achieve FDA approval for the treatment of men with nonmetastatic CRPC. The men who are expected to benefit from this agent are those who have castration levels of testosterone with chemically active disease, which is identified through a PSA doubling time of less than 10 months (Smith et al., 2018). This subset of patients has a known risk of developing metastases.

An additional AR inhibitor, enzalutamide (Xtandi), has been studied in the PROSPER trial for use in a similar patient population to the SPARTAN trial. The data presented through the PROSPER trial are similar to that presented in the SPARTAN trial, thus making it a competitor to apalutamide. These data allowed enzalutamide to receive FDA approval in July 2018 for the treatment of both nonmetastatic and metastatic prostate cancer (Hussain et al., 2018).

The NCCN Guidelines for prostate cancer (2018) promote the use of apalutamide as a Category 1 recommendation for systemic therapy in individuals with nonmetastatic CRPC in combination with ADT that maintains castration serum levels of testosterone. The Guidelines also state that the other second-generation antiandrogen, enzalutamide, can also be used as a Category 1 recommendation for either nonmetastatic CRPC or metastatic CRPC (NCCN, 2018).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Apalutamide is a once-daily oral tablet used for nonmetastatic CRPC. This agent is used as a means to expand treatment options for a subset of patients with prostate cancer and allow for the delay of metastases.

Table 1. Secondary Endpoints and Results of SPARTAN Trial

	Apalutamide (n = 806)	Placebo (n = 401)	Hazard ratio (95% CI)	*p* value
Median time to metastasis	40.5	16.6	0.27 (0.22–0.34)	< .001
Median PFS	40.5	14.7	0.29 (0.24–0.36)	< .001
Median time to symptomatic progression	NR	NR	0.45 (0.32–0.63)	< .001
Median overall survival	NR	39.0	0.70 (0.47–1.04)	.07
Median time to initiation of cytotoxic chemotherapy	NR	NR	0.44 (0.29–0.66)	–

Note. CI = confidence interval; PFS = progression-free survival; NR = not reported.

Dosing

The recommended dose of apalutamide is 240 mg (four 60-mg tablets) with the concurrent administration of a GnRH analog or a bilateral orchiectomy. Apalutamide is dispensed in bottles of 120 tablets, which is a 30-day supply. The medication is to be taken at the same time each day without regard to food, and the tablets should be swallowed whole. If a dose is missed, patients should take the missed dose as soon as possible on the same day and return to the normal dosing schedule the following day. If a missed dose is not remembered on the same day, extra tablets should not be taken to make up for the missed dose.

Dose adjustments for apalutamide are not necessary for renal or hepatic impairment. If a patient develops a grade 3 or higher toxicity or an intolerable side effect, the dose is to be held

Table 2. Incidence of Adverse Events in the SPARTAN Trial

	Apalutamide (n = 803), no. (%)		Placebo (n = 398), no. (%)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	–	92 (23.1)	–
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	–	28 (7.0)	–
Adverse event associated with death	10 (1.2)	–	1 (0.3)	–
Adverse events that occurred in ≥ 15% of patients in either group				
Fatigue	244 (30.4)	7 (0.9)	84 (21.2)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash	191 (23.8	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls	125 (15.6)	14 (1.7)	37 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder	41 (5.1)	0	12 (3.0)	0
Seizure	2 (0.2)	0	0	0

until symptoms improve to less than or equal to a grade 1 toxicity. The drug may be resumed at the same dose or reduced dose of 180 mg or 120 mg, if appropriate.

Drug Interactions

Apalutamide is hepatically metabolized by CYP2C8 and CYP3A4. This action leads to altered drug exposure when the drug is coadministered with inhibitors and inducers of CYP2C8 and CYP3A4. Coadministration with agents that are strong inhibitors of CYP2C8 and CYP3A4 leads to an increase serum concentration of apalutamide. See Table 3 for a list of CYP2C8 and CYP3A4 inhibitors. The most significant drug interactions with apalutamide are due to its strong induction of CYP3A4, especially when coadministered with agents that have narrow therapeutic windows. This interaction serves as a major concern when coadministered with agents such as apixaban, buspirone, clopidogrel, isavuconazonium sulfate, itraconazole, quetiapine, risperidone, ticagrelor, tolvaptan, and warfarin, as it could lead to a decrease in the concentration of these agents by more than 90%. See Table 4 for a list of CYP3A4 substrates.

Protein binding status can alter a drug's performance. Apalutamide and its metabolite are highly protein bound (96% and 95% respectively), which means they are unable to penetrate tissues as well and are excreted much slower than other agents. Systemic exposure of this drug could be altered by changes in the plasma protein content of the body. It is important to keep in mind that the decrease in the concentration of plasma protein, such as albumin, can enhance the exposure of apalutamide and its metabolite.

Table 3. List of Strong CYP2C8 and CYP3A4 Inhibitors

Strong CYP2C8 inhibitors	Strong CYP3A4 inhibitors
Gemfibrozil	Amiodarone
Trimethoprim	Aprepitant
Lapatinib	Clarithromycin
	Cyclosporine
	Dasatinib
	Diltiazem
	Erythromycin
	Fluconazole
	Fluoxetine
	Grapefruit juice
	Imatinib
	Isoniazid
	Itraconazole
	Ketoconazole
	Lapatinib
	Miconazole
	Posaconazole
	Ritonavir
	Verapamil
	Voriconazole

Managing Adverse Events

The major adverse events that led to dose reductions in the SPARTAN trial were rash, hypothyroidism, and fracture risk. The skin rash that occurs with apalutamide resembles a maculopapular rash. It was reported in 23.8% of the patients in the apalutamide group, and 5.2% of the patients in the apalutamide group suffered a grade 3 rash, which was defined as covering greater than 30% of the patient's body surface area. The onset of rash occurs at a median of 82 days and resolves in approximately 60 days after the start of treatment. Treatment of the rash included topical corticosteroids, oral antihistamines, systemic corticosteroids, drug interruption, and dose reduction.

Hypothyroidism was reported in 8.1% of patients in the apalutamide group in the SPARTAN study. Hypothyroidism was worsened in patients already receiving thyroid replacement therapy. The onset of an increase in thyroid-stimulating hormone occurs approximately 113 days after treatment initiation. Treatment of hypothyroidism includes initiation of thyroid replacement therapy.

Fracture risk is increased with apalutamide and in men receiving long-term ADT. Patients who are at an increased risk of fracture (determined by Fracture Risk Assessment Tool [FRAX]) should be actively monitored with a baseline dual energy x-ray absorptiometry (DEXA) scan followed by an additional scan 1 year after the start of therapy. Patients who are determined to be at

Table 4. List of Strong CYP3A4 Substrates Leading to Drug Interactions With Apalutamide

Category X	Category D	Category C
Abemaciclib	Abiraterone acetate	Brentuximab vedotin
Apixaban	Afatinib	Cannabidiol
Aprepitant	Amiodarone	Cannabis
Bortezomib	Aripiprazole	Carfilzomib
Bosutinib	Buspirone	Carvedilol
Ceritinib	Carbamazepine	Clindamycin (systemic)
Clozapine	Carisoprodol	Clopidogrel
Crizotinib	Clarithromycin	Codeine
Dabigatran	Dasatinib	Corticosteroids
Dronedarone	Dexamethasone (systemic)	Dronabinol
Duvelisib	Doxorubicin (conventional and liposomal)	Estriol (systemic)
Fosaprepitant	Enzalutamide	Estriol (topical)
Ibrutinib	Etoposide phosphate	Fentanyl
Irinotecan (conventional and liposomal)	Everolimus	Hydrocodone
Isavuconazonium sulfate	Ketoconazole (systemic)	Hydrocortisone (systemic)
Itraconazole	Methylprednisolone	Ifosfamide
Midostaurin	Quetiapine	Oxcarbazepine
Mifepristone	Risperidone	Posaconazole
Nifedipine	Sunitinib	Prednisolone (systemic)
Nilotinib	Tadalafil	Prednisone
Nimodipine	Tiagabine	Ramelteon
Panobinostat	Vemurafenib	Rosuvastatin
Pazopanib		Saxagliptin
Ponatinib		Sertraline
Rivaroxaban		Sitagliptin
Tofacitinib		Sufentanil
Tolvaptan		Tetrahydrocannabinol
Toremifene		Thyroid, desiccated
Venetoclax		Tramadol
Vincristine (liposomal)		Triamcinolone (systemic)
		Tropisetron
		Warfarin
		Zolpidem

Note. Category X: avoid combination; category D: consider therapy modification; category C: monitor therapy.

high risk for fracture risk should be managed with agents that can enhance bone density such as denosumab, zoledronic acid, or alendronate (NCCN, 2018; Smith et al., 2018). The National Osteoporosis Foundation guidelines also recommend the intake of calcium (1,000–1,200 mg daily from food or supplements) and vitamin D_3 (400–1,000 IU daily; Cosman et al., 2014)

Additional adverse effects associated with the use of apalutamide include seizures, hypertension, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hyperkalemia, and fatigue. Patients with a history of seizure, predisposing factors for seizure, or those who are receiving medications known to reduce seizure threshold or induce seizures should not be prescribed apalutamide. If a patient develops seizures while receiving treatment with apalutamide, the drug must be discontinued permanently. To note, there are no data suggesting the benefit of antiepileptic agents to prevent seizures in patients receiving apalutamide. Additional monitoring should include factors such as blood pressure, lipids, blood glucose, and electrolytes at a frequency that is up to the discretion of the practitioner (NCCN, 2018; Smith et al., 2018).

SUMMARY

Historically, there have been a limited number of treatment options for men receiving ADT who also had a rising PSA and nonmetastatic disease. Options were limited to active observation or cy-

totoxic chemotherapy. Apalutamide serves as the first agent to achieve FDA approval for the treatment of men with nonmetastatic CRPC based on randomized controlled trials such as SPARTAN. This allows for alternative treatment options that prolong the development of metastatic cancer in a vulnerable patient population.

Disclosure

The authors have no conflicts of interest to disclose.

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