

# *How I do it: Apalutamide use in non-metastatic castrate resistant prostate cancer*

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*Urologists have been using oral nonsteroidal antiandrogens (AA) for 30 years as a component of combined androgen blockade. In February 2018, a new third generation AA, apalutamide, became available for the first time for non-metastatic (M0) castrate resistant prostate cancer (CRPC). Apalutamide was found to delay the presence of metastases (metastases free survival-MFS) by approximately 2 years versus placebo in M0 CRPC. While overall survival benefit has yet to be established,*

*the MFS benefit is clinically meaningful and urology practices should be equipped to manage patients using this new oral agent. Since the majority of patients remain under urologic care when this disease stage develops and because the drug is straightforward to administer, urology practices are ideal to identify and treat. The objective of this brief article is to discuss the typical patient profile for use of apalutamide and to review the pros and cons of use and common side effects and management.*

**Key Words:** apalutamide, prostate cancer, castrate-resistant, non-metastatic disease, antiandrogen

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## Introduction

Apalutamide is a third generation, nonsteroidal androgen receptor inhibitor or antiandrogen that was FDA-approved on February 14, 2018 as the first medication specifically indicated for non-metastatic (M0) castrate resistant prostate cancer (CRPC).<sup>1</sup> This drug is particularly important and relevant to urologists because most of the men in the M0 prostate cancer disease state are in the care of urologists and not in the care of medical oncologists or other specialists. The drug is straightforward to administer and is in the

therapeutic realm of urologists with special training or special interest in urologic oncology.

Apalutamide was originally known as ARN-509 when it was in development, has a trade name of Erleada, and is marketed by Janssen Oncology. This oral agent emerged from the same medicinal chemistry laboratory as enzalutamide, in which more potent antiandrogens with no significant agonistic activity were sought.<sup>2</sup> Apalutamide has similar in vitro activity but greater in vivo activity in xenograft models compared with enzalutamide.<sup>3</sup> Furthermore, it has a higher therapeutic index than enzalutamide, with maximal antitumor activity at a 3 times lower dose, and plasma levels almost 9 times lower, than enzalutamide. In mouse studies, after 28 days of therapy (10 mg/kg/day), steady-state brain tissue levels of apalutamide were 4 times lower compared with enzalutamide, suggesting that seizures may not be problematic.

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In a first-in-human, phase 1 study of 30 patients with progressing CRPC treated with apalutamide, 46.7% of patients experienced  $\geq 50\%$  decline from baseline in PSA levels.<sup>4</sup> Fatigue was the most frequently reported AE (47% of patients). The dose-limiting toxicity was a single case of grade 3 abdominal pain. Results of a subsequent phase 2 study of apalutamide in CRPC showed that 89% of patients with nonmetastatic disease had a  $\geq 50\%$  decline from baseline in prostate-specific antigen (PSA) levels, with a median time to PSA progression of 24 months.<sup>5</sup> In 46 patients with metastatic CRPC, the 12 week PSA response rate was 88% among patients naïve to abiraterone acetate plus prednisone and 22% among previously treated patients; the median time to PSA progression was 18.2 months and 3.7 months, respectively. The most common AE was fatigue (mainly grade 1 or 2), and the only grade 3 AEs reported in  $> 1$  patient receiving apalutamide were anemia and back pain (2 patients each). Based on the activity and favorable toxicity profile of apalutamide in these studies, a pivotal phase 3 trial (SPARTAN) in nonmetastatic CRPC was conducted. These data show significantly longer metastasis-free survival with apalutamide compared with placebo (40.5 months versus 16.2 months; HR 0.28 [95% CI 0.23-0.35];  $p < 0.0001$ ).<sup>6</sup>

### Brief historical perspective

Flutamide was the first nonsteroidal oral antiandrogen that was FDA-approved in the US in 1989. Urologists quickly embraced the concept of combined androgen blockage/maximal androgen blockade (CAB/MAB) and became very comfortable prescribing flutamide and later nilutamide and bicalutamide. In this era of first and second generation AA's, the potency and efficacy was less than the newer third generation apalutamide and enzalutamide. In the CAB/MAB era, the earlier agents only resulted in a very modest survival benefit measured in a few to generally less than 12 months for most patients and enthusiasm for using these agents waned. In fact, we may have trained a generation of urologists more recently who have little experience and exposure to using AA therapy as compared to urologists who trained in the 1990's and early 2000's. When apalutamide (and later enzalutamide) showed a greater than 2 year MFS benefit in M0 CRPC, it heralds a new era for urologists to re-embrace the concept of CAB/MAB. The only difference between then and now is that the new use of CAB/MAB is in M0 CRPC as opposed to new M1 hormone sensitive prostate cancer (however, it is likely that both apalutamide and enzalutamide will show efficacy in new M1 disease or even in biochemical recurrence with release of future randomized clinical trials).

Therefore, we seem to be coming full circle in my "urologic lifetime" with initial enthusiasm for CAB/MAB, followed by frustration and dis-use, now with new excitement with the latest trials with these newer much more potent oral AA agents.

### Who are the ideal candidates for prescribing apalutamide?

In a typical urology practice, we have abundant patients who are on continuous traditional hormonal therapy (i.e LH-RH agonists or GN-RH antagonists - ADT) for biochemical recurrence of prostate cancer after prior surgery, radiotherapy, cryotherapy or HIFU. Once these men demonstrate a rising PSA while on continuous ADT, they may be candidates for apalutamide. It is important to document:

1. Rising PSA while on ADT. Men must be on continuous ADT and have a castrate serum testosterone level ( $< 50$ ). If a patient is on intermittent hormonal therapy-IHT- it will be necessary to document a rising PSA on continuous ADT before prescribing apalutamide.
2. They have no metastatic disease by traditional imaging with standard bone scan and CT of the abdomen and pelvis (positive pelvic lymph nodes below the bifurcation of the aorta are NOT considered metastatic; these nodes are N1, not M1). Men with node only disease-N1- are eligible for apalutamide. Novel imaging, such as newer generation PET scanning is not required. In fact, novel imaging might "find" metastatic disease which might render a patient ineligible for use of apalutamide.
3. The level of PSA before starting apalutamide nor the PSA doubling (PSA-DT) time is not specified in the FDA-approval. In other words, there is no specific PSA or PSA-DT threshold for prescribing. In the phase III SPARTAN trial, patients had to have a PSA-DT less than 10 months and a total PSA above 2.0 to be eligible. However, this criteria was not maintained in the FDA-approval leaving urologists the discretion to use the drug at lower values of PSA or PSA-DT as long as they diagnose M0 CRPC.

### Further identification-practical considerations

When apalutamide was approved in February of 2018, our team had to think differently about "advanced" prostate cancer. Since this was the first FDA-approved therapeutic specific for M0 CRPC, we had to start to have our antenna up to identify candidates. Since there is no specific ICD-9 or ICD-10 code that is specific for M0-CRPC, it has been challenging for us to do a

simple electronic medical record (EMR) database query to identify men who may be eligible. Certainly, your EMR database administrator could initially query for all men who are on LH-RH agents but this might not be able to identify men who are on intermittent ADT. Secondly, one would look for men with a rising PSA while on continuous ADT. In our EMR search, we used the cut point of men on ADT who had a PSA of 2.0 or greater. However, we had to do a manual chart review to weed out the men on IHT. Once we identified this cohort, we manually looked for men who had a PSA-DT less than 10 months. Initially, I desired to gain clinical experience with patients who were most similar to the men enrolled in SPARTAN.

### Practice prescribing information

1. Apalutamide is administered as four 60 mg tablets for a total daily dose of 240 mg taken all at the same time once daily either with or without food.
2. There are no pre-medications required.
3. There is no specific pre-treatment lab screening required- there is no specific need to monitor liver function tests, renal function tests or thyroid tests.

### Side effects of apalutamide

In my experience now with about 8-10 of my own patients that I have treated since February 2018 (9 months), the drug is very well tolerated. However, prescribing urologists must be mindful of the risks and side effects, Table 1.

- What are the common side effects (occurring in 10% or more of trial participants in any degree)?
  - a. Hematologic: anemia, leukopenia, lymphocytopenia.
  - b. Cardiovascular: hypertension, peripheral edema
  - c. GI: diarrhea, nausea, decreased appetite.
  - d. General: fatigue, falls.
  - e. Dermatologic: generally mild maculopapular skin rash.
  - f. Endocrine and metabolic: elevated lipids, hyperglycemia, hyperkalemia, hot flashes.
  - g. Neuromuscular and skeletal: arthralgias and bone fracture.

All these men should remain on their traditional ADT unless they have had an orchiectomy. Some of these side effects are likely related to the ADT and not specific to apalutamide.

**TABLE 1. Apalutamide for non-metastatic castrate resistant prostate cancer: major or unique side effects, frequency and management strategies**

Side effect	Frequency/incidence	Management
Falls not associated with loss of consciousness or seizure	16%	Ensure patients are aware; Fall risk precautions
Bone fracture	12%	Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.
Seizure	0.2%	Permanently discontinue drug in patients who develop a seizure during treatment. Unknown if anti-epileptic medications will prevent seizures.
Maculo-papular skin rash	24% (all grades) 5% (grade 3-4)	Alert patients of possibility. Drug holiday for 1-2 weeks and reintroduce drug at 50%-75% Dose; topical steroids; systemic steroids (e.g. dose pack taper) if grade 3-4
Hypothyroidism	8% (no grade 3-4)	Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

However, there are some side-effects that we should specifically discuss with patients because they are either unique or serious. Our patients should know that seizure, falls and fracture can occur.

While seizure rate was 0.2% in SPARTAN, patients should immediately discontinue apalutamide and seek immediate medical attention if they develop a seizure. Permanently discontinue apalutamide in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with apalutamide.

Falls and fractures occurred in 16% and 12% of patients treated with apalutamide compared to 9% and 7% treated with placebo, respectively. Falls were not associated with loss of consciousness or seizure. Urologists should evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Rash associated with apalutamide was most commonly described as macular or maculopapular. The onset of rash occurred at a median of 82 days of starting treatment. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Overall, any degree of rash occurred in 24% with apalutamide versus 6% with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with apalutamide treatment (5%) versus placebo (0.3%). Four percent of patients treated with apalutamide received systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with the drug. I have had one of my patients to date experience a rash. We gave the patient a 2 week drug holiday then restarted apalutamide at 120 mg and later increased to full dose after several weeks and the rash has not recurred to date. The patient was managed using an over-the-counter moisturizing cream (Eucerin) but did not require topical or systemic corticosteroids. He described himself like a Dalmatian dog with red spots but it was not painful or pruritic.

Hypothyroidism was reported for 8% of patients treated with apalutamide and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with apalutamide and 7% of patients treated with placebo. The median onset was day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted. The FDA does not recommend baseline thyroid function testing in men prior to the start of apalutamide. Furthermore, there is no recommended monitoring requirement. In my patients to date, I

have not done baseline thyroid testing nor obtained periodic follow up testing. However, this is certainly at the discretion of the prescribing urologist and would certainly seem prudent in patients who already have thyroid disease although this is speculative.

## Practical counseling of urologic patients

Patients with rising PSA are worried about developing metastases and clinical progression of their disease. They also have usually been followed by their urologist or the urologic practice for quite some time and are not generally keen to lose their customary urologic providers. They are also generally fearful of needing to transition to systemic chemotherapy and moving on to medical oncology care which they may signal and the "beginning-of-the-end". It is in this context that apalutamide may allow the patient to remain with his urologic provider, delay metastatic disease for 2 years or more and to remain generally asymptomatic.

However, we must also be open and honest and discuss the possible side effects and down sides including that it is currently unclear if apalutamide will allow the patient to have a longer life. The overall survival advantage of apalutamide vs placebo is not yet statistically significant in the SPARTAN trial. Furthermore, most men with M0 CRPC are asymptomatic (except for the anxiety of a rising PSA). Some men started on apalutamide could be potentially harmed if they develop a fall or fracture or other side effect as noted earlier.

In my experience trying to honestly and openly counsel men on the pros and cons of starting apalutamide for M0 CRPC, I have found that my men seem to really respond to the MFS difference of 2 years or more despite me telling them that we are uncertain if the drug will ultimately allow them to live a longer life. The prospect of longer life without metastatic disease, particularly, the feared bone metastases, seems to trump the possible lack of overall survival for the patients I have treated so far.

However, the drug is expensive. With a retail cost of over \$10,000 USD per year, apalutamide (or enzalutamide) cannot be prescribed by simply handing a patient a prescription. Urology practices will have to work with practice or health system specialty pharmacy professionals. In my initial experience with US Medicare patients (generally 65 years of age or older), the typical annual out of pocket costs I have seen is about \$10,000 USD. However, for low or borderline income patients, there are assistance programs such that some men may have little or no out of pocket cost.

## Conclusions

Apalutamide is third generation oral nonsteroidal antiandrogen indicated for treating men with non-metastatic castrate resistant prostate cancer. It was the first therapeutic agent specifically indicated for this stage of advanced prostate cancer. It has been shown to extend metastases-free-survival by approximately 2 years versus placebo in the phase III SPARTAN trial. However, an overall survival benefit is yet to be confirmed. In general, this oral agent is straightforward for urologists to administer as long as providers are familiar with possible side effects and comfortable counseling and managing patients. □

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