Review

Apalutamide: Emerging Therapy for Non-Metastatic Castration-Resistant Prostate Cancer

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Abstract

Prostate cancer is the second deadliest cancer in the US and the fourth most common cancer among Saudi males. Patients usually present with non-metastatic disease and treated with localized therapy. However, up to 40% of the patients will experience biochemical recurrence, within 10 years. Androgen deprivation therapy (ADT) is used in this setting to delay metastatic disease. Patients with high prostate-specific antigen (PSA), despite appropriate ADT, are diagnosed with castrate-resistant prostate cancer (CRPC). A subset of those patients will be presented with a shorter PSA doubling time (PSA-DT) < 10 months. These patients are identified at higher risk for metastatic disease and death from prostate cancer, which represents a challenging dilemma where optimal management is unclear. Apalutamide was the first drug to get approved in the localized setting to delay metastatic disease from occurring. This review article will discuss the development, safety, and efficacy of apalutamide and its current place in therapy.

Contents

1. Introduction ......................................................................................................... 368
2. Development of apalutamide ......................................................................................... 369
3. Pharmacokinetics of apalutamide ................................................................................. 370
   3.1. Special population ............................................................................................... 370
   3.2. Apalutamide drug Interactions ............................................................................. 370
4. Apalutamide in clinical trials ......................................................................................... 370
   4.1. Phase II trial – safety and activity of apalutamide (ARN-509) ............................................................ 370
   4.2. SPARTAN trial – a study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer ................................................................... 370
5. Apalutamide adverse effects ......................................................................................... 371
   5.1. Apalutamide AE management ............................................................................. 371
6. Apalutamide place in therapy ......................................................................................... 372
7. Conclusion ......................................................................................................... 372

Conflict of interest .......................................................................................... 372
Funding resource .......................................................................................... 372
References ......................................................................................................... 372

1. Introduction

Prostate cancer is the second deadliest cancer in the United States. In 2018, the American Cancer Society estimates that there were around 165,000 new cases of prostate cancer, and 30,000 men will die from the disease (Scher et al., 2015; Siegel et al., 2018). The rates of prostate cancer in Saudi Arabia are lower than the US due to the differences in the practice of prostate-specific antigen (PSA) testing and subsequent biopsy. Thus, prostate cancer...
cases are usually under-reported (Al-Abdin and Al-Beeshi, 2018; Aljabran et al., 2018). However, prostate cancer was ranked as the fourth most common cancer among Saudi males in the 2015 Saudi Cancer Registry (SCR) report (Saudi Cancer Registry. Annual Report, 2015).

At the onset, more than 90% of prostate cancer patients will present with localized disease, and around 20–40 percent will experience a biochemical recurrence within 10 years, following localized therapy (Moul, 2004; NCCN: prostate cancer, 2018). Patients with biochemical recurrence following localized therapy will usually receive androgen deprivation therapy (ADT) to delay the onset of metastatic disease, Fig. 1. However, a subset of those patients will still have a rising PSA level, despite appropriate ADT, and will be diagnosed with castrate-resistant prostate cancer (CRPC) (Smith et al., 2005; Cancian and Renzulli, 2018). Patients with shorter PSA doubling time (PSADT), less than or equal to 10 months, are identified at higher risk for metastatic disease and death from prostate cancer. This represents a challenging dilemma where optimal management is unclear (Geynisman et al., 2016). Apalutamide was the first drug to be approved to delay metastatic disease in the localized setting for patients with high-risk non-metastatic CRPC with PSADT of ≤10 months, Table 1 (Hussain et al., 2018; Smith et al., 2018). This review article will discuss the development, safety, and efficacy of apalutamide and its current place in therapy.

2. Development of apalutamide

Apalutamide (ARN-509) is developed by Aragon Pharmaceuticals, Inc. In xenograft models, apalutamide achieved maximal antitumor efficacy in lower dose when compared to enzalutamide. Thus, it had a higher therapeutic index and was able to induce partial or complete remission during preclinical studies (Clegg et al., 2012). Apalutamide is a potent and competitive second-

![Fig. 1. Systemic therapy landscape of prostate cancer. Apalutamide is used in patients with castrate-resistant prostate cancer (CRPC), who present with rising PSA levels, despite appropriate ADT.](image)

| Non-Metastatic CRPC: |
|----------------------|
| Apalutamide |

| Metastatic CRPC: |
|------------------|
| Docetaxel |
| Abiraterone/ Prednisone |
| Enzalutamide |
| Radium-223 |
| Sipuleucel-T |
| Mitoxantrone |

| Metastatic CSPC: |
|------------------|
| Docetaxel |
| Abiraterone + Prednisone |

| Subsequent mCRPC: |
|-------------------|
| Cabazitaxel |
| Pembrolizumab |

| PSA |

Table 1
Apalutamide and enzalutamide dosing and adjustments in patients with NM-CRPC.

| Apalutamide | Enzalutamide |
|-------------|-------------|
| **Dose strength** | 240 mg by mouth daily + ADT (4 tablets × 60 mg oral tablet) | 160 mg by mouth daily + ADT (4 tablets × 40 mg oral tablet) |
| **Meal requirement** | With or without food | With or without food |
| **Dose adjustment** | Renal: CrCl < 30 ml/min, not studied | Renal: CrCl < 30 ml/min not studied Hepatic: no dose adjustment needed |
| **Monitoring** | TSH | Hypersensitivity reactions seizures |
| | Rash seizures | Risk of falls or fracture |
| | QTc prolongation, risk of falls or fracture | Cardiovascular effects (blood pressure) |
| **Drug interactions and dose modifications** | No initial dose adjustment is necessary, monitor and adjust per AE’s | Strong CYP2C8 Inhibitors: reduce the dose to 80 mg by mouth daily Strong CYP3A4 Inducers: increase the dose to 240 mg by mouth daily |
| **Dose-limiting toxicities** | Grade 3 or higher toxicity: hold dosing until symptoms improve to less than or equal to Grade 2, then resume at the same dose or a lower dose (180 mg or 120 mg) | Grade 3 or higher toxicity: withhold dosing for one week or until symptoms resolved to less than or equal to Grade 2, then resume at the same or a lower dose (120 mg or 80 mg) |

* Astellas Pharma US (2018), Hussain et al. (2018), Janssen Products (2018), Smith et al. (2018).
generation anti-androgen agent that inhibits androgen receptor (AR) with similar mechanisms of action to enzalutamide, Fig. 2 (Clegg et al., 2012; Crona and Whang, 2017). It has a tri-modal mechanism of action; binds to the AR ligand-binding domain (AR-LBD) and prevents AR activation, inhibits the translocation of AR in the nucleus, and inhibits the transcription of target genes via preventing the AR and DNA incorporation.

3. Pharmacokinetics of apalutamide

Apalutamide pharmacokinetics were studied in patients with mCRPC (Rathkopf et al., 2013). Apalutamide was fully absorbed (~100%) following oral administration, with a dose range of 30–480 mg with or without food. The mean volume of distribution was around 276 L and the median time to achieve peak plasma concentration (Tmax) was 2 h and ranged between 1 and 5 h. Apalutamide was metabolized majorly to the active metabolite N-desmethyl apalutamide and both had an excellent plasma-proteins bound concentrations. After administering the recommended dose of apalutamide, the maximum plasma concentration (Cmax) of apalutamide and its active metabolite was 6.0 mcg/mL and 5.9 mcg/mL and the area under the curve (AUC) was 100 mcg h/mL and 124 mcg h/mL at steady state, respectively. The metabolism of apalutamide to its active metabolite N-desmethyl apalutamide was primarily through the liver enzymes CYP3A4 and CYP2C8. The mean clearance was 2 L per hour, and the mean half-life was ~3 days.

3.1. Special population

No differences in apalutamide pharmacokinetics were noticed in extreme ages or different races, and mild to moderate renal and hepatic dysfunction (Rathkopf et al., 2013). However, apalutamide was not studied in patients with severe renal (CrCl < 30 ml/min/1.73 m², MDRD) and hepatic (Child-Pugh C) dysfunction.

3.2. Apalutamide drug Interactions

Apalutamide and N-desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, and moderate inhibitors of CYP2B6 and CYP2C8 (Smith et al., 2018). Co-administration of apalutamide with CYP3A4 and CYP2C9, 2C19 and P-gp substrates, decreases the AUC of those medications. Additionally, apalutamide is metabolized by the CYP2C8 and CYP3A4. Therefore, the Cmax was decreased and AUC was increased when used with strong CYP2C8 and CYP3A4 inhibitors.

4. Apalutamide in clinical trials

4.1. Phase II trial – safety and activity of apalutamide (ARN-509)

The activity and safety of apalutamide were established in a phase II trial (Civelek et al., 2014). A total of 51 patients with high risk for disease progression, defined as PSA level of ≥8 ng/ml or a PSA doubling time of <10 months were included. Patients received apalutamide 240 mg by mouth daily and ADT. At a median follow-up of 28 months, the primary endpoint was the 12-wk PSA response, where 89% of patients had above or equal to 50% PSA decline at 12 weeks. For secondary endpoints, the time to PSA progression was 24 months, and the metastasis-free survival was not reached. A total 22% of the patients discontinued the study drug due to disease progression, and 18% due to the adverse event including fatigue (61%), diarrhea (43%), and nausea (39%).

4.2. SPARTAN trial – a study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer

A phase III, randomized, double-blind, and placebo-controlled trial, included 1207 patients with NM-CRPC (Smith et al., 2018). The purpose of the trial was to evaluate the effect of apalutamide on metastasis-free survival (MFS) in men with NM-CRPC and a PSADT of ≤10 months. This was the first time that the FDA used MFS (the time from randomization to the time of first evidence of distant metastasis, or death due to any cause, whichever occurred first), as the primary endpoint in its decision making.

Patients were randomized in 2:1 fashion to receive either apalutamide and ADT or a matched placebo and ADT (Smith et al., 2018). Patients were stratified based on PSADT, use of bone-sparing agents and the classification of nodal disease and follow-up imaging were performed every 16 weeks, for disease assessment to measure the primary endpoint MFS. Not all adults patients with confirmed disease and good performance status were included in the trial. Only patients at high risk of developing metastasis who had a castration-resistant disease with a PSA doubling time of ≤10 months during continuous ADT, were included, with N0 or N1 disease. Patients, treated previously with abiraterone, enzalutamide, radiopharmaceutical agents or chemotherapy were excluded. As a class effect, androgen receptor antagonists have been associated with seizures due to the off-target GABAA
inhibition. Thus any patients with a history of seizure or condition that may predispose to seizure were excluded. In addition to, patients on concurrent therapy with any of the medications that are known to lower the seizure threshold, herbal and non-herbal products that may decrease PSA levels, and systemic corticosteroids. Short-term use (<4 weeks) of corticosteroids during the study is allowed if clinically indicated, but it should be tapered off as soon as possible. An appropriate sample size and statistical tests were used in the trial.

The median age was 74 years for patients in both groups, with approximately 8 years since prostate cancer was first diagnosed (Smith et al., 2018). The median PSA doubling time was around 4 and a half months, 70% of those patients had a PSA doubling time of 6 months or less, and only 10% or less of the patients where on Bone-targeted agents. Patients were followed for a median of 20.3 months, and the MFS was significantly higher in the apalutamide arm 40.5 months vs 16.2 months in the placebo arm. Thus, apalutamide reduced the risk of metastasis or death by 72% in patients with NM-CRPC. Time to symptomatic progression was longer with apalutamide compared to placebo; HR = 0.45, 95% CI, 0.32–0.63, P < 0.001. The interim overall survival (OS) analysis showed a trend favoring apalutamide, as the median OS was 39 months in the placebo arm and was not reached in the apalutamide arm; HR = 0.70, p = 0.07.

Progression-free survival 2 (PFS2) is a unique endpoint that looked at PFS during second treatment and although the trial was not powered to detect PFS2, men received apalutamide had a 51% risk reduction in PFS2 compared to men treated with placebo; HR = 0.49, p < 0.0001 (Smith et al., 2018). The median time to PSA progression was not reached in the apalutamide group as compared with 3.7 months in the placebo group; HR = 0.06; 95% CI, 0.05 to 0.08, and the median PSA level (At 12 weeks) was decreased by 89.7% with the apalutamide group.

5. Apalutamide adverse effects

The grade 3-4 adverse events (National Cancer Institute, 2017) were slightly higher in the apalutamide arm 45% vs. 34% in the placebo arm, Table 2 (Smith et al., 2018). Similar to enzalutamide, and although patients with uncontrolled hypertension were excluded from the trial, the incidence of grade 3/4 HTN was 14.3% in the treatment group. Adverse events of skin rash were reported for 23.8% of patients in the apalutamide group versus 5.5% in the placebo group. Grade 3 rashes were reported with apalutamide 5.2% versus placebo 0.3%, and the onset of skin rash occurred at a median of 82 days of treatment and resolved within a median of 60 days for 80.6% of patients. Around 16% and 12% of patients on apalutamide experienced falls and fractures, respectively. It is well known that ADT is associated with bone mineral density reduction causing a greater risk of clinical fractures, however, it appears that treatment with apalutamide further increases the risk.

Hypothyroidism was reported in 8.1% of patients in the apalutamide group versus 2.0% in the placebo group and only grade 1 and grade 2 events were observed and hypothyroidism worsened in patients on thyroid replacement therapy (Smith et al., 2018). Generally, elevations in thyroid-stimulating hormone (TSH) occurred early in treatment; median time to first TSH elevation was 113 days. Importantly, seizures were rare and were never Grade 3 or 4. Treatment discontinuation due to adverse events was around 11% vs. 7% in the placebo group vs. apalutamide, respectively. Skin rash led to treatment discontinuation in 19 patients, followed by fatigue in 8 patients, sepsis in 4 patients and only 1 patient were discontinued due to dizziness. Only 5% of the 804 patients who received apalutamide had dose reduction, 22 patients due to rash, 14 due to fatigue and 4 due to diarrhea.

5.1. Apalutamide AE management

Patients with history of seizures were excluded from the apalutamide clinical trial due to the off-target GABA-A inhibition of AR antagonists (Janssen Products, 2018; Smith et al., 2018). Exercise caution in patients with a history of seizures or on medications that lower seizure threshold. It is important to consider discontinuing any concurrent medications that are known to lower the seizure threshold. Discontinue apalutamide permanently in case of seizures. Additionally, patients with uncontrolled hypertension (>160/100 mmHg) were excluded from the trial. It is important to optimize antihypertensives and ensure patients adhere to blood pressure therapies prior to apalutamide initiation. Monitor patients for macular or maculopapular rash as it was reported in over 20% of the treated patients. Rashes <30% of the body surface area were reported in 5% of the patients. The median onset of the rash was approximately 80 days. Systemic corticosteroids were used in 4% of the patients with rash and the dose was reduced according to the grade of rash (rash of grade 3 or above). It is recommended to check TSH levels prior to initiating and during the treatment with apalutamide, initiate thyroid replacement therapy when clinically indicated. Prior to

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Table 2

| Adverse events (AE) in (%) occurring in patients treated with apalutamide vs. enzalutamide. |
|---------------------------------------------------------------|
| Apalutamide + ADT 240 mg daily (n = 803) | Enzalutamide + ADT 160 mg daily (n = 930) |
|---------------------------------------------|---------------------------------------------|
| All grades | Grade 3/4 | All grades | Grade 3/4 |
| Fatigue | 30.4 | 0.9 | 33 | 3 |
| Rash | 23.8 | 5.2 | – | – |
| Falls | 15.6 | 1.7 | 11 | 1 |
| Fractures | 11.7 | 2.7 | 9.8 | – |
| Hypothyroidism | 8.1 | 0 | – | – |
| Hypertension | 24.8 | 14.3 | 12 | 5 |
| Diarrhea | 20.3 | 1 | 10 | <1 |
| Nausea | 18.1 | 0 | 11 | <1 |
| Weight loss | 16.1 | 1.1 | 6 | <1 |
| Seizure | 0.2 | 0 | <1 | <1 |
| Dizziness | 9.3 | 0.3 | 12 | 0.5 |
| Hot flashes | 14 | 0 | 13 | <1 |
| Decreased appetite | 10 | <1 | 9.6 | <1 |
| Mental impairment disorders | 5.1 | 0 | 5 | <1 |

1 Mental impairment disorders includes: memory impairment, disturbance in attention, cognitive disorders, amnesia, Alzheimer’s disease, senile dementia, mental impairment, and vascular dementia.

2 Astellas Pharma US (2018), Hussain et al. (2018), Janssen Products (2018), Smith et al. (2018).
initiating apalutamide assess the patients for fracture risk, as it was reported in more than 10% of the patients. When patients present with AE’s of grade 3 or higher, it is recommended to hold apalutamide until symptoms resolution to grade 1 or less and re-initiate apalutamide therapy with the same or lower dose.

6. Apalutamide place in therapy

Shortly after the approval of apalutamide in men with NM-CRPC, the FDA approved enzalutamide for the same indication. The approval was based on the safety and efficacy results of enzalutamide in patients with NM-CRPC – PROSPER trial (Astellas Pharma US, 2018; Hussain et al., 2018). The phase III randomized, placebo-controlled, double-blind trial, included a total of 1401 patients. Patients were randomized in 2:1 fashion to receive either enzalutamide or placebo. Similar to the SPARTAN trial, the primary endpoint MFS was superior in the enzalutamide arm 36.6 months vs 14.7 months in the placebo arm, HR = 0.29, p < 0.0001, and the premature data trended toward significant in the enzalutamide arm, HR = 0.80, 95% CI 0.58–1.09, p = 0.15. The safety profile of enzalutamide was comparable to apalutamide, Table 2.

The NCCN guidelines were updated recently to recommend using apalutamide or enzalutamide in patients with NM-CRPC and a PSA-DT ≤ 10 months, with continuous ADT therapy, Table 1 (NCCN: prostate cancer, 2018). In the clinical setting, it is essential to identify the subset of patients who will benefit the most from second generation AR antagonists (Mateo et al., 2018). The emerging quality of life data from the SPARTAN trial (Saad et al., 2018) showed that the overall health-related quality of life (HRQOL) was maintained in asymptomatic CRPC patients while receiving apalutamide. However, the long-term toxicities associated with the prolonged use of AR antagonist are needed to be taken into consideration before initiating the therapy, Table 2. Furthermore, health-economic studies are needed to evaluate the impact of treating NM-CRPC patients earlier vs. delaying it until symptomatic progression.

7. Conclusion

Men with NM-CRPC with short PSA-DT (<10 months) can be offered apalutamide or enzalutamide as therapy options to delay the disease metastasis. Data regarding OS prolongation is still premature, however, it is trending toward favoring therapy. Prior to therapy initiation, it is important to assess the patient willingness, discuss the long-term toxicities, and evaluate comorbidities including but not limited to; cardiovascular diseases, risk of fall and fractures, and history of seizures.

Conflict of interest

No actual or potential conflicts of interest

Funding resource

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Al-Abdin, O.Z., Al-Beeshi, I.Z., 2018. Prostate cancer in the Arab population: an overview. Saudi Med. J. 39, 453–458. https://doi.org/10.15537/smj.2018.5.21986.
Aljubran, A., Abusamra, A., Alkatheeb, S., Alotaibi, M., Rabah, D., Bazarbashi, S., Alkushi, H., Al- Mansour, M., Alharbi, H., Eltitjani, A., Alghamdi, A., Alsharm, A., Ahmad, I., Murshid, E., 2018. Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for prostate cancer 2017. Urol. Ann. 10, 138–145. https://doi.org/10.4103/UAA.UA_177_17.
Astellas Pharma US, 2018. XTANDI: Highlights of Prescribing Information. Cancian, M., Renzulli, J.F., 2018. Nonmetastatic castration-resistant prostate cancer: a modern perspective. Urology 116, 13–16. https://doi.org/10.1016/j.urology.2018.01.010.
Civelek, M., Lusis, A.J., Genetics, M., Angeles, L., 2018. First phase 2 and safety and anti-tumor assessment of Apalutamide (AR-N-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant. Prostate Cancer 15, 34–48. https://doi.org/10.1038/nr3575.Systems.
Clegg, N.J., Wongvipat, J., Joseph, J.D., Tran, C., Ouk, S., Dihlars, A., Chen, Y., Grillot, K., Bischoff, E.D., Cai, L., Aparicio, A., Dorov, S., Arora, V., Zhao, G., Qian, J., Zhao, H., Yang, G., Cao, C., Sensinstaffar, J., Wasielewksa, T., Herbert, M.R., Bonnefous, C., Darimont, B., Scher, H.J., Smith-Jones, P., Klang, M., Smith, N.D., De Stanchina, E., Wu, N., Ouerfelli, O., Rix, P.J., Heyman, R.A., Jung, M.E., Sawyer, C.L., Hager, J.H., 2012. AR-N-509: a novel antiandrogen for prostate cancer treatment. Cancer Res. 72, 1494–1503. https://doi.org/10.1158/0008-5472.CAN-11-3946.
Crona, D.J., Whang, Y.E., 2017. Androgen receptor-dependent and -independent mechanisms involved in prostate cancer therapy resistance. Cancers (Basel). https://doi.org/10.3390/cancers9060057.
Geynisman, D.M., Plimack, E.R., Zibelman, M., 2016. Second-generation androgen receptor–targeted therapies in nonmetastatic castration-resistant prostate cancer: effective early intervention or intervening too early? Eur. Urol. 70, 971–973. https://doi.org/10.1016/j.eururo.2016.05.026.
Hussain, M., Fizazi, K., Saad, F., Rathenborg, P., Shore, N., Ferreira, U., Iashchenko, P., Demirhan, E., Modeliska, K., Phung, D., Krivoshik, A., Sternberg, C.N., 2018. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer: results from a phase III randomised, placebo-controlled trial. Lancet Oncol. 19, 662–670. https://doi.org/10.1016/S1470-2045(18)30456-X.
Geynisman, D.M., Plimack, E.R., Zibelman, M., 2016. Second-generation androgen receptor–targeted therapies in nonmetastatic castration-resistant prostate cancer: effective early intervention or intervening too early? Eur. Urol. 70, 971–973. https://doi.org/10.1016/j.eururo.2016.05.026.
Bronskill, S.E., Aparicio, A., Dorow, S., Arora, V., Zhao, G., Qian, J., Zhao, H., Yang, G., Cao, C., Sensinstaffar, J., Wasielewksa, T., Herbert, M.R., Bonnefous, C., Darimont, B., Scher, H.J., Smith-Jones, P., Klang, M., Smith, N.D., De Stanchina, E., Wu, N., Ouerfelli, O., Rix, P.J., Heyman, R.A., Jung, M.E., Sawyer, C.L., Hager, J.H., 2012. AR-N-509: a novel antiandrogen for prostate cancer treatment. Cancer Res. 72, 1494–1503. https://doi.org/10.1158/0008-5472.CAN-11-3946.
Crona, D.J., Whang, Y.E., 2017. Androgen receptor-dependent and -independent mechanisms involved in prostate cancer therapy resistance. Cancers (Basel). https://doi.org/10.3390/cancers9060057.
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Funding resource

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