INVITED RESEARCH HIGHLIGHT

Darolutamide: a novel androgen-signaling agent in nonmetastatic castration-resistant prostate cancer

Jeanny B Aragon-Ching

Asian Journal of Andrology (2020) 22, 76–78; doi: 10.4103/aja.aja_52_19; published online: 21 June 2019

A RAMIS is an international Phase III trial demonstrating the beneficial role of darolutamide, a novel anti-androgen that has been found to prolong metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer. Darolutamide is a novel nonsteroidal androgen receptor antagonist that has unique structurally distinct properties with low blood-brain barrier penetration that was shown to improve metastasis-free survival by 22 months compared to placebo (40.4 months vs 18.4 months), reducing the risk of metastasis or death by 59%. Darolutamide also showed improvement in secondary and exploratory endpoints including progression-free survival, prolonged time to PSA progression, PSA response and time to initiating additional antineoplastic therapy, time to pain progression, and time to cytotoxic chemotherapy, but overall survival is not yet reached in either the darolutamide or the placebo arm. Adverse events leading to trial discontinuation were similar at 8.9% and 8.7% in the darolutamide and placebo arms, respectively. Darolutamide was filed as a new drug application to the United States Food and Drug Administration (US FDA) for use in the setting of nonmetastatic castration-resistant prostate cancer.

Biological recurrence of prostate cancer occurs in up to one-third of men who are committed to curative treatment with either surgery or radiation. Most patients who present with biochemical recurrence are treated with androgen deprivation therapy (ADT) in the United States. ADT is often effective in the majority of cases although castration resistance ensues, leading to a disease state referred to as nonmetastatic castration-resistant prostate cancer (nmCRPC) which is a state where ADT is often employed, but the absence of radiographic progression is seen on conventional imaging. This is a state where anti-androgens in the form of apalutamide and enzalutamide, in the SPARTAN3 and PROSPER2 trials, respectively, received recent US FDA approval for the treatment of men with nmCRPC. Darolutamide is structurally distinct from other anti-androgens with active diastereomers. In an initial Phase I and Phase 2 trial development called ARADESS4 and ARAFOR5 trials, PSA decline of ≥50% was seen in 65%–83% of chemotherapy-naive metastatic castration-resistant prostate cancer patients with 30% RECIST responses, leading to further development in a Phase III registrational trial called ARAMIS.6

ARAMIS is a Phase III, double-blinded, randomized, placebo-controlled international trial that was conducted worldwide in 36 countries at 409 centers. The trial enrolled 1509 patients in an intention-to-treat fashion between September 2014 and March 2018 in a 2:1 double-blinded fashion (955 in the darolutamide group and 554 in the placebo group) to receive two 300-mg darolutamide tablets twice a day.7 The primary endpoint was metastasis-free survival defined as time from randomization to distant metastases or death, with the goal of evaluating 385 primary endpoint events which would provide the trial with 91% power to detect a significant difference in metastasis-free survival with the use of a log-rank test at a two-sided significance level of 0.05. Secondary endpoints including overall survival, time to pain progression, time to first symptomatic skeletal-related event, and time to first cytotoxic chemotherapy were evaluated. The study enrolled patients who were at high risk for developing metastases; randomization was made according to PSA doubling times (PSADT) of ≤6 months compared to >6 months and the use of bone-targeted osteoclastic therapy. The use of GnRH-agonist was continued on both arms. Eligibility included (PSADT) of 10 months or less, no evidence of metastatic disease on conventional scans although lymph nodes <2 cm in size and located below the aortic bifurcation were allowed, at least a PSA level of 2 ng ml\(^{-1}\) was required for trial entry, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients were randomized in a 2:1 fashion to receive darolutamide plus continued androgen-deprivation therapy (ADT) with 955 patients versus 554 patients who received placebo plus androgen-deprivation therapy. Results showed that demographics were similar in both treatment groups at baseline in terms of age (median of 74), ECOG performance status (majority 68%–71% had ECOG 0), median serum PSA levels, and doubling times as well as use of a bone-targeting agent (majority 94%–97% of whom had none). The median PSA was around 9 ng ml\(^{-1}\) and 9.7 ng ml\(^{-1}\), for the darolutamide and placebo arms, with a short median PSADT of 4.4 months and 4.7 months, respectively, with majority of patients (around 67%–70%) having PSADT of <6 months.

The primary endpoint of the trial was metastasis-free survival (MFS), which was met after 437 events have occurred. The median metastasis-free survival was 40.4 months in the darolutamide arm versus 18.4 months in the placebo group, translating to a 59% reduction in the risk of death or metastasis (hazard ratio [HR] for metastasis or death in the darolutamide group, 0.41; 95% confidence interval [CI], 0.34–0.50; \(P < 0.001\)), meeting the primary endpoint of the study. The study had
Invited Research Highlight

Table 1: Comparison of oral androgen receptor antagonists for nonmetastatic castration-resistant prostate cancer

| Drug and key phase III trial name | Apalutamide: SPARTAN trial | Enzalutamide: PROSPER trial | Darolutamide: ARAMIS trial |
|-----------------------------------|-----------------------------|----------------------------|---------------------------|
| Patient (n)                       | 1207                        | 1401                       | 1509                      |
| Approval status                   | FDA approved                | FDA approved               | Submission to FDA as NDA   |
| Oral dosing                       | 240 mg once daily           | 160 mg once daily          | 600 mg twice daily        |
| Primary endpoint (MFS results of drug vs placebo) | 40.5 months versus 16.2 months | 36.6 months versus 14.7 months | 40.4 months versus 18.4 months |
| Frequent AEs of interest          | Rash 24%; fracture 12%; hypothyroidism 8%; Fatigue 30.4%; Hypertension 24.8%; Falls 15.6%; Seizure 0.2% | Fatigue 33%; Hypertension 12%; Mental impairment disorders 5% | Fatigue 15%; rash 2.9%; Hypertension 6.6%; fracture 4.2% |

FDA: Food and Drug Administration; NDA: new drug application; MFS: metastasis-free survival; AEs: adverse events

a median follow-up time of 17.9 months, with 64% of the patients in the darolutamide group and 36% in the placebo group still receiving active treatment assignments at the time of reporting. The secondary endpoints were also in favor of those receiving darolutamide, with a trend toward improvement in overall survival compared to placebo after 136 deaths (78 in the darolutamide group and 58 in the placebo group) with hazard ratio (HR) for death: 0.71; 95% CI: 0.50–0.99; P = 0.045, a statistically significantly longer time to pain progression in the darolutamide arm compared to placebo (median of 40.3 months compared to 25.4 months; hazard ratio, 0.65; 95% CI, 0.53–0.79; P < 0.0001). The median time to first use of a subsequent cytotoxic agent was also significantly longer in those receiving darolutamide (not reached) versus placebo (38.2 months) with HR: 0.43; 95% CI: 0.31–0.60, P < 0.001. Time to the first symptomatic skeletal-related event was not reached for both arms, HR: 0.43, 95% CI: 0.22–0.84; P = 0.01. Other exploratory endpoints similarly favored darolutamide arm, including the progression-free survival (PFS) at 36.8 months, compared to 14.8 months for placebo, and time to PSA progression at 33.2 months compared to 7.3 months in placebo, P < 0.001.

Adverse events in both groups were similar with only fatigue that occurred in >10% in the darolutamide group (15.8% in the exposure-adjusted incidence) compared to 11.4% in the placebo arm. Seizures occurred rarely in either arm at 0.2%, whereas other adverse events were commonly seen in other androgen-signaling agents such as rash that occurred rarely at 2.9% in darolutamide compared to 0.9% in the placebo arm, with fractures occurring at 4.2% versus 3.6% in the placebo arm. This adverse event profile makes use of darolutamide much more attractive in this otherwise relatively asymptomatic group of men.

The promising results from ARAMIS trial have brought to the forefront the beneficial effects of darolutamide in an already emerging crowded field of androgen-signaling agents in the nonmetastatic CRPC space. Metastasis-free survival has emerged as an acceptable surrogate endpoint for survival that is increasingly recognized in clinical trials from the US FDA standpoint for regulatory approval.7 However, there are certain seeming advantages of darolutamide based on the results of the ARAMIS trial. There seems to be less incidence in the side effects that are deemed concerning for the early use of these androgen-signaling inhibitors, particularly the CNS effects, as darolutamide has a unique structural composition that serves to lower the blood–brain barrier penetrance. Compared to other drugs apalutamide and enzalutamide (Table 1), these adverse events appear far less common. Seizure events, in particular, occurred less frequently despite allowing patients with prior seizure predisposition to enroll in the study, whereas it was an explicit exclusion in both the SPARTAN and PROSPER trials. It would be interesting to see how the landscape of treatment in nmCRPC evolves considering the two other currently available potent anti-androgens already available in the market. The additional value of another endpoint called PFS2, or 2nd progression-free survival that is technically defined as the time from randomization to investigator-assessed disease progression via PSA progression, detection of metastatic disease on imaging, symptomatic progression, or any combination thereof during the first subsequent treatment for metastatic castration-resistant disease or death from any cause, was used in the SPARTAN trial as an additional gauge of benefit for apalutamide. Apalutamide’s PFS2 was not reached compared to 39 months for placebo, HR: 0.49 (95% CI: 0.36–0.66), P < 0.0001, suggesting benefit despite and beyond its use as a first-line androgen-signaling agent. This endpoint has been used as a safeguard against using a drug inadvertently in an earlier disease course in a largely asymptomatic population. On the other hand, abiraterone was the drug mostly offered in patients in the SPARTAN trial (given the same company-sponsored drug), while reports of PFS2 are not currently available in either the enzalutamide or darolutamide trials. Nevertheless, the safety profile lends to the easy use of darolutamide in this earlier disease setting.

While the primary endpoint was met and majority of the secondary endpoints did favor darolutamide use, similar to other anti-androgens in the same setting, the median overall survival was not reached in either arm of the study with hazard ratio of 0.71 (95% CI: 0.50–0.99), P = 0.045. It remains to be seen if overall survival will eventually show vast improvement in this population of patients. Darolutamide was also evaluated in a metastatic castration-sensitive setting in combination with docetaxel in the ARASENS trial (clinicaltrials.gov identifier NCT02799602), perhaps establishing the role of additional or combinational androgen-signaling agent with chemotherapy in the early metastatic castration-sensitive setting.

In conclusion, the findings of this trial support the use of darolutamide for men who have nonmetastatic, castration-resistant prostate cancer, and the results of the ARAMIS trial have heralded the filing for a new drug application for the indication of darolutamide in this space with the US FDA in February 2019, but pending full approval as of this writing.

COMPETING INTERESTS

JBAC has previously served in the Speakers’ Bureau of Astellas/Medivation and has served in the Advisory Board for Janssen and Bayer. JBAC serves as an investigator for the ARAMIS trial.

REFERENCES

1 Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378: 1408–18.
2 Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, et al. Enzalutamide in men with nonmetastic, castration-resistant prostate cancer. N Engl J Med 2018; 378: 2465–74.
3 Fizazi K, Massard C, Bono P, Jones R, Kataja V, et al. Activity and safety of DNX-201 in patients with progressive metastatic castration-resistant prostate cancer. N Engl J Med 2018; 378: 2475–84.
prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. Lancet Oncol 2014; 15: 975–85.

4 Fizazi K, Massard C, Bono P, Kataja V, James N, et al. Safety and antitumour activity of ODM-201 (BAY-1841788) in castration-resistant, CYP17 Inhibitor-naive prostate cancer: results from extended follow-up of the ARADES trial. Eur Urol Focus 2017; 3: 606–14.

5 Massard C, Penttinen HM, Vjaters E, Bono P, Lietuvietis V, et al. Pharmacokinetics, antitumor activity, and safety of ODM-201 in patients with chemotherapy-naive metastatic castration-resistant prostate cancer: an open-label phase 1 study. Eur Urol 2016; 69: 834–40.

6 Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; 380: 1235–46.

7 Beaver JA, Kluetz PG, Pazdur R. Metastasis-free survival – A new end point in prostate cancer trials. N Engl J Med 2018; 378: 2458–60.