PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

The Addition of Darolutamide to Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Fred Saad, MD
Professor and Chair of Surgery
Raymond Garneau Chair in Prostate Cancer
Director of GU Oncology
University of Montréal
Montréal, Québec, Canada

H&O What was the impetus for the ARANOTE trial?

FS The ARANOTE trial[1] was a follow-up to 2 other large phase 3 studies that looked at the role of darolutamide (Nubeqa, Bayer HealthCare) in advanced prostate cancer. In the phase 3 ARAMIS trial, darolutamide was able to delay the appearance of metastatic disease significantly and actually improve overall survival (OS) in patients with nonmetastatic castration-resistant prostate cancer (CRPC).[2] This finding was similar to those seen with apalutamide (Erleada, Janssen Biotech) and enzalutamide (Xtandi, Astellas), establishing the effectiveness of all 3 androgen receptor pathway inhibitors (ARPIs) in delaying metastases in patients with nonmetastatic CRPC at high risk for the development of metastases according to the prostate-specific antigen (PSA) doubling time.

In the phase 3 ARASENS trial, the addition of darolutamide to androgen deprivation therapy (ADT) plus docetaxel reduced the risk of overall mortality by 32.5% in patients with metastatic hormone-sensitive prostate cancer (HSPC).[3] This finding led to the rapid approval of darolutamide in combination with docetaxel, changed the standard of care for patients with metastatic HSPC, and raised the question of whether darolutamide was effective in HSPC only if it was added to docetaxel. Could we use darolutamide without docetaxel?

Because we already had 2 phase 3 studies showing that darolutamide improved OS, we designed our study to address this question with a primary endpoint of radiographic progression-free survival (rPFS). We used rPFS instead of OS as the primary endpoint because we wanted the study to read out in a relatively short time. Our study also was designed to enroll fewer than 700 patients, whereas phase 3 studies in metastatic HSPC typically enroll more than 1000 patients. Some experts have wondered if we even needed to do this study because the previous research suggested that darolutamide was the driver of the improvement, but we still wanted data to confirm the efficacy of darolutamide when used without docetaxel.

H&O Could you describe the study design in more detail?

FS We enrolled 670 patients who had metastatic HSPC and randomized them in a 2:1 ratio to darolutamide plus ADT or to placebo plus ADT. In addition to the primary endpoint of rPFS, secondary endpoints included OS, time to metastatic CRPC, time to PSA progression, time to pain progression, and time to subsequent therapy. We also wanted to look at the tolerability profile and adverse events in a monotherapy setting because it is difficult to figure out which adverse events are caused by darolutamide when it is used in a combination setting.

H&O What were your results?

FS The study reached it primary endpoint, with patients in the darolutamide group exhibiting a 46% reduction in the risk of radiographic progression or death that was highly statistically significant. Patients in the darolutamide group also did better than those in the placebo group regarding all the secondary endpoints, time to metastatic CRPC, and time to PSA progression. The delay to pain

progression was especially interesting because this has not been seen in many studies. The study was underpowered to show an improvement in OS, especially given the 2:1 randomization, but a 19% reduction in OS was noted that did not reach statistical significance. Our follow-up was approximately 2 years, which is way too early to be looking at OS because patients with metastatic HSPC have a median survival of more than 3 years.

H&O What adverse events were seen with darolutamide in the trial?

FS We saw very few adverse events that were more frequent in the darolutamide arm than in the placebo arm. In fact, the discontinuation rate was slightly higher in the placebo arm than in the darolutamide arm, which was both surprising and reassuring. It points to patients likely discontinuing treatment because of progression of disease rather than because of adverse events. The most common adverse event reported by patients who are on ADT and ARPIs is fatigue, but we actually saw less fatigue in the darolutamide arm than in the placebo arm. What this tells us is that the fatigue may be coming from the progression of cancer. Overall, it was reassuring to see that we were not adding much in terms of adverse events to those we would expect with ADT.

The addition of darolutamide led to a greater decrease in radiographic progression or death among patients in the low-volume group than among those in the high-volume group.

H&O Why did the control patients in ARANOTE continue to receive ADT alone in 2021 and 2022, after treatment intensification had been established?

FS That is a fair question because at that point we had trial results showing that we could improve results by adding treatment to ADT. In an ideal world, every patient would be getting more than ADT. The reality is that additional treatment is not always available or affordable. Even in the United States and Canada, a significant proportion of patients with metastatic HSPC do not receive anything more than ADT. We conducted our study in countries where patients were treated primarily with ADT for metastatic HSPC or did not have easy access to more than ADT. As a result, the patients in the study were benefiting from the fact that two-thirds of them received more than ADT alone. Patients who would have otherwise received chemotherapy were not eligible for the study.

H&O What other relevant research has been released since the publication of ARANOTE?

FS We presented additional research at the 2025 American Society of Clinical Oncology Genitourinary Cancers Symposium, in which we compared patients with high-volume vs those with low-volume disease from ARANOTE.[4] More than 70% of the patients in our study had high-volume disease, and we found that patients benefited whether their disease was high- or low-volume. The addition of darolutamide led to a greater decrease in radiographic progression or death among patients in the low-volume group than among those in the high-volume group: approximately 70% vs 40%. This finding tells us that although darolutamide is efficacious in both groups, we may need to do more for patients with high-volume disease; perhaps these patients would benefit from the addition of docetaxel to darolutamide to improve their outcomes further.

We also presented data from ARANOTE on PSA responses at the European Association of Urology (EAU) Congress in March of this year. This presentation was chosen as a game-changer because we saw that we were able to attain very significant declines in the PSA nadir with darolutamide. Many use a measurement of 0.2 ng/mL or lower as an indicator of a very good response and long-term improved outcome. We saw very good PSA responses in ARANOTE overall; the likelihood of reaching that level was 3-fold greater with darolutamide and ADT than with ADT alone. The percentage of patients in whom an undetectable PSA level was reached was less than 20% with ADT alone and was more than 60% with darolutamide plus ADT. The percentage of patients in whom an undetectable PSA level was reached was 55% among those with high-volume disease, which is very good, and was higher than 80% for those with low-volume disease. So maybe we can stick with an ARPI alone for most of the patients with low-volume disease and possibly improve outcomes for the patients who have high-volume disease by adding docetaxel.

Also at the EAU Congress, I presented data regarding PSA levels when patients entered the trial. The baseline

median PSA level in ARANOTE was a little higher than 21 ng/mL, whereas the median PSA in several other trials was between 4 and 6 ng/mL. We saw that among the patients in ARANOTE whose baseline PSA level was approximately 4 ng/mL—those in the lowest quartile—the rate of undetectable PSA level was 88%. On the other hand, among those whose baseline PSA level was higher than 21 ng/mL, the rate of undetectable PSA level was approximately 50%. The higher the PSA level at baseline, the harder it is to reach that undetectable level. An undetectable PSA level was achieved in only 10% of these patients with ADT alone, so this finding indicates a 5-fold increase in the likelihood of reaching an undetectable PSA level.

We presented additional data regarding PSA levels at the American Urological Association (AUA) Annual Meeting in April of this year. We found that a very high percentage of patients had an undetectable PSA level—less than 0.02 ng/mL—if they received darolutamide on top of ADT. Research is ongoing to find novel and personalized intensification strategies to get the PSA levels to undetectable and further improve outcome.

We will also be presenting quality-of-life data from ARANOTE at the ASCO Annual Meeting.

H&O Is there a particular ARPI that you prefer to use?

FS I would be hard pressed to say that one is clearly better than another. We have several very effective ARPIs, and they are well tolerated in general. We will sometimes consider factors such as drug-drug interactions, patient comorbidities, and patient tolerance when choosing an ARPI, but all of them are extremely effective and great choices.

H&O Which do you recommend at this point: doublet therapy with ADT plus an ARPI or triplet therapy with the addition of docetaxel?

FS That is the million-dollar question. Some patients do very well on doublet therapy; this seems to be most of those with low-volume disease who do not have any visceral metastatic disease. Patients who do not do very well on doublet therapy are those with high-volume disease, especially if they have visceral metastases and even more especially if they have liver metastases. The best option we have now for these patients is to consider adding chemotherapy if they are able to tolerate it. I discuss triplet therapy with young patients who have low-volume disease and are willing to accept chemotherapy in the hope of a long-term remission.

We have level 1 evidence from 2 phase 3 trials establishing that we can improve outcomes with ADT and docetaxel by adding an ARPI. Where we lack evidence is regarding whether the addition of docetaxel can improve results in patients who receive ADT plus an ARPI. Should we intensify treatment if the PSA level fails to become undetectable after a few months? This is a reasonable strategy, but that trial remains to be conducted. I am also concerned about patients who have low PSA levels with metastatic disease because this may indicate that much of their disease is likely not androgen receptor–dependent. Therefore, we need to address this situation by using an agent with a different mechanism of action.

H&O What are you most looking forward to in terms of new trials for men with metastatic HSPC?

FS I am looking forward to the intelligent selection of specific therapies for specific patients. We have been using a shotgun approach in which everybody is given the same thing, but now the whole field is moving toward a more rational, biologically driven approach. I hope to see prostate cancer go the same way as other tumors—where we can combine enough treatments to cure patients. My hope is that we will be able to stop keeping patients with prostate cancer on treatment for the rest of their life, especially when that means being on ADT forever. We need to start thinking about hitting hard and then backing off, the way we do with many other cancers.

Disclosures

Dr Saad has received honoraria from Astellas Pharma, Janssen Oncology, Sanofi, Bayer, AstraZeneca, AbbVie, Sumitomo Pharma, Pfizer, Bristol Myers Squibb, Novartis, Merck, TerSera Therapeutics, and Tolmar; has served in a consulting or advisory role to Astellas Pharma, Janssen Oncology, Sanofi, AstraZeneca/MedImmune, Bayer, Pfizer, Sumitomo Pharma, AbbVie, Novartis, TerSera, and Tolmar; and has received research funding through his institution from Astellas Pharma, Bayer, Janssen Oncology, Sanofi, AstraZeneca, Pfizer, Bristol Myers Squibb, Novartis, and Merck.

References

1. Saad F, Vjaters E, Shore N, et al; ARANOTE Study Investigators. Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial. *J Clin Oncol*. 2024;42(36):4271-4281.
2. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383:1040-1049.
3. Smith MR, Hussain M, Saad F, et al; ARASENS Trial Investigators. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132-1142.
4. Saad F, Shore N, Vjaters E, et al. Darolutamide plus ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC) by disease volume: subgroup analysis of the phase 3 ARANOTE trial. Poster presented at: ASCO Genitourinary Cancers Symposium. February 26-28, 2025; San Francisco, CA. Abstract 151.