Key updates on mOCRPC treatment

Balancing benefits, patient individual factors, and risks

Prof. Dr. Axel Merseburger
EUSP Chair, University Hospital Schleswig-holstein, Campus Lübeck, Dept. of Urology Lübeck (DE)
axel.merseburger@uksh.de

Prostate cancer progression is a continuous process and can occur in different stages. A sole prostate-specific antigen (PSA)-progression following androgen deprivation therapy (ADT) can occur upon different patient histories such as local recurrence in the prostate after prostatectomy or persistent local disease after radical radiation therapy with absence of metastatic disease or with no detectable recurrent disease in the primary site and no detected involved lymph nodes, bone or visceral organs. Overall, absence of distant metastases (M1a-M1c) defines the non-metastatic disease state, lymph below aortic bifurcation (N1) are not considered, whereas all studies leading to an approval of systemic therapy for this disease state used conventional imaging modalities: MRI or CT in combination with bone scans.

One definition of progression during ADT is based on PSA increases and follows the PCWG3 consensus: a 25% increase from nadir with a starting value of 1.0 ng/ml, with a minimum rise of 2 ng/ml, while maintaining castrate testosterone values (<50 ng/dl) [1].

The European Association of Urology (EAU) defines castration-resistant prostate cancer (CRPC) as either biochemical progression (three consecutive rises in PSA one week apart and a PSA > 2 ng/mL) or radiologic progression (at least two new bone scan lesions or a soft tissue lesion using Response Evaluation Criteria in Solid Tumors [RECIST]) in the presence of serum testosterone < 50 ng/dl or 1.7 mol/l [2].

Table 2: Cross-trial efficacy comparison in mOCRPC

Drug	Study	Median MFS (months)	Median TTPP (months)	median OS (months)
Enzalutamide	PROSPER	36.6 vs. 14.7 (HR=0.29; p<0.001)	37.2 vs. 3.9 (HR=0.07; p<0.001)	NR vs. NR (HR=0.73; p=0.001)
Apalutamide	SPARTAN	40.5 vs. 16.2 (HR=0.28; p<0.001)	NR vs. 3.7 (HR=0.06; p N/A)	NR vs. 39.0 (HR=0.78; p=0.016)
Darolutamide	ARAMIS	40.4 vs. 18.4 (HR=0.41; p<0.001)	33.2 vs. 7.3 (HR=0.13; p<0.001)	NR vs. NR (HR=0.69; p=0.003)

MFS metastasis-free survival, *TTPP* time to PSA progression, *OS* overall survival

Patients with CRPC but no distant metastasis (non-metastatic CRPC [nmCRPC/mOCRPC]) are especially at high risk of developing metastases if the PSA-doubling time is shorter than 10 months. Thus, a careful monitoring of patients treated with ADT with a regular calculation of PSA-DT is recommended. Since PSA-DT is based on a rather complex algorithm, web-based calculators should be used. [3]

Approved systemic treatment options for mOCRPC

Apalutamide, darolutamide, and enzalutamide are second generation non-steroidal anti-androgens with a higher affinity for the androgen receptor (AR) than bicalutamide. While first generation non-steroidal anti-androgens still allow transfer of ARs to the nucleus, apalutamide, enzalutamide and darolutamide also block AR translocation in the nucleus and therefore suppress transcriptional activity. [4-6] Darolutamide has structurally unique properties with a more flexible and polar structure, thus leading to different pharmacokinetic properties. [7] In particular, preclinical studies and a Phase I study with healthy volunteers showed darolutamide did not cross the blood-brain barrier. [8-9] Furthermore due to increased polarity, the interactions and metabolism via CYP P 450 system differed and resulted to less potential drug-drug interaction of darolutamide [10] (Figure 1). The key substance characteristics of all three agents are summarised in table 1.

Clinical data of apalutamide, enzalutamide, and darolutamide in nmCRPC patients

Three large randomised-controlled phase III trials, PROSPER [4], SPARTAN [5] and ARAMIS [6], evaluated metastasis-free survival (MFS) as the primary endpoint in patients with nmCRPC (mOCRPC) treated with enzalutamide vs. placebo (PROSPER) or apalutamide vs. placebo (SPARTAN) or darolutamide vs. placebo (ARAMIS), respectively. The non-metastatic (M0) status was determined by MRI, CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 months were included in all three trials. Patient characteristics in both trials revealed that about two-thirds of participants had a PSA-DT of six months.

All three trials showed a significant MFS benefit, as well as, significant overall survival benefit (OS) [14-16], as summarised in Table 2.

In addition, for the benefit of delaying progression to metastatic disease or death in patients with nmCRPC, the risk of treatment-emergent adverse events (AEs) and Quality of Life (QoL) should be considered in this mainly asymptomatic patient population. In the primary analysis of the SPARTAN trial, 96.5% and 93.2% of patients experienced an AE of any grade in the apalutamide and placebo group, respectively [5]. The incidence of Grade 3–4, the AEs was 45.1% for apalutamide and 34.2% in the placebo arm. The incidences of fatigue, rash, falls, fractures, mental impairment, and hypothyroidism were higher compared to placebo [5]. The final analysis of the SPARTAN trial reported a safety profile of apalutamide similar to that in the primary analysis (Fig. 2A) [14]. Grade 3–4 hypertension and falls occurred more frequently in the apalutamide arm compared to placebo arm [14].

In the primary analysis, AEs associated with death occurred in 10 patients treated with apalutamide wherein in some of the cases, the causes of death wereacute myocardial infarction, cardiorespiratory arrest, cerebral haemorrhage, myocardial infarction, multiple organ dysfunction, and pneumonia. In two patients, the causes of death were prostate cancer and sepsis. One patient in the placebo arm died due to cardiorespiratory arrest [5].

In the primary analysis, treatment discontinuation due to AEs were 10.6% in the apalutamide arm compared with 7.0% in the placebo arm; the most common AEs leading to treatment discontinuation were rash, fatigue, sepsis, and dizziness [5]. In the final analysis, discontinuation rates in apalutamide and placebo groups due to progressive disease

Table 1: Comparison of the second-generation androgen receptor antagonists for nmCRPC

	APALUTAMIDE	ENZALUTAMIDE	DAROLUTAMIDE
Half-life	3-4 days	5.8 days	20 hours
Status	FDA & EMA approved	FDA & EMA approved	FDA & EMA approved
Dosage	240 mg po once daily	160 mg po once daily	600 mg po twice daily
Blood-Brain Barrier penetration	Yes	Yes	no
CYP Induction	Strong: CYP3A4 & CYP2C19 Moderate: - Weak: CYP2C9	Strong: CYP3A4 Moderate: CYP2C9 & CYP2C19 Weak:-	Strong: - Moderate: - Weak: CYP3A4
Increase of serum testosterone level	Yes	Yes	no
Key phase III trial	SPARTAN	PROSPER	ARAMIS
N (patients)	1207	1401	1502

Abbreviations: EMA: European medicines agency; FDA, Food and Drug Administration; nmCRPC, non-metastatic castration-resistant prostate cancer.

were 43% and 74%, and discontinuation rates due to AEs increased to 15% and 8.4%, respectively [14].

In the PROSPER trial, treatment-related AEs were mostly consistent with the established safety profile of enzalutamide. In the primary analysis, the incidence of any-grade AEs was 87% and 77% in the enzalutamide and placebo arm, respectively. Grade 3–4 AEs were experienced by 31% in the enzalutamide arm and 23% of patients in placebo arm. Compared with the placebo arm, fatigue, hypertension, mental impairment disorders, major cardiovascular AEs, as well as, fall and fracture occurred with a higher incidence in the enzalutamide arm (Fig. 2B) [4].

The final analysis of PROSPER reported a safety profile of enzalutamide comparable to that at the time of primary analysis. AEs of Grade 3 or higher were experienced by 48% of patients receiving enzalutamide compared with 27% receiving placebo. [15].

Treatment discontinuation due to an AE occurred in 9% of patients in the enzalutamide arm compared with 6% in the placebo arm in the primary analysis of PROSPER, increasing to 17% and 9%, respectively, in the final analysis [4, 15]. A total of 32 patients who received enzalutamide and four patients in the placebo arm died without evidence of radiographic progression [4].

The primary analysis of ARAMIS reported 83.2% and 76.9% of patients with an AE of any grade in the darolutamide and placebo arms, with Grade 3–4 AEs occurring in 24.7% and 19.5% patients, respectively [6]. In terms of tolerability, darolutamide was well tolerated with no clinically relevant difference compared to the placebo arm was observed for the incidence of AEs typically associated with ARIs, including falls, hypertension, and mental impairment [6]. The most common adverse reactions frequently reported in the active treatment versus placebo arm of ARAMIS were fatigue, extremity pain, and rash. Only fatigue had an incidence higher than 10% with darolutamide [6].

With longer follow-up time and duration of treatment in the final analysis of ARAMIS, the incidence of AEs with darolutamide remained low. The minimal or no difference for darolutamide compared with placebo was confirmed for most ARI-associated AEs, such as fatigue, falls, fractures, rash, mental impairment disorders, and hypertension. (Fig. 2C), [16, 17]. Moreover, drug discontinuation rates due to AEs in the final analysis of ARAMIS were similar in the darolutamide and placebo arms (8.9% vs. 8.7%) and remained unchanged from those at the primary analysis [6, 16, 17]. On a related note, the incidence of Grade 5 AEs was similar in both treatment arms (4.0% vs. 3.4% in the darolutamide and placebo arms, respectively). In ARAMIS, 37 deaths were reported in the darolutamide arm with one death considered related to treatment (perforation of the small intestine), 18 deaths in the placebo arm two deaths considered treatment-related (myocardial infarction and intracranial haemorrhage) [6].

Current treatment guidelines

Following the approval the FDA and the EMA, international guidelines such as from the National Comprehensive Cancer Network (NCCN) and the EAU, as well as, national guidelines (e.g. German S3 guideline prostate cancer) now recommend that patients with nmCRPC/moCRPC and a PSADT ≤ 10 months should be treated with enzalutamide, apalutamide, or darolutamide in addition to continuing ADT, to delay metastasis and prolong OS [2, 18, 19]. Guideline recommendations are based on high-level evidence of efficacy, which all three ARIs demonstrated in their respective phase 3 clinical trials with MFS being the primary efficacy endpoint. Final analysis of all three trials revealed significant OS, suggesting that MFS can be considered a sufficiently strong surrogate of OS [20, 21]. Taking the general high QoL in a rather asymptomatic patient population into account, it is important to take possible treament-emergent AEs and maintenance of QoL in consideration.

Conclusions

High-risk nonmetastatic CRPC or moCRPC is a heterogeneous state defined by rising PSA, as short PSA-DT ≤ 10 months and absence of distant metastasis in conventional imaging. In the past two years, treatment options for high-risk-nmCRPC-patients evolved rapidly with the FDA and EMA approval of the second-generation ARIs apalutamide, enzalutamide, and darolutamide. All three agents have demonstrated significant prolongation of MFS and a significant OS benefit in patients with high-risk nmCRPC, resulting in international and national guideline recommendation for treatment of castration resistant disease [4-6, 14-17].

Second-generation ARIs have overall acceptable tolerability in general and maintain QoL in patients with non-metastatic disease. Their distinct safety profiles and potential for drug–drug interactions with frequent co-medications in this patient population should be considered for treatment decision, whereas therapeutic options that do not escalate ADT-related AEs or contribute to additional therapeutic burden due to drug–drug interactions may be preferred. In conclusion, recently 3 efficacious second-generation ARIS became available and are recommended for the treatment of nmCRPC. Balancing benefits, patient individual factors, and risks is important for the appropriate treatment decisions for these patients [22].

References

1. Scher HI, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J ClinOncol 2016;34:1402–18.
2. Mottet N, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. https://uroweb.org/guideline/prostate-cancer/, Accessed January 2022
3. ANTON PONHOLZER A et al, Proposal for a Standardized PSA-doubling time calculation, Anticancer Research May 2010, 30 (5) 1633-1636;
4. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2018;378:2465–74.
5. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378:1408–18.

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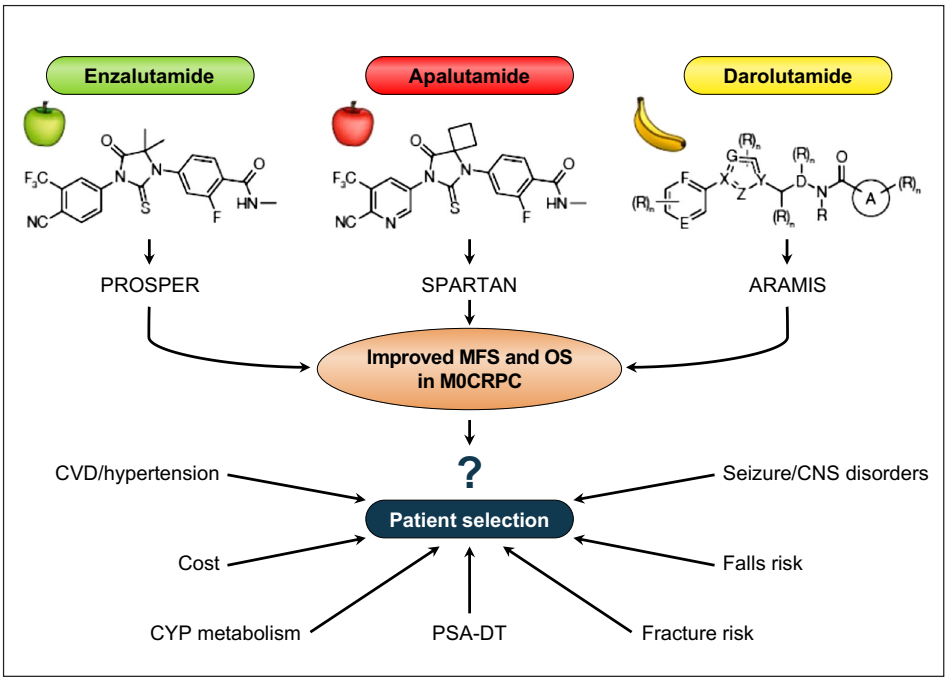

Overview on structure and factors that are important in selecting the right substance for the right patient