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Editorial

Prostate cancer—highlights from American Society of Clinical Oncology virtual meeting 2020



1. Advanced prostate cancer (PCa)

Patients with advanced PCa should receive a chemical castration, which may be either a luteinizing hormone-releasing hormone analogue or a luteinizing hormone-releasing hormone antagonist. The advantage of the antagonist is mainly the absence of a flare-up effect, allowing a rapid decrease in testosterone. The only antagonist currently available is degarelix. Relugolix is a novel oral gonadotropin releasing hormone (GnRH) receptor antagonist that suppresses both luteinizing hormone and follicle stimulating hormone through its direct inhibitory effect on pituitary GnRH receptors. This direct inhibition does not lead to a testosterone surge. Relugolix has been developed as a highly selective, first-in-class GnRH receptor antagonist, administered orally once a day. HERO [1] is a multinational, randomised, open-label, parallel-group, phase III study designed to evaluate the efficacy and the safety of relugolix in men with advanced PCa. A total of 934 patients with advanced PCa were randomised to receive for 48 weeks either relugolix 120 mg orally once daily after a single loading dose of 360 mg or leuprolide 22.5 mg injected every 3 months.

The primary endpoint of this study was the suppression of testosterone at a castration level (<50 ng/dL) for 48 weeks. Secondary endpoints included non-inferiority to leuprolide on the primary endpoint, early and deep castration rates on Days 4 and 15, prostatic-specific antigen (PSA) response on Day 15, and follicle stimulating hormone at Week 25. On the primary endpoint, relugolix achieved a 96.7% response rate with sustained castration through Week 48 versus 88.8% in the leuprolide group, which results in a 7.9% between-group difference. Testosterone suppression to castrate levels occurred rapidly in the relugolix arm. Mean testosterone levels on Day 4 were below 50 ng/dL for relugolix and then maintained a castrate level throughout the study until treatment ended. Regarding the secondary

endpoints, all were in favor of relugolix. Tolerance was relatively similar in both groups, except for diarrhea which was more reported with relugolix and hypertension which was more frequent with leuprolide acetate. In contrast, cardiovascular (CV) events were more frequently observed in the leuprolide arm, particularly major CV events which included myocardial infarction, stroke, and death. This represented a 54% decrease in the risk of major CV events. In conclusion, relugolix allows a more rapid sustained castration than leuprolide; moreover, it halves the CV risk. With these very impressive results, this novel oral GnRH antagonist has the potential to become a new standard for testosterone suppression in advanced PCa [1].

2. Non-metastatic castration resistant PCa (nmCRPC)

Left without therapeutic options for a long time, patients with nmCRPC could now be treated with three molecules: apalutamide (SPARTAN study), enzalutamide (PROSPER study), or darolutamide (ARAMIS study). In these phase III studies, which all included patients with an nmCRPC with a PSA of >2 ng/mL and a PSA doubling time of ≤ 10 months, the primary endpoint was metastasis-free survival (MFS) and all three treatments showed a benefit on MFS. However, none has shown a difference in overall survival (OS). In the American Society of Clinical Oncology (ASCO) virtual meeting 2020, the results of OS were presented.

2.1. Apalutamide

The SPARTAN, a phase III randomised trial evaluated apalutamide, a next-generation androgen receptor (AR) inhibitor plus androgen deprivation therapy (ADT) versus placebo (PBO) plus ADT in patients with nmCRPC with a PSA of >2 ng/mL and a PSA doubling time of ≤ 10 months. A total of 1207 patients were included; there was a

<https://doi.org/10.1016/j.ajur.2021.10.005>

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crossover, as 76 patients receiving PBO were switched to apalutamide. The median follow-up of the study was 52 months. The median OS with apalutamide group was 73.9 months, compared to PBO group with 59.9 months (hazard ratio [HR] 0.784; $p=0.0161$). In an analysis of OS excluding the patients who were switched to the experimental arm, the PBO group had OS median of 52.8 months (HR 0.685; $p=0.0002$). The time to initiation of chemotherapy has also been improved with apalutamide; although the median has not yet been reached, the HR favourable for apalutamide was 0.629 ($p=0.0002$). Regarding safety, there were no surprises in this last analysis. All in all, 15.2% of patients on apalutamide group discontinued treatment due to events compared to 8.4% in the PBO group [2].

2.2. Darolutamide

The second drug is darolutamide, a structurally distinct AR inhibitor; its safety and efficacy were evaluated in the ARAMIS phase III trial in combination with castration in nmCRPC [3]. At primary analysis, median MFS was prolonged by 22 months in the darolutamide arm as compared with the PBO arm with a HR of 0.41 and a highly significant p -value of 0.003. At final analysis, a statistically significant difference was observed in favour of darolutamide with a 31% reduction in the risk of death. After a median follow-up of about 29 months, the OS rate at 3 years was 83% with darolutamide and 77% with PBO. Secondary endpoints were all in favour of darolutamide, whether in terms of time of pain progression, time to first cytotoxic chemotherapy, or time to first symptomatic skeletal event [3]. The safety profile of darolutamide was consistent with the primary analysis. After adjustment for treatment exposure, there was still little or no difference in the incidence of adverse events (AEs; including falls, central nervous system effects, and hypertension) between darolutamide group and PBO group. AEs in the crossover group were consistent with those for the darolutamide treatment arm [3]. The profile tolerance of darolutamide seemed very favorable since it had a low blood brain barrier penetration and low potential for drug–drug interaction.

2.3. Enzalutamide

Like its counterparts SPARTAN and ARAMIS, a previous report of the test PROSPER, a phase III, randomised, double-blind trial, evaluating enzalutamide in men with nmCRPC [4] noted an improvement in MFS with enzalutamide versus PBO. The final analysis of OS again showed that the benefit in MFS has resulted in an almost 1-year-long benefit of OS in patients with nmCRPC who received enzalutamide. The median OS was 67.0 months for enzalutamide and 56.3 months for the PBO, despite the crossover.

The tolerance profile was consistent with the known profile for enzalutamide. Grade 3 or higher AEs occurred in 48% of men in the enzalutamide group and 27% in the PBO group. The mainly AEs observed were falls, fatigue, and hypertension. These data are reassuring because

OS was improved with enzalutamide in patients with nmCRPC [4].

2.4. Comparison between the three drugs (apalutamide, darolutamide, and enzalutamide)

A match-adjusted indirect comparison of safety outcomes of darolutamide compared with apalutamide and enzalutamide in high-risk nmCRPC was conducted [5]. It confirmed that darolutamide had statistically significant lower absolute risks compared with apalutamide after matching for falls, rash, and fractures by a risk difference of 6%, 16%, and 6%, respectively. Darolutamide also had a statistically significant lower risk of falls, dizziness, mental impairment, fatigue, and severe fatigue compared to enzalutamide. Although head-to-head trials are the gold standard for comparative clinical assessment, these results are instructive for shared decision making between patient and clinician [5].

3. Metastatic hormone-sensitive PCa (mHSPC)

A phase III randomized trial ARCHES [6] previously published showed that enzalutamide with ADT significantly reduced the risk of radiological progression and death in men with mHSPC. Given that patients with mHSPC represent a prognostically heterogeneous group, depending on their metastatic location, at ASCO congress of 2020, the results were reported of this post-hoc analysis [7], which evaluated the impact of metastatic localization on efficacy of enzalutamide with ADT in patients enrolled in ARCHES. The patients with mHSPC were randomised 1:1 to enzalutamide (160 mg/day) with ADT versus PBO with ADT. The stratification was done according to tumour volume and previous treatment with docetaxel. The primary endpoint was survival without radiological progression-free survival (rPFS). Secondary assessment criteria included the time to progression of PSA, the time to first symptomatic bone event, the delay until resistance to the castration, and the delay before the start of a new anti-neoplastic therapy. Among the overall population with known metastases at screening ($n=1146$), the largest subgroups of patients were those with only bone metastases ($n=513$) and those with bone metastases and soft tissue only ($n=351$); there were fewer M0 patients or patients with soft tissue metastasis only ($n=154$) and patients with visceral metastases with or without bone metastases ($n=128$). Enzalutamide with ADT reduced the risk of rPFS and other secondary assessment criteria compared to PBO with ADT in all the subgroups, with a greater relative efficacy observed in patients without visceral metastases.

Therefore, enzalutamide with ADT provided improvement in rPFS and other secondary endpoints compared to PBO with ADT in patients with mHSPC regardless of metastatic site, especially in patients without visceral metastases. These results highlighted the importance of patient and physician discussion regarding the use of enzalutamide in the treatment of mHSPC [6].

4. Metastatic castration-resistant PCa (mCRPC)

4.1. Efficacy and safety in older patients with mCRPC receiving cabazitaxel versus abiraterone or enzalutamide was evaluated in the CARD study [8]

It was a phase III trial that prospectively compared cabazitaxel (25 mg/m² intravenous injection [iv] every 3 weeks [Q3W] with prednisone and granulocyte-colony stimulating factor) for the first time with new hormone therapy (NHT) (abiraterone 1000 mg per os with prednisone) or enzalutamide (160 mg per os) until disease progression, in patients with mCRPC previously treated with docetaxel and NHT (enzalutamide or abiraterone) with a duration of response to NHT <1 year. The study showed superiority of cabazitaxel in terms of OS and progression-free survival. Although cabazitaxel is generally better tolerated than docetaxel, this chemotherapy is sometimes poorly tolerated, particularly in elderly patients, leading clinicians to sometimes prefer the administration of a NHT with a generally better safety profile.

The authors therefore studied the subgroup of 135 elderly patients (>70 years of age) who had been included in CARD study, and compared them to patients aged <70 years ($n=120$); this subgroup analysis had been planned in the original design to study rPFS.

With regard to efficacy, the results remained in favour of cabazitaxel with an rPFS of 8.2 months on cabazitaxel versus 4.5 months on NHT (HR 0.58; 95% confidence interval [CI] 0.38–0.89). In contrast, side effects were more frequent in patients >70 years of age. Nevertheless, the percentage of side effects was relatively close between cabazitaxel and NHT with different tolerance profiles. The most frequent Grade 3 effects on cabazitaxel were asthenia, diarrhea, and febrile neutropenia. The most frequent Grade 3 effects under NHT were kidney problems and heart problems [11].

These results thus confirmed that cabazitaxel remains the treatment of choice in patients pre-treated with docetaxel and having responded within 1 year to hormonal therapy, including elderly patients.

4.2. OS analysis of patients with mCRPC receiving cabazitaxel versus abiraterone or enzalutamide

The post-hoc analyses evaluated the OS at different times and the impact of the prognostic factors. OS was calculated from the date of diagnosis of metastatic disease, the date of mCRPC, and the start of 1st, 2nd, or 3rd life-extending therapy. A multivariate Cox regression analysis evaluated the impact of 14 prognostic factors on OS using a stepwise model selection approach with a significant level of 0.10 for model entry and 0.05 for withdrawal. Median OS was longer with cabazitaxel versus abiraterone or enzalutamide (13.6 months vs. 11.0 months; HR 0.64, 95% CI 0.46–0.89; $p=0.008$).

OS was numerically improved for cabazitaxel compared to abiraterone or enzalutamide when evaluated from the time of diagnosis of metastatic disease or castration resistance, or from the start of 1st or 2nd life-prolonging

therapy. In the multivariate analysis, a low rate of hemoglobin, a high ratio of neutrophils to lymphocytes, and a high ratio of high PSA values at baseline were associated with poor OS. In the presence of these factors, the OS benefit observed with cabazitaxel versus abiraterone or enzalutamide remained significant (HR 0.63, 95% CI 0.42–0.94; $p=0.022$). These analyses confirmed the robustness of the statistically significant association between improved OS and treatment with cabazitaxel after docetaxel and progression on ADT within 12 months [9].

4.3. The impact of prostate-specific membrane antigen (PSMA) targeted imaging with positron emission tomography (PET) radiotracer, ¹⁸F-DCFPyL on clinical management of patients with biochemically recurrent PCa: results from a phase III, prospective, multicenter study (CONDOR)

The superiority of PET-PSMA over bone scan or PET-choline to detect distant lesions in PCa has already been demonstrated. Nevertheless, this examination is not yet available in routine management. Two phase III studies are currently evaluating its value in a prospective manner: the OSPREY study [10] (conducted in localised and metastatic diseases, with histology as the reference test), and the CONDOR study were presented [11].

The ¹⁸F-DCFPyL is a new radiotracer with high affinity for PSMA, antigen overexpressed by PCa cells. The objective of this study was to evaluate the role of PET-PSMA in biological relapses after local treatment (defined as a PSA >2 ng/mL compared to nadir in the case of radiotherapy treatment or a PSA >0.2 ng/mL in the case of prostatectomy). Patients, to be included, had to have a negative or contentious conventional imaging workup and be naïve to any systemic treatment.

The main assessment criterion was the concordance between the recurrence site(s) objectified by the PET-PSMA scan and the reference examinations (including one of these three items: histology, PSA evolution with radiotherapy treatment on the lodge, or dedicated morphological imaging such as magnetic resonance imaging or choline PET scan). In order to limit bias, the PET-PSMA scans were interpreted independently by three nuclear physicians. The secondary endpoint was the impact of the results of the PET-PSMA scans on the therapeutic strategy. A total of 208 patients were included. The median PSA level was 0.8 ng/mL. Depending on the nuclear medicine physician interpreting the PET scan, 60%–68% of the patients had a positive PET-PSMA scan. The rate of correct localisation of recurrence by PSMA was approximately 85%. This rate remained similar regardless of the PSA level (including in patients with PSA of <0.5 ng/mL). Management was modified by PET-PSMA in 64% of patients. In 79% of cases, this modification was related to a positive PET scan. The consequence was either a switch from local to systemic treatment for 28% of patients ($n=58$), or treatment rather than simple monitoring for 24% ($n=49$), or local curative treatment rather than systemic non-curative treatment for 21% ($n=43$) [11].

4.4. A randomised phase II trial of Lutetium 177 PSMA-617 (LuPSMA) theranostic versus cabazitaxel in mCRPC progressing after docetaxel

The LuPSMA is a ready-labelled small molecule which bonds with high affinity to PSMA, a cell surface glycoprotein over-expressed in metastatic PCa. It delivers therapeutic β -radiation to PSMA-expressing tumours, resulting in high tumour targeting but with a very limited damage to surrounding normal tissue. Encouraging efficacy and safety have been shown in non-randomised studies of mCRPC. The ANZUP 1603 study [12] is a phase II randomised trial with LuPSMA. It compared the efficacy of LuPSMA with cabazitaxel in patients with castration-resistant PCa previously treated with docetaxel in the metastatic stage. In the screening assessment, all patients underwent both fluorodeoxyglucose-PET and PET-PSMA scans, and only patients with both negative fluorodeoxyglucose-PET and positive ^{68}Ga -PET-PSMA on all secondary lesions could be included. They also had to have a biological progression and a PSA greater than 20 ng/mL.

LuPSMA was given at a dose of 8.5 GBq weekly for 6 weeks, and cabazitaxel at a dose of 20 mg/m² Q3W for up to 10 cycles. The primary endpoint was biological response (PSA decrease >50%). The biological response rate was statistically better in the LuPSMA arm compared to the cabazitaxel arm (66% vs. 34%, $p < 0.0001$). The safety profile was different; in the cabazitaxel arm, the most frequent events were diarrhea, dysgeusia, neuropathy, and neutropenia as for LuPSMA, and the most common side effects were dry eyes, dry mouth, and thrombocytopenia. However, Grades 3 and 4 side effects were more frequent with cabazitaxel (54%) than with LuPSMA (35%).

This study is the first to compare LuPSMA to a systemic therapy that has demonstrated efficacy in mCRPC. The results on the biological response rate seem promising in this population of patients with PSMA positive PCa. We are waiting to see if the superiority of LuPSMA over cabazitaxel will also be seen in progression-free survival (secondary endpoint) [12].

4.5. Immunotherapy in mCRPC

4.5.1. KEYNOTE-199 cohort (C) 4 and C5: Phase II study of pembrolizumab (Pembro) plus enzalutamide for enzalutamide-resistant mCRPC

Previous studies have suggested Pembro with enzalutamide activity in enzalutamide-resistant patients. KEYNOTE-199 is a multicohort phase II study. C4 (RECIST-measurable disease) and C5 (bone-predominant disease) tested this combination (Pembro with enzalutamide) in chemotherapy-naïve patients with mCRPC and having progressed on enzalutamide. In this study, patients with or without prior abiraterone had clinically significant response and benefit to enzalutamide followed by disease progression. These patients received Pembro 200 mg Q3W with continuation of enzalutamide for up to 35 cycles or until progression or intolerable toxicity.

The main objective of the study was to determine the objective response rate (ORR) by RECIST. For C4 patients, the ORR was 12% and the median ORR was 6 months. The delay median time before PSA progression was 4 months in C4 and 4 months in C5. The median rPFS was 4 months for

C4 and 4 months for C5. The median OS was not achieved in C4 [13].

The addition of Pembro to enzalutamide after enzalutamide-resistance was objective to have modest antitumor activity in patients with mCRPC.

4.5.2. Pembro plus olaparib in patients with docetaxel-pretreated (KEYNOTE-365 cohort): an efficacy, safety, and biomarker results

Pembro with olaparib has shown antitumour activity and acceptable safety in docetaxel-pretreated patients with mCRPC enrolled in KEYNOTE-365 study [14].

Updated results with new biomarker data were reported. Patients with mCRPC pretreated by who progressed within 6 months of screening received Pembro 200 mg iv Q3W with olaparib 400 mg capsule or 300 mg tablet twice a day. They might have received one other chemotherapy and less than two lines of second generation ADT. Eighty four of the 87 included patients were treated; 48/84 (57.1%) had measurable disease; confirmed PSA response rate was 9% (95% CI 3.5%–16.8%) in 82 patients with a baseline assessment of the PSA. Median time to progression of PSA was 3.8 months (95% CI 2.9–4.4 months). In 24 patients with measurable disease and follow-up ≥ 27 weeks, the ORR was 8.3%. In all patients, the median rPFS was 4.3 months and the median OS was 14.4 months. The rate of treatment related AEs of Grade ≥ 3 was 35% [14]. The combination of Pembro with olaparib continued to show acceptable activity and safety in patients with mCRPC pretreated with docetaxel. A phase III study of this combination is ongoing (KEYLYNK-010, NCT03834519).

5. Conclusion

Recent findings were discovered concerning PCa during the 2020 ASCO international congress; relugolix, a novel oral GnRH antagonist allows a rapid sustained castration in advanced setting. nmCRPC can now be treated with three molecules: apalutamide, enzalutamide, or darolutamide. As for metastatic castration resistant setting, treatment with cabazitaxel improved OS including elderly patients after progression on docetaxel and on ADT. PET-PSMA in men with biochemically relapsed PCa was confirmed to be performant even at very low PSA values. Furthermore, Lutetium 177 PSMA-617 was more efficient than systemic treatment at the metastatic castration resistant stage whereas more studies evaluating the efficacy of immunotherapy are still in progress in this setting.

Author contributions

Study concept and design: Nora Naqos

Data acquisition: Nora Naqos

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Drafting of manuscript: Nora Naqos, Wafaa Kaikani

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Conflicts of interest

The authors declare no conflict of interest.

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21 January 2021