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European Association of Urology

Platinum Opinion

Use of Chemotherapy and Androgen Signaling–targeted Inhibitors in Patients with Metastatic Prostate Cancer

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In metastatic hormone-sensitive prostate cancer, docetaxel or androgen receptor (AR)-targeted therapies in combination with androgen deprivation therapy (ADT) are the standard of care. AR-targeted therapies are also used in high-risk nonmetastatic castration-resistant disease to prolong metastasis-free and overall survival [1]. For metastatic castration-resistant PC (mCRPC), taxanes (docetaxel, cabazitaxel) and AR-targeted therapies (abiraterone, enzalutamide) are also approved and widely used [1]. The optimal treatment sequence remains to be fully established; treatment choices may depend on patient health status, disease characteristics, patient and physician preferences, and treatment costs.

In real life, many patients receive both AR-targeted therapies sequentially (back-to-back) before receiving chemotherapy [2]. These agents are routinely prescribed and have an established safety profile. While the decision to use back-to-back AR-targeted therapies is probably driven by patient fears about chemotherapy toxicity, the suitability of such an approach is questionable. Because these agents target the AR pathway, cross-resistance is significant. Indeed, most patients progressing on abiraterone respond poorly to subsequent enzalutamide, and vice versa [3]. In a recent prospective, crossover study in patients with newly diagnosed mCRPC who received abiraterone until prostate-specific antigen (PSA) progression and then enzalutamide, or the inverse sequence, the median time to PSA progression after receiving the second AR-targeted therapy was less than 3 mo for either treatment arm [3].

Given the poor response of patients with mCRPC to a second AR-targeted therapy, the use of chemotherapy instead may offer a benefit. A real-world evidence study suggested that clinical outcomes were better among patients with mCRPC receiving taxanes after early progression on prior AR-targeted therapies when compared to those receiving sequential AR-targeted therapies [2]. However, until recently, no trial data were available to guide treatment for patients in this setting.

Results from the pivotal CARD study were reported at the European Society for Medical Oncology 2019 meeting and simultaneously published in the *New England Journal of Medicine* [4]. CARD compared the efficacy and safety of cabazitaxel versus abiraterone or enzalutamide in patients with mCRPC who had previously received docetaxel and progressed within 12 mo on the alternative AR-targeted therapy (Fig. 1). Patients ($n = 255$) were randomly assigned 1:1 to cabazitaxel or the alternative AR-targeted therapy (abiraterone or enzalutamide) until radiographic progression, unacceptable toxicity, the start of subsequent treatment, or patient request to discontinue treatment. CARD met its primary endpoint; patients receiving cabazitaxel had significantly longer radiographic progression-free survival (PFS) than patients receiving abiraterone or enzalutamide (Fig. 1). Key secondary endpoints including overall survival (OS), PFS, and PSA and tumor responses were also all significantly better with cabazitaxel than with abiraterone or enzalutamide. Cabazitaxel significantly reduced the risk of death by 36% [4]. Furthermore, cabazitaxel significantly improved pain responses (45.0% vs 19.3%; $p < 0.0001$), time to pain progression, and time to symptomatic skeletal events in comparison to abiraterone or enzalutamide. Lastly, there was no deleterious effect of cabazitaxel on patient-reported outcomes when compared to abiraterone or enzalutamide [4,5].

In a post hoc analysis evaluating the impact of AR-targeted therapy sequence (abiraterone followed by enzalutamide or vice versa) on the CARD primary endpoint, radiographic PFS (rPFS) remained significantly longer for

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https://doi.org/10.1016/j.eururo.2020.10.016

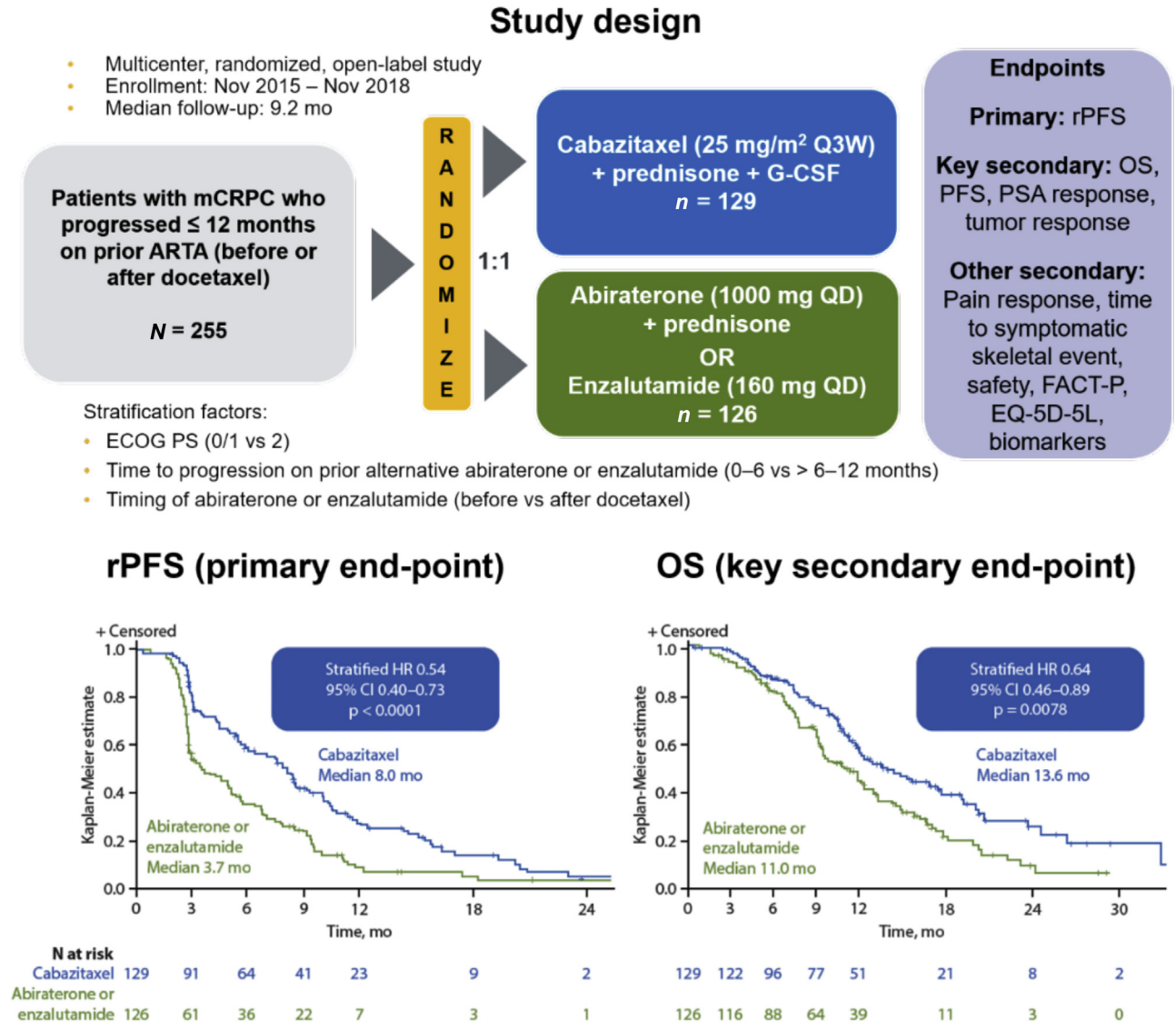

Fig. 1 – Results for the CARD trial. The duration of one cycle was 3 wk in each arm. Treatment was continued until image-detected progression, unacceptable toxicity, or further study treatment. ARTA = androgen receptor–targeted agent; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; G-CSF = granulocyte colony-stimulating factor; HR = hazard ratio; HRQoL = health-related quality of life; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; QD = once daily; Q3W = every 3 wk; rPFS = radiographic PFS.

patients receiving cabazitaxel compared with the second AR-targeted therapy whatever the sequence (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.36–0.90 vs enzalutamide; HR 0.44, 95% CI 0.29–0.67 vs abiraterone).

A key consideration is whether the CARD population reflects typical mCRPC patients in clinical practice. CARD enrolled patients who had experienced progression within 12 mo of starting an AR-targeted therapy. This included patients who had PSA progression within 12 mo but received treatment for a longer period of time [4]. In the pivotal registration studies in the pre- and post-docetaxel setting, treatment with abiraterone and with enzalutamide resulted in a median time to PSA progression (PSA-PFS) of <12 mo in all four trials, but many patients were kept on treatment until rPFS, in accordance with the protocols. In addition, in a recent randomized trial of abiraterone and enzalutamide in chemotherapy-naïve mCRPC, the median PSA-PFS on first-line treatment was <8 mo for both agents [3,6–9]. Hence, CARD reflects clinical practice for the majority of patients. One-fifth of the patients in CARD had continued the first AR-targeted therapy for >12 mo. Among these 44 patients, the probability of no radiographic progression at 3 mo similarly favored cabazitaxel over AR-targeted inhibitors (80.4% vs 56.7%), and the HR for rPFS for these patients (0.59, 95% CI 0.27–1.30) was identical to that for the total patient population (Supplementary Table 1).

Although many patients receive sequential AR-targeted therapies in the clinic, the CARD data demonstrate that cabazitaxel is the superior option for patients with mCRPC who previously received docetaxel and experienced progression within 12 mo on a prior AR-targeted therapy [4]. Although chemotherapy is often perceived as a “last

resort" treatment option, it is important to consider that if chemotherapy is delayed, the patient may become too frail to receive treatment. In the CARD study, of patients in the abiraterone or enzalutamide treatment arm who experienced progression, 22.2% went on to receive palliative radiotherapy as their first subsequent therapy and 35.7% received no subsequent therapy, suggesting that more than 50% of those with progression may have lost the window of opportunity to receive systemic treatment [4].

It is clear that for many patients, sequential use of AR-targeted therapies is associated with worse outcomes and should be avoided. There is now level 1 evidence that cabazitaxel doubles rPFS and robustly reduces the risk of death compared with crossover between abiraterone and enzalutamide for patients previously treated with docetaxel and the alternative AR-targeted therapy. These recent study results firmly establish the preferred use of cabazitaxel over abiraterone or enzalutamide as the standard of care in this setting, and this applies for the majority of patients previously treated with an AR-targeted agent and docetaxel.

Conflicts of interest: Ronald de Wit has received speaker or advisory fees from Merck, Sanofi, Astellas, Janssen, Roche, and Bayer, and institutional research grants from Sanofi and Bayer. Bertrand Tombal has received advisory fees from Amgen, Astellas, Bayer, Janssen, Ferring, Myovant, and Sanofi. Stephen Freedland has received advisory fees from Astellas, Pfizer, Bayer, Janssen, Ferring, Merck, AstraZeneca, Myovant, Clovis, and Sanofi.

Acknowledgments: The research and analysis for the CARD study were supported by Sanofi. The authors are responsible for all content and editorial decisions and received no honoraria for development of this commentary. The sponsor was involved in the design and conduct of the study; data collection, management, and analysis; and approval of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.10.016.

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