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EDITORIAL

Adding Androgen-Receptor Pathway Inhibition with Enzalutamide to Androgen Deprivation Therapy in Prostate Cancer Patients with High-Risk Biochemical Relapse: New Options, New Challenges

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Dear Colleagues,

The positive results of the phase III EMBARK trial (NCT02319837)[1] recently led to extended approval of the androgen receptor pathway inhibitor (ARPI) enzalutamide in prostate cancer (PCa). This study defined a new group of patients with high-risk, biochemically relapsed, non-metastatic (on conventional imaging) hormone-sensitive PCa according to the following inclusion criteria: prostate-specific antigen (PSA) ≥1 ng/mL after radical prostatectomy (RPE) as prior definitive curative treatment and >2 ng/mL after curative radiotherapy (RT), PSA doubling time (PSAdt) ≤9 months and testosterone ≥150 ng/dl. Patients (n=1068) were randomized 1:1:1 to receive androgen deprivation therapy (ADT), ADT plus enzalutamide or enzalutamide monotherapy. The primary endpoint was metastasis-free survival (MFS) with ADT versus ADT plus enzalutamide. The key secondary endpoint was MFS with ADT versus enzalutamide monotherapy and other secondary endpoints included overall survival (OS), safety, time to PSA progression and time to first new antineoplastic therapy. Treatment was suspended after 36 weeks in case of PSA <0.2 ng/mL and re-challenged if PSA was ≥5 ng/ml without prior RPE and ≥2 ng/ml with prior RPE. Patients who did not reach PSA <0.2 ng/ml at Week 36 continued the assigned treatment until progression to metastasis. The study was reported to be positive for its primary endpoint of MFS (ADT vs ADT plus enzalutamide) at the American Urology Association (AUA) meeting already in 2023[2] and consequently published in the New England Journal of Medicine.[1] In summary, the addition of enzalutamide to ADT was superior compared to ADT monotherapy (HR: 0.42 [95% CI: 0.31–0.61]) in prolonging MFS. The key secondary endpoint of interest was the comparison between enzalutamide monotherapy and ADT. Enzalutamide monotherapy also demonstrated statistically significant and clinically meaningful improvements in MFS (HR: 0.63 [95% CI: 0.46–0.87; p=0.0049), time to PSA progression and time to first new antineoplastic therapy. OS data are still pending; health-related quality of life (HRQoL) data were presented twice

at the European Society for Medical Oncology (ESMO) Annual Congress 2023[3] and recently at the Annual Meeting of the American Society of Clinical Oncology (ASCO) 2024.[4]

The EMBARK study has brought up two novelties: first, the concept of de-escalation with intermittent treatment in a high-risk biochemical relapse PCa population, including an ARPI in addition to ADT or as monotherapy; and second, the use of enzalutamide without testosterone suppression.

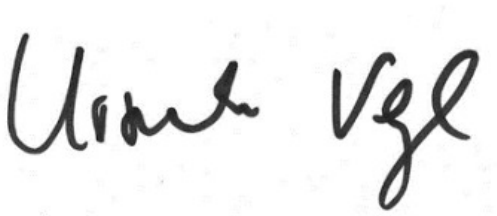
The results are encouraging for patients with biochemical relapse after curative treatment who are at high risk for the development of metastases. It is important to underline that enzalutamide showed a significant benefit in combination with ADT compared to ADT monotherapy. Therefore, patients with the characteristics of the inclusion criteria of EMBARK should be offered the addition of enzalutamide to ADT with the concept of de-escalation after nine months in case of PSA <0.2 ng/mL. The magic goal of reaching a nadir of 0.2 ng/mL (mostly at seven months) has been demonstrated in metastatic hormone-sensitive PCa in various prospective trials to be prognostic for ADT monotherapy, as well as for combination treatments with docetaxel and ARPIs.[5-9] Therefore, there is a strong rationale for suspending treatment in case of this deep and favorable PSA response.

The EMBARK study also showed us interesting results with enzalutamide monotherapy without testosterone suppression, which seems to be superior to ADT. Enzalutamide monotherapy is an option in selected cases in which ADT is not feasible or the patient strongly opts to avoid ADT. Notably, the toxicity of enzalutamide monotherapy is not negligible. EMBARK reports grade 3 toxicity with 5.9% cardiovascular events, 4.8% fatigue, falls, fractures and hypertension in the range of ADT monotherapy or combination treatment, but a significant percentage of all-grade gynecomastia (45%) and nipple pain (15.6%). Gynecomastia is a typical adverse event associated with ARPIs in the absence of testosterone suppression that influences the patient's QoL. In the EMBARK trial, no prophylaxis guidance was foreseen in the protocol against gynecomastia; in real-world practice, prophylactic breast radiation before starting enzalutamide or even treatment with tamoxifen must be discussed. One would assume that sexual functioning and activity were better in patients who received enzalutamide monotherapy. As reported in the HRQoL data from EMBARK, sexual activity was slightly better in enzalutamide monotherapy, but not sexual functioning. Although testosterone is not suppressed with enzalutamide monotherapy, these patients pre-treated with curative local treatment (prostatectomy, radiotherapy or both) have impaired baseline sexual functioning, and the median age of patients is approximately 70 years; therefore, these results are not surprising. A quite complex analysis of longitudinal change in HRQoL in patients who suspended treatment after Week 37 until Week 109, was recently presented at

the ASCO annual meeting in Chicago.[4] Interestingly, there was no significant change and, therefore, no improvement after treatment suspension in various QoL categories.

In summary, the positive EMBARK phase III study led to the approval of enzalutamide in combination with ADT by Swissmedic in high-risk PCa patients with biochemical relapse and is a new therapeutic option. Implementation of modern imaging with prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET-CT) will identify more patients being metastatic hormone-sensitive (mostly low volume) with the biochemical characteristics of EMBARK, since EMBARK used only conventional imaging.[10]

Best wishes,



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Conflict of interest

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