Prostate cancer

Many interesting studies in the field of prostate cancer (PC) were presented at ESMO 2024. In my opinion three studies deserve to be highlighted: one in the localized setting, one in the metastatic hormone-sensitive setting (mHSPC) and one in the metastatic castration resistant setting (mCRPC).

A large randomized study in patients with localized PC planned to undergo androgen deprivation therapy (ADT) evaluated the use of transdermal oestradiol (te2) compared with LHRH analogue (LHRHa) (1). It is known that LHRHa cause hot flushes which negatively affect patients' quality of life (2). LHRHa also cause long-term side effects such osteoporosis, metabolic syndrome and cardiovascular events (3). The rationale of using te2 to achieve castration is to reduce these side effects compared to LHRHa. This phase 3 non-inferiority study showed that te2 is non-inferior to LHRHa regarding metastasis free survival (MFS) and overall survival (OS) and it achieved a similar castration rate. In terms of side effects, a reduction in hot flushes (44% vs 89%) was seen on te2, but it had a greater risk of developing gynecomastia (85% vs 42%). No data on cardiovascular events, bone health or metabolic syndrome were presented. Transdermal estrogen appears to be an interesting option but many questions remain especially regarding prophylaxis of gynecomastia and patient compliance (need to change 4 patches twice per week). Finally, only data from non-metastatic patients were presented so we do not know the effect of this therapy in patients with metstatic disease who should receive an ARPI.

ARANOTE study

The ARANOTE study was done in the mHSPC setting. This is a phase 3 study evaluating the benefit of the addition of darolutamide to ADT (4). It demonstrated a statistically significant reduction (-46%) in the risk of radiographic progression (rPFS) compared to ADT alone (primary endpoint). Although the overall survival (OS) is still immature, I think that darolutamide could become a new therapeutic option in addition to ADT in patients with mHSPC. It is important to emphasize the very favorable toxicity profile of darolutamide, almost similar to placebo. The only side effect that seems to increase with darolutamide is bone fractures highlighting the importance to evaluate bone health in all patients with mHSPC. Overall this is a potentially practice-changing study altough we have to wait final OS data.

PEACE-3 study

Finally, in the mCRPC setting, the PEACE-3 study was presented by Prof. Silke Gillessen at the plenary session (5). This study demonstrated that the combination of enzalutamide + radium-223 improved radiographic progression-free survival (rPFS) compared to enzalutamide monotherapy in patients with mCRPC and bone metastases. A combination therapy between radium-223 and an androgen receptor pa-

thway inhibitor (ARPI) had already been evaluated in the ERA-223 study (abiraterone + radium-223) (6). However, this trial was unblinded early after more fractures and deaths were observed in the experimental arm. Analyzing the fractures, it was found that in the majority of cases they were osteoporotic and non-pathological. Following the release of the ERA-223 data, the PEACE-3 study was amended with an urgent safety letter to investigators: bone protecting therapy with either zoledronic acid or denosumab became mandatory at the monthly dose. The introduction of bone potecting agents (BPA) achieved a massive reduction in the risk of fractures in both treatment arms, further underlining the importance of BPA in this setting (7). In view of the changed landsacpe where the vast majority of patients receive an ARPI-based therapy (8) in the mHSPC setting the impact of the findings of PEACE-3 is difficult to estimate since only 2-3% of the patients received an ARPI (abiraterone) in this trial. However, for patients with mCRPC and bone metastases who received ADT or ADT + docetaxel in mHSPC setting, enzalutamide + radium-223 represents a new standard of care. □

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