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The earlier the better? Apalutamide for non-metastatic castration resistant prostate cancer

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Until very recently, patients with non-metastastic castration resistant prostate cancer (nmCRPC, M0CRPC) and rising prostate-specific antigen (PSA) despite a low testosterone level on androgen deprivation therapy (ADT) were managed either with endocrine manipulations (without a proven survival benefit) or watched with repeated PSA testing. The European Association of Urology guidelines 2018[1] did not recommend treatment for such patients outside a clinical trial setting. However, 86% of experts at the St Gallen Advanced Prostate Cancer Consensus Conference 2015[2] would have offered patients secondary hormone therapies without any evidence of benefit in randomised controlled trials and in particular without a proven survival benefit or any other clinically meaningful advantage besides a potential PSA reduction. The National Comprehensive Cancer Network guidelines listed several such secondary hormonal therapies in particular, for patients with a short PSA-doubling time (PSA-DT).[3] The risk for metastatic disease and death has been shown to increase significantly with a shortening PSA-DT, therefore highlighting an unmet need for the treatment of nmCRPC. The cut-off period has been determined to be 10 months.[4]

Several considerations must be sort out when focusing on this unmet need; measurable and non-measurable parameters and those that are equally as important to the stakeholders.

- Reducing patients' anxiety and physicians' unease when observing an increase in PSA levels.
- Anticipation of a substantial risk for apparent metastases in the very near future.
- Concerns that obvious metastases would give rise to complications and symptoms such as pain, skeletal events and medical interventions. It is not given that severe medical events could be prevented or controlled in time with a more delayed treatment approach with approved drugs for metastatic castration resistant prostate cancer (CRPC) (mCRPC).
- Concerns that the window of opportunity to improve outcome might get lost.

IS EARLIER TREATMENT REALLY BETTER AND HOW BEST TO PROVE IT?

Treating asymptomatic patients who are non-metastatic on conventional imaging with drugs that have potential side effects implicates the responsibility to prove a relevant benefit.

In general, drug treatments should improve lives and allow patients to live longer. For metastatic hormone-naive prostate cancer, earlier use of docetaxel or abiraterone acetate with prednisolone demonstrated a significant overall survival (OS) benefit while maintaining quality of life (QoL) versus standard of care (SOC). However, the unequivocally convincing endpoint of OS becomes more and more difficult to implement in current clinical trials. The pressure for intermediate clinical endpoints that could serve as surrogates for OS is increasing with the rapid development of prostate cancer therapies. For example, in hormone sensitive and still localised prostate cancer, the metastasis-free survival endpoint showed to be a strong surrogate of OS. This was evaluated in patients with a 15% chance of dying of the disease over a 10-year period despite potentially curative local therapy and independent of adjuvant and other subsequent therapies.[5] Surrogate endpoints have the potential to facilitate future drug development, and faster as well as less expensive clinical trials.

Following the recent presentation of two randomised controlled trials for nmCRPC (SPARTAN, NCT01946204, apalutamide vs placebo and PROSPER, NCT02003924, enzalutamide vs placebo), a lively debate

argued the suitability and appropriateness of using MFS as the primary endpoint for nmCRPC.

Delaying metastases in CRPC has been endorsed as a new endpoint in prostate cancer trials by the Food Drug Administration (FDA) based on intensive discussions by the Oncologic Drugs Advisory Committee as elucidated by Beaver *et al*.[6] Confirmation in a draft FDA guidance for clinical trial sponsors stated that consideration will be given for the use of MFS as an endpoint inferring its appreciation in long-term diseases such as nmCRPC (with many years to develop fatal events) since it has become increasingly difficult to use OS rates as a primary endpoint in clinical trials.[7]

In November 2018, the Committee for Medicinal Products for Human Use recommended the granting of a marketing authorisation for apalutamide (Erleada), for the treatment of nmCRPC. Apalutamide is an oral selective androgen receptor inhibitor that binds directly to the ligand binding domain of the androgen receptor. It is the first approved indication for this agent: 'Erleada is indicated in adult men for the treatment of non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease'.[8]

Recommendation was based on the results from the SPARTAN data, a randomised double-blind, placebo-controlled phase 3 trial,[9] that included patients with nmCRPC based on imaging with CT, bone scan and with a PSA-DT ≤10 months. Stratification was according to PSA-DT being above or below 6 months, the use of bone sparing agents and for local or regional lymph nodes (N0 vs N1). The primary endpoint was MFS defined as the time from randomisation to the first detection of distant metastasis on imaging or death. Secondary endpoints included OS and progression-free survival (PFS), in particular PFS2.

In a 2:1 fashion, 1207 men were randomised to receive apalutamide or placebo. The median MFS in the apalutamide group was 40.5 months compared with 16.2 months in the placebo group (HR 0.28, 95% CI 0.23 to 0.35). This impressive gain in more than 2 years metastasis free or 72% reduction in the risk of developing metastases or death was highly statistically significant. Other secondary endpoints such as time to symptomatic progression (HR 0.45, 95% CI 0.32 to 0.63) for apalutamide versus placebo, respectively, were also significant.

From a clinical perspective, the results were very encouraging with respect to subsequent treatments and the exploratory endpoint of PFS2 (PFS was measured from randomization until second documented progression or death). A total of 52.5% of patients who discontinued treatment in the apalutamide group received subsequent approved therapies for mCRPC and 77.8% in the placebo group (mostly abiraterone acetate plus prednisolone in both groups). PFS2 was significantly longer for apalutamide-treated patients (HR 0.49, 95% CI, 0.36 to 0.66) which alleviates prior concerns that subsequent treatments may no longer be effective after extensive pretreatment with apalutamide and thus reduce the chance of an OS benefit. The secondary endpoint in the SPARTAN trial was OS, which showed a positive trend; however, the data were premature at the time of data cut-off for the first presentation and publication.[9] QoL was maintained despite the addition of apalutamide to ADT versus placebo which strengthens the actual clinical benefit requirement for patients. Overall, apalutamide was well tolerated. The most reported side effects were fatigue, skin rash, weight decrease, arthralgia, fractures and falls. The full publication supplement includes a chapter on rash data, outcome and management.

Of note, similar results were recently published with enzalutamide in the PROSPER trial.[10]

To support the MFS surrogacy for OS, individual patient-level data from SPARTAN were used to undertake a landmark analysis for MFS. It was concluded that MFS has a significant association with OS and is predictive of OS in high-risk nmCRPC. Patients who developed metastases at 6, 9 and 12 months had significantly shorter median OS compared with patients without metastasis, for example, 12 months (n=230 patients with metastases): HR for OS 6.95 (95% CI 4.59 to 10.53).[11]

Earlier treatment of CRPC with apalutamide provides a meaningful clinical benefit with a significant improvement in MFS, and a favourable toxicity profile while maintaining QoL. MFS has been accepted as a valid endpoint for nmCRPC. The European Medicines Agency (EMA) recommended approval of apalutamide for nmCRPC patients at high risk for developing metastasis. Publication of EMA's full scientific assessment report is awaited following the implementing decision by the European Commission. The FDA approved apalutamide highlighting the consideration regarding PSA-DT and the actual risk of developing metastasis at the discretion of the treating physician and the discussion with the patients.[6] A similar indication was recommended for enzalutamide: the treatment of adult men with high-risk nmCRPC.[12]

Finally, the time is over for placebo-controlled trials in nmCRPC since apalutamide and enzalutamide can now serve as valid controls. More trials are required to move known drug combinations and new agents earlier up in the treatment sequence including the nmCRPC setting.

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