Highlights in Prostate Cancer from ESMO 2021

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Findings from the STAMPEDE trial present a new standard of care in high-risk, localized non-metastatic prostate cancer

Prior to ESMO 2021, 20% of localized prostate cancers were considered high risk at diagnosis, accounting for the majority of relapses and deaths. Androgen deprivation therapy (ADT) is recommended for 2–3 years in combination with local radiotherapy to the prostate and pelvis, which improves life expectancy. The addition of docetaxel has been shown to prolong the time to relapse but did not prolong the overall survival (OS) in this patient population. The practice-changing STAMPEDE trial is a multi-arm, multi-stage trial ongoing at over 100 hospitals in the UK and Switzerland where patients with either high risk, localized or locally advanced (M0) or metastatic disease (M1) were enrolled.[1] The primary results showed that a consistent OS benefit was observed by the addition of abiraterone acetate and prednisolone (AAP). The STAMPEDE trial focused on high-risk localized or locally advanced prostate cancer patients who were given abiraterone in addition to ADT. Overall, 1,974 enrolled patients underwent conventional imaging and bone scan.[2] Patients were either N1, positive disease, non-metastatic high risk or N0 with ≥2 of the following characteristics: either clinical stage T3 or T4, prostate-specific antigen (PSA) level ≥40 ng/ml and a Gleason score of ≥8. A small proportion of patients were enrolled who relapsed after curative local treatment with radical prostatectomy or radiotherapy as well as a PSA score ≥40 ng/ml (rising) and a PSA doubling time <6 months. Patients with N1 disease constituted 39% of the population, 3% of whom had suffered a relapse. Patients were randomized 1:1 to either standard of care (ADT for three years plus radiotherapy), or standard of care (SOC) plus AAP for two years. At a median follow-up of 72 months, there was a significant improvement in 6-year metastasis-free survival, from 69-82%, with the addition of abiraterone to the standard of care ADT (HR: 0.53 [95% CI: 0.44–0.64]; p=2.9 x 10^{-11}).[2] In addition, 6-year OS improved from 77-86% after 72-month follow-up (HR: 0.60 [95% CI: 0.48–0.73]; p=9.3 x 10^{-7}). However, the addition of enzalutamide to AAP was related to a higher rate of high-grade toxicities and had no important effect on efficacy. Overall, the findings of the STAMPEDE trial showed that abiraterone in combination with prednisolone and ADT should be the new standard of care for high-risk, localized non-metastatic prostate cancer and patients should be informed of this treatment option if they fulfill the STAMPEDE inclusion criteria (thus not yet approved).

Triplet therapy: A potential first-line treatment in *de novo* mHSPC

The PEACE-1 trial is a phase III study with a 2x2 factorial design which investigated men with *de novo* metastatic castration-sensitive prostate cancer (mCSPC).[3] The primary endpoint of this study was OS. Patients were enrolled if they possessed distant metastatic disease of ≥1 lesion on bone scan and/or CT scan, as well as an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0–2. Patients were also required to maintain ADT therapy throughout the study. Randomization was 1:1:1:1 where patients (n=1173) received either standard of care (SC), which in this study was ADT plus docetaxel or SOC plus abiraterone or SOC plus radiotherapy or a triplet therapy of SOC plus abiraterone plus radiotherapy. The first co-primary endpoint was radiographic progression-free survival (rPFS) with abiraterone in the ADT plus docetaxel population. The majority of the patients (63%) had a high disease burden and a high proportion of patients (80%) had bone disease. There was a highly significant benefit of adding abiraterone to SOC with a median rPFS of 4.5 years compared with 2 years of SOC alone (HR: 0.50 [95% CI: 0.40–0.62]; p<0.0001).[3] The second co-primary endpoint OS was reported with a median not yet reached in the SOC plus abiraterone arm versus 4.4 years in the SOC alone group (HR: 0.75 [95% CI: 0.59–0.95]; p=0.017). Docetaxel is known to be beneficial in patients with high volume disease as reported in the CHAARTED trial;[4] this benefit is pronounced in the high volume population, with a median OS of 5.1 years versus 3.5 years in the SOC alone group (HR: 0.72). Toxicity is not elevated with the addition of docetaxel to abiraterone as initially feared, thus the quality of life data have not been reported yet. Prevalent side effects pertained to those typical of abiraterone, such as hypertension and hypokalemia. Subsequent therapy for patients under the triplet regimen included 60% of whom received cabazitaxel, which is the approved SOC for patients with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel failure. Overall, docetaxel plus ADT plus abiraterone/prednisone should be considered the new standard of care for *de novo* metastatic hormone-sensitive prostate cancer (mHSPC) patients with a high-volume disease deemed fit for the triplet approach. In high volume *de novo* mHSPC, there has been a prolongation in OS of 1.5 years in these patients. The treating physicians are obliged to inform patients with these characteristics of the significant benefit. The results of the arm with additional radiotherapy have to be awaited as additional information and the quality of life data. The triplet approach is promising but not yet approved and is considered off-label treatment as of now.

Lutetium-117 PSMA-617 improves the quality of life in patients with mCRPC

Quality of life data from the practice-changing, phase III VISION study of Lutetium-177 (^{177}Lu)-prostate-specific membrane antigen (PSMA)-617 has recently been reported in patients with mCRPC.[5] The OS benefit justifies it is one of the standards of care in pretreated mCRPC patients and will hopefully soon be approved in Switzerland. The treatment is generally well-tolerated and delayed the time to worsening in health-related quality of life (HRQoL) and the time to first symptomatic skeletal event versus the protocol permitted standard of care alone.

Enzalutamide plus ADT shows long-term survival benefit in patients with mHSPC

In addition, final OS data from the phase III ARCHES trial after 44 months of follow-up has been reported.[6] Patients with mHSPC were randomized to either enzalutamide plus ADT or placebo plus ADT. While patient crossover was permitted, the benefit of the addition of enzalutamide to ADT versus placebo continued in this long-term follow-up. After 44 months, 71% of patients were alive in the enzalutamide combination arm, compared to 57% in the placebo plus ADT arm. ADT plus enzalutamide is one of the established standards of care in *de novo*, metachronous, high and low-volume mHSPC patients.

Darolutamide maintenance is a promising option in patients with mCRPC

In the randomized, double-blind, phase II, SAKK 08/16 trial, darolutamide maintenance was investigated in mCRPC patients, previously treated with novel hormonal agents (NHA) and non-progressive to taxane treatment.[7] In routine practice, after taxane treatment in mCRPC, patients usually initiate a treatment break continuing with ADT alone after a certain amount of chemotherapy cycles. Darolutamide is a novel hormonal agent with a favorable side effect profile, making it ideal for maintenance therapy. The primary endpoint of rPFS at 12 weeks was met in this study with darolutamide maintenance. The data reported from this study warrant further investigation of darolutamide maintenance in a phase III trial.

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