Nature Reviews Urology **11**, 243 (2014); published online 29 April 2014; doi:10.1038/nrurol.2014.98

PROSTATE CANCER

Enzalutamide impresses in European studies

Enzalutamide continues to extend its potential in men with prostate cancer. New data, published in the *Lancet Oncology*, suggest it might be a viable alternative to castration for patients with advanced disease, and subpopulation analysis of the PREVAIL study, presented at the European Association of Urology (EAU) annual meeting in Stockholm, confirms its benefit as first-line therapy for European patients with castration-resistant prostate cancer (CRPC).

The study published in the *Lancet Oncology* is a primary analysis of the first phase II trial of enzalutamide monotherapy in men with hormone-naive prostate cancer. Patients with advanced disease are usually treated with androgen deprivation therapy (ADT), which can be surgical (bilateral orchiectomy) or medical (with luteinising hormone-releasing hormone analogues), but these options are hampered by adverse effects caused by low testosterone levels, including sexual dysfunction, decreased bone mineral density and loss of muscle mass.

The possibility of replacing these methods of castration with a nonsteroidal antiandrogen has previously been explored with the androgen receptor inhibitor bicalutamide, with mixed results. However, encouraging findings for enzalutamide—another androgen receptor inhibitor—in clinical studies of men with CRPC and in preclinical experiments provided the rationale for researchers to evaluate its efficacy in patients who would normally undergo ADT.

For this study, 67 men with hormone-naive prostate cancer, noncastration levels of testosterone (≥8 nmol/l), PSA ≥2 ng/ml, ECOG performance status of 0 and a life expectancy of ≥12 months were enrolled at 12 centres across Europe to receive 160 mg enzalutamide daily for 24 weeks. These selection criteria led to a cohort of patients with various stages of disease; 26 men had metastases, 16 patients had previously received radiotherapy and 24 men had undergone prostatectomy.

In the absence of established clinical trial end points for agents tested in hormone-naive prostate cancer, the investigators chose PSA response as the primary outcome of this study. At week 25, 62 men (92.5% of the cohort) had achieved a PSA decline of ≥80%; the remaining four patients discontinued treatment early and were classified as nonresponders. Moreover, 30 patients (45%) had undetectable PSA levels (≤0.1 ng/ml) at this time point. These responses are similar to those reported for patients treated with luteinising hormone-releasing hormone analogues, orchiectomy or the gonadotropin-releasing hormone antagonist degerelix.

Men who received enzalutamide experienced a boost in testosterone levels compared with baseline, providing a benefit over ADT in terms of hot flushes (experienced by 18% of patients) and bone mineral density, which remained largely stable throughout the study period. Lean body mass decreased by 4.1% and fat mass increased by 6.9%; these changes were considered small by the investigators but they refrain from making any conclusions in the absence of long-term outcomes.

However, high testosterone levels bring adverse effects of their own, including gynaecomastia (reported by 36% of patients), nipple pain (19%) and breast pain (6%). No additional treatment was needed, and no patients discontinued treatment owing to these breast-related events, so enzalutamide was considered well-tolerated in this cohort.

These promising findings suggest that enzalutamide monotherapy might be considered early in the disease process to treat men with hormone-naive prostate cancer of varying severity, and it is hoped that future trials will be developed to overcome the limitations of this single-arm, short-term study.

Meanwhile, evidence continues to accumulate in support of prechemotherapy administration of enzalutamide for men

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with CRPC, with release of the European subanalysis of the phase III PREVAIL study. Bertrand Tombal, one of the lead investigators of the trial, presented the data in the Late Breaking News plenary session of the 29th Annual EAU Congress in Stockholm on the 15th of April.

PREVAIL was halted in October 2013 owing to the unprecedented benefits in overall survival and radiographic progression-free survival experienced by patients who received enzalutamide compared with placebo. 53% of the 1,715 men enrolled in this trial were from Europe, and Tombal took to the stage to reassure clinicians and patients that geographical location did not affect these positive results.

Consistent with the overall data, radiographic progression-free survival (13.8 months versus 3.8 months for placebo; HR 0.21), initation of chemotherapy (at 26 months versus 9.9 months for placebo; HR 0.34) and adverse event profile were significantly better for men who received enzalutamide.

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Original articles Tombal, B. *et al.* Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol.* doi:10.1016/S1470-2045(14)70129-9 | Tombal, B. *et al.* Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC): Primary and European regional results of the phase 3 prevail study [abstract LBA3]. Presented at the 29th Annual EAU Congress (Stockholm).