Editorial

Enzalutamide (formerly MDV3100) prolongs survival in docetaxel-pretreated castration-resistant prostate cancer patients

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Until lately, castration-resistant prostate cancer (CRPC) patients who progressed following docetaxel chemotherapy had no treatment alternative with proven survival benefit. This changed with a series of recently published phase III trials that lead to approval of several new, life-prolonging agents by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

In 2010, cabazitaxel, a second-generation taxane that inhibits cell division by blocking the depolymerisation of microtubuli, was shown to have a survival benefit of 2.4 months post-docetaxel in a randomized trial (TROPIC) (1). In 2011, abiraterone acetate, a steroidal androgen biosynthesis inhibitor that leads to suppression of androgen synthesis in testicular tissue, adrenal cortex and tumor tissue itself, demonstrated a survival benefit of 4.6 months post-docetaxel in a double-blinded, randomized trial (COU-AA-301) (2,3).

Enzalutamide (formerly called MDV3100) now joins the list of drugs that were shown to prolong suvival following docetaxel chemotherapy. In August 2012, results of a double-blinded, randomized trial comparing enzalutamide with placebo in 1,199 CRPC men were reported (AFFIRM) (4). Enzalutamide is an androgen-receptor antagonist that blocks androgens from binding to the androgen receptor, prevents nuclear translocation of the androgen receptor and inhibits the androgen receptor from associating with DNA to induce transcription of target genes (5). In the AFFIRM-trial patients were randomized 2:1 in a verum-arm treated with 160 mg enzalutamide daily (800 patients) or a placebo-arm (399 patients).

The trial was stopped early following an interim analysis at the time of 520 deaths that revealed a survival benefit of 4.8 months (median overall survival of 18.4 months in the enzalutamide group versus 13.6 months in the placebo group) and a 37% reduction in the risk of death (P<0.001) in patients treated with enzalutamide. As a result, the study was unblinded and enzalutamide was offered to patients of the placebo-group.

The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region and type of disease progression at entry. Furthermore, superiority of enzalutamide was achieved for all secondary end points, including PSA-level response rate (54% *vs.* 2%, P<0.001), soft-tissue response rate (29% *vs.* 4%, P<0.001), quality-of-life response (43% *vs.* 18%, P<0.001), the time to PSA progression (8.3 *vs.* 3.0 months, P<0.001), radiographic progression-free survival (8.3 *vs.* 2.9 months, P<0.001) and the time to the first skeletal-related event (16.7 *vs.* 13.3 months, P<0.001).

Noteworthy, the enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3% *vs.* 53.1% in the placebo group). The most common adverse events that were reported more frequently in the enzalutamide group included fatigue, diarrhea and hot flashes. Seizures were reported in 5 of 800 (0.6%) patients treated with enzalutamide versus none (0%) in the placebo group. Therefore, the investigators suggested that enzalutamide should be used with caution in patients with a history of seizure, with predisposing factors, e.g., brain injury, stroke, brain metastases, alcoholism or with concomitant medication that may lower the seizure threshold.

In conclusion, the androgen-receptor antagonist enzalutamide prolongs survival in docetaxel-pretreated CRPC patients and has an excellent safety profile that compares favourably to other agents such as cabazitaxel with a risk of neutropenia and abiraterone acetate with a risk of mineralocorticoid side-effects. Enzalutamide has been

approved by the FDA in August 2012 for CRPC patients following docetaxel-chemotherapy. It is marketed under the name Xtandi by Medivation and Astellas.

For a future assessment of the optimal position of enzalutamide in the treatment sequence in CRPC, important pending results on a randomized phase III trial with enzalutamide in chemo-naïve patients are yet to be awaited (PREVAIL).

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Footnote

Conflict of Interest: The corresponding author gives notice of the following relationships: Dr M. Heck acts as a consultant for Astellas, Janssen-Cilag and Sanofi Aventis; Prof. Dr J. Gschwend acts as a consultant and advisor for Astellas, Janssen-Cilag and Sanofi Aventis; PD Dr M. Retz acts as a consultant and advisor for Astellas, Janssen-Cilag and Sanofi Aventis.

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