Enzalutamide: new second-line treatment for prostate cancer

Steve Chaplin BPharm, MSc and Heather Payne FRCP, FCR

Enzalutamide is a new second-line treatment for castration-resistant prostate cancer. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Heather Payne discusses its place in treatment.

The recommended treatment for metastatic castration-resistant prostate cancer (mCRPC) is chemotherapy with docetaxel. Until recently, effective options were limited when disease progression occurs on or after treatment with docetaxel. NICE has now recommended abiraterone acetate (Zytiga), but not cabazitaxel (Jevtana), as an option for second-line therapy and in October 2013 issued draft guidance recommending enzalutamide (Xtandi – Astellas) as an option for treating hormone-relapsed metastatic prostate cancer in adults.

Enzalutamide
Enzalutamide is an androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. It is licensed for the treatment of metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

The recommended dose is 160mg orally once daily. No adjustment in dose is recommended for older people or patients with mild hepatic impairment or mild or moderate renal impairment. Due to lack of evidence, caution is recommended in patients with moderate hepatic impairment and in those with severe renal impairment, and enzalutamide is contraindicated in patients with severe hepatic impairment.

Treatment should also be prescribed with caution in patients with a history of, or factors predisposing to, seizures. There is a lack of clinical trial experience in patients with cardiovascular disease.

Enzalutamide should not be given with drugs that are strong CYP2C8 inhibitors. It is a potent enzyme inducer and should not be prescribed with warfarin or coumarin anticoagulants. Full details of drug interactions are listed in the Summary of Product Characteristics.

Clinical trial evidence
The key evidence for enzalutamide is provided by AFFIRM (A study evaluating the efficacy and safety of the investigational drug MDV3100). This double-blind trial randomised 1199 men with progressive CRPC after treatment with docetaxel (confirmed radiographically or by prostate-specific antigen levels) to treatment with enzalutamide or placebo. The primary end-point was overall survival, defined as...
the time from randomisation to death from any cause.

The trial was terminated when a pre-planned interim analysis demonstrated a significant advantage for enzalutamide. At this time, the median time on treatment with enzalutamide was 8.3 months (vs 3.0 months with placebo) and the median duration of follow-up was 14.4 months.

Median overall survival was 18.4 months with enzalutamide and 13.6 months with placebo (see Figure 1). After adjustment for prognostic factors, this was equivalent to a 42 per cent reduction in the risk of death.

Enzalutamide also increased the time to progression and progression-free survival (from about 3.0 to 8.3 months each) and the time to the first skeletal-related event (from 13.3 to 16.7 months), and it improved quality of life scores.

After stopping treatment, more patients assigned to placebo received further treatment (61 vs 42 per cent with enzalutamide), with both receiving abiraterone or cabazitaxel.

**Adverse effects**

The overall frequency of reported adverse events was similar in the two groups. Fatigue (34 vs 29 per cent with placebo), diarrhoea (21 vs 18 per cent), hot flushes (20 vs 10 per cent), musculoskeletal pain (14 vs 10 per cent) and headache (12 vs 6 per cent) were more common with enzalutamide than placebo, though severe forms of these events were equally frequent.

Seizures occurred in five patients (0.6 per cent) treated with enzalutamide; this may have been dose related and several patients had risk factors for seizures.

**References**


**Declaration of interests**

Steve Chaplin has been paid to write about treatments for advanced prostate cancer, including enzalutamide.

**Steve Chaplin is a pharmacist who specialises in writing on therapeutics**

### Place in therapy

For many years the treatment options for the management of advanced prostate cancer were limited and this stage of the disease was approached with a resigned nihilism by many clinicians.

The last decade has changed this attitude to one of extreme optimism as a number of new drugs have been shown to increase survival in addition to reducing symptoms and improving quality of life for men suffering with this stage of prostate cancer.

### Advances in treatment

The mainstay of therapy for men with advanced prostate cancer is the use of androgen-deprivation therapy. The majority of men will have good biochemical and clinical response for several years but ultimately the cancer will progress despite castrate levels of serum testosterone.

There were previously few options in this setting until 2004 when the TAX327 study demonstrated a survival benefit with the chemotherapy agent docetaxel when compared to mitoxantrone (both drugs given in combination with prednisolone).

In 2010 further survival advantages were shown in addition to symptomatic benefits in phase 3 clinical trials for the hormone drug abiraterone acetate and the chemotherapy agent cabazitaxel (both in combination with prednisolone) when investigated in the postdocetaxel setting.

Enzalutamide

Recent data from the large, phase 3, multicentre AFFIRM study have also shown a significant survival advantage for the novel antiandrogen enzalutamide when randomised to placebo in men with CRPC following progression after docetaxel chemotherapy.

Enzalutamide demonstrated a highly significant improvement in overall survival of 4.8 months and also significant advantages in terms of radiographic progression-free survival and time to first skeletal event.

In addition, highly significant improvements in quality of life measurements were seen that are vitally important to men with this stage of prostate cancer.
Enzalutamide was shown to be extremely well tolerated with adverse events seen equally in the treatment and placebo groups. It is interesting to note that any serious adverse events were documented more commonly in the placebo group (39 per cent) than for the men treated with enzalutamide (34 per cent). The reported cardiac toxicity and liver function test abnormalities were also more commonly seen in the placebo group. There was a less than 1 per cent incidence of seizures in the enzalutamide patients.

Fatigue was seen slightly more frequently in the enzalutamide group with an incidence of 34 per cent compared to 29 per cent for placebo.

The efficacy and toxicity data reported from the AFFIRM trial parallel my own experience of treating a large number of men with CRPC in clinical studies and also prescribing enzalutamide via an access scheme and the Cancer Drugs Fund. I have seen excellent durable responses to enzalutamide, in some cases for several years. The improvement in cancer pain and reduction of tumour burden has meant that some men were able to return to work or other important activities.

The fact that enzalutamide is administered as an oral preparation means that it is easily accessible and convenient and does not require long hospital appointments for infusions.

There are also advantages in that enzalutamide does not have to be given with concomitant steroids, patients do not need to fast before and after taking the drug and there are no additional monitoring requirements.

It seemed unlikely a decade ago that we would be debating the way in which to sequence a number of effective drugs for CRPC. At the present time there are no robust data to suggest the order in which these agents should be prescribed.

The situation may be even more difficult when further data from clinical studies investigating enzalutamide in the pre-chemotherapy setting become available. Algorithms are under development to suggest which patients may respond better to chemotherapy or hormone manipulations as a result of disease characteristics.

At the present time all options should be discussed with patients, but in terms of efficacy, tolerability and quality of life enzalutamide is likely to play a key and important role in the early management of CRPC in the coming years.

**Declaration of interests**

Dr Payne has received honoraria for advisory boards, travel expenses for attending medical meetings and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferring, Sandoz and Novartis.

Dr Payne is consultant in clinical oncology, University College London Hospitals