New drugs

Enzalutamide

Approved indication: metastatic prostate cancer
Xtandi (Astellas)
40 mg capsules
Australian Medicines Handbook section 14.3.1

Prostate cancer is an androgen-dependent malignancy. Although medical or surgical castration reduces progression in the earlier stages, the cancer eventually becomes resistant and requires chemotherapy. The median survival time for men with castration-resistant disease is 1–2 years.

Androgen receptor signalling is increased at this late stage of the disease and is thought to be driven, in part, by over-expression of the androgen receptor. Anti-androgen treatments have therefore become a focus of research. Like abiraterone (Aust Prescr 2012;35:128-35), enzalutamide has been approved for patients with metastatic castration-resistant prostate cancer. Enzalutamide is an inhibitor of androgen receptor signalling and works by competitively blocking the binding of androgen to its receptor.

The efficacy and safety of enzalutamide has been assessed in a phase III trial.[1] Men who had already been treated with docetaxel were randomised to enzalutamide 160 mg once daily (800 patients) or placebo (399 patients). Corticosteroids were allowed during the study and patients continued androgen deprivation therapy.

Enzalutamide treatment was continued until the disease progressed. The median duration of treatment was 8.3 months in the enzalutamide group versus 3 months in the placebo group. Median overall survival was significantly longer for enzalutamide than with placebo (18.4 vs 13.6 months, $p<0.001$). Because of the observed benefit, the study was stopped at the prespecified interim analysis and patients in the placebo group were offered enzalutamide.

The most common adverse events with enzalutamide were asthenia or fatigue (50.6% of people), back pain (26.4%), arthralgia (20.5%), hot flushes (20.3%), peripheral oedema (15.4%), musculoskeletal pain (15%) and headache (12.1%). These were more frequent with enzalutamide than with placebo. Neutropenia was also more common with enzalutamide than with placebo (15% vs 6%), and 1% of men in the enzalutamide group died from an infection compared to 0.3% in the placebo group. Falls or injuries from falls (4.6% vs 1.3%) and hallucinations (1.6% vs 0.3%) were also more frequently reported with enzalutamide.

Enzalutamide comes with a warning about seizures. In the trial, 7 of 800 men given enzalutamide had a seizure, compared to no seizures with placebo.[1] Caution is urged in patients with a history of seizures, brain injury, stroke, tumours in the brain, alcoholism or concomitant use of medicines that reduce the seizure threshold.

Cardiac disorders were reported in 6% of those taking enzalutamide[1] even though men with recent cardiovascular disease were excluded from the trial (recent myocardial infarction or unstable angina, a long QT interval, bradycardia or uncontrolled hypertension). Hypertension (6.6%) has also been reported with enzalutamide.

Following oral administration of enzalutamide, maximum plasma concentrations are observed within 1–2 hours. Oral bioavailability is high (≥84.2%). The mean terminal half-life is approximately six days and steady state is reached after a month. Most of the dose is excreted in the urine (71%), with a minor portion excreted in the faeces (13.6%).

Caution is urged when prescribing enzalutamide to people with moderate hepatic impairment and it is not recommended in those with severe impairment. Care should also be taken in those with severe renal impairment or end-stage renal disease.

Enzalutamide is extensively metabolised, mainly by cytochrome P450 (CYP) 2C8, so strong inhibitors (gemfibrozil) or inducers (rifampicin) of this enzyme should be avoided if possible. If a CYP2C8 inhibitor is co-prescribed, the enzalutamide dose should be halved. Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19 so there is potential for drug interactions with substrates of these enzymes such as midazolam, warfarin and omeprazole. Enzalutamide may also affect P-glycoprotein so substrates of this transporter with a narrow therapeutic range (e.g. colchicine, dabigatran, digoxin) may require dose adjustment. There may be an increased risk of liver injury with paracetamol in patients being treated with enzyme inducers.

Enzalutamide provides another option for men with metastatic castration-resistant prostate cancer. Although it prolongs survival by a median of 4.8 months, enzalutamide carries a risk of seizures as well as numerous drug interactions. It is not known

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

how it will compare to abiraterone. Enzalutamide is also being investigated in the treatment of metastatic prostate cancer before chemotherapy.[2]

X manufacturer did not supply data

REFERENCES *†

1. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.
2. Beer TM, Armstrong DE, Rathkopf Y, Loriot CN, Sternberg CS, Higano P, et al. Enzalutamide in metastatic prostate cancer before therapy. N Engl J Med 2014;371:424-33.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)