NEW DRUGS

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Apalutamide

Approved indication: prostate cancer

Erlyand (Janssen-Cilag)
60 mg film-coated tablets
Australian Medicines Handbook section 14.3.1, Anti-androgens

Apalutamide has been approved in Australia for non-metastatic, castration-resistant prostate cancer. It is an oral anti-androgen which binds to the androgen receptor, reducing cell proliferation and increasing apoptosis.

The approval of this drug is mainly based on a placebo-controlled phase 3 trial (SPARTAN) in 1207 men who had prostate cancer with a high risk of developing metastatic disease.[1] This was defined as a prostate-specific antigen (PSA) doubling time of 10 months or less while they were receiving androgen-deprivation therapy. Metastatic disease was ruled out with imaging before randomisation. The men were randomised to receive apalutamide (240 mg a day) or placebo in a 2:1 ratio. They also continued androgen-deprivation therapy.

The primary end point of the study was metastasis-free survival. This was defined as the time from randomisation to first detection of a distant metastasis on imaging, or death from any cause. Median metastasis-free survival was significantly longer with apalutamide compared to placebo (40.5 vs 16.2 months). Median progression-free survival was also significantly longer. At the final analysis, median overall survival had not been reached with apalutamide.[1]

Serious adverse events (grades 3–4) were more common with apalutamide than with placebo – the most frequently reported were hypertension (14.3 vs 11.8%), rash (5.2 vs 0.3%), fracture (2.7 vs 0.8%), falls (1.7 vs 0.8%), diarrhoea (1 vs 0.5%), fatigue (0.9 vs 0.3%) and weight loss (1 vs 0.3%).[1] Although not serious, hypothyroidism was much more common with apalutamide than with placebo (8.1 vs 2%) and was considered to be related to treatment.[1] Dysgeusia, pruritus, depression, heart failure and ischaemic heart disease were also more frequent with apalutamide and three patients died of myocardial infarction. Treatment had to be stopped because of an adverse event in 11% of men receiving apalutamide and 7% of men receiving placebo. About a third of the discontinuations with apalutamide were due to a rash.

There is evidence that apalutamide prolongs the QT interval so prescribers should consider an electrocardiogram and electrolyte monitoring in patients with a history of QT prolongation or who are taking other drugs that prolong the QT interval.

Two patients taking apalutamide had a seizure even though people with a predisposition to seizures were excluded from the study. Patients should be warned of this risk and apalutamide should be permanently discontinued if seizure occurs.

People on prolonged androgen-deprivation therapy have an increased risk of osteopenia and osteoporosis. As apalutamide adds to this risk, patients should be monitored for fall and fracture risk and treated if necessary.

The recommended dose of apalutamide is 240 mg taken once a day. Tablets should be swallowed whole (with or without food). Dose adjustment is not required in patients with mild or moderate hepatic or renal insufficiency (eGFR ≤29 mL/1.73 m^2). However, there is no experience of the drug in those with severe impairment.

Following administration, maximum plasma concentrations are reached within 1–5 hours. Oral bioavailability is 100% and the drug is excreted in the urine (65%) and faeces (24%). Apalutamide is metabolised by cytochrome P450 (CYP) 2C8 and 3A4 so concomitant use of strong inhibitors of these enzymes (e.g. gemfibrozil, clarithromycin) may increase apalutamide exposure. Apalutamide is a strong inducer of CYP3A4 and 2C19 and a weak inducer of CYP2C9 so it may decrease the efficacy of substrates of these enzymes such as midazolam, omeprazole and warfarin respectively. It also weakly induces P-glycoprotein, breast cancer resistance protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1).

Apalutamide provides a new treatment option for men with castration-resistant prostate cancer who have not yet started chemotherapy. It prolongs metastatic-free survival by a median of two years when added to androgen-deprivation therapy. However, treatment comes with some serious adverse effects and numerous potential drug interactions.

T T manufacturer provided additional useful information

REFERENCE

1. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastatis-free survival in prostate cancer. N Engl J Med 2018;378:1408-18. https://doi.org/10.1056/NEJMoa1715546

FURTHER READING

Body A, Pranavan G, Hsiang Tan T, Slobodian P. Medical management of metastatic prostate cancer. Aust Prescr 2018;41:154-9. https://doi.org/10.18773/austprescr.2018.046

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the Therapeutic Goods Administration.