New drugs

Darolutamide

Approved indication: prostate cancer

Nubeqa (Bayer)

300 mg film-coated tablets

Androgen deprivation therapy (gonadotrophin-releasing hormone analogues or castration) is a key part of the medical management of prostate cancer.[1] It reduces tumour growth by lowering serum testosterone. Despite this treatment the cancer will eventually progress and become 'castration-resistant'. Anti-androgens such as apalutamide and enzalutamide may then be prescribed to delay metastasis. Darolutamide is an anti-androgen that acts as an antagonist at the androgen receptor.

The recommended dose of darolutamide is 600 mg twice daily with food. The drug undergoes metabolism by several enzyme systems. They include cytochrome P450 (CYP) 3A4, so inhibitors of this enzyme, such as itraconazole, will increase concentrations of darolutamide and concentrations will be decreased by enzyme inducers such as rifampicin. The half-life is approximately 20 hours with the metabolites being excreted in the urine and faeces. A reduced dose (300 mg twice daily) is recommended if the patient has severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) or moderate hepatic impairment.

The approval of darolutamide appears to be mainly based on one phase III double-blind, randomised trial. This was the Androgen Receptor Antagonising Agent for Metastasis-free Survival (ARAMIS) trial.[2] It involved 1509 men with castration-resistant prostate cancer who had a rising concentration of prostate-specific antigen, but no detectable metastases. They added darolutamide or a placebo to their androgen deprivation therapy. The 955 men in the darolutamide group remained free of metastasis for a median of 40.4 months. This compares with a metastasis-free survival of 18.4 months in the 554 who took a placebo. The median progression-free survival was 36.8 months with darolutamide and 14.8 months with placebo. Although darolutamide delayed the progression of pain (40.3 vs 25.4 months), its effect on the quality of life was similar to placebo.[2]

During the trial 83.6% of the darolutamide group and 76.9% of the placebo group had an adverse event. Most adverse events occurred with a similar frequency, including death (3.9% vs 3.2%). Approximately 9% of each group withdrew from the trial because of adverse events. Fatigue was more frequent with darolutamide (12.1% vs 8.7%). Hypertension affected 6.6% of the darolutamide group. This could be a problem in practice as patients with a recent history of cardiovascular events were excluded from the ARAMIS trial.[2]

As anti-androgen therapy is known to delay the progression of prostate cancer, it is not surprising that darolutamide has greater efficacy than a placebo. Although there has not been a comparative trial, for patients with non-metastatic castration-resistant cancer the median metastasis-free survival appears to be similar for darolutamide, apalutamide and enzalutamide. When the results of the ARAMIS trial were published the median overall survival could not be calculated. There had been 78 deaths with darolutamide and 58 with placebo.[2] A preliminary report of longer term data gives the three-year survival as 83% for darolutamide and 77% for placebo.[3]

T manufacturer provided the product information

REFERENCES

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3. ASCO 2020: ARAMIS shows improved overall survival with darolutamide for nonmetastatic castration-resistant prostate cancer. Practice Update Oncology, News 2020 Jun 9. https://www.practiceupdate.com/content/asco-2020-aramis-shows-improved-overall-survival-with-darolutamide-for-nonmetastatic-castration-resistant-prostate-cancer/102001 [cited 2020 Aug 20]

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 European Medicines Agency.

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Some of the views expressed 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.