NEW DRUGS

Alpelisib

Approved indication: breast cancer

Piqray (Novartis)
50 mg, 150 mg and 200 mg tablets

The medical management of breast cancer is guided by the histopathological subtype of the tumour. Most cancers are positive for hormone receptors and negative for human epidermal growth factor receptor 2 (HER2). Treatment options for patients with this tumour type include endocrine therapies such as tamoxifen (an estrogen receptor modulator), fulvestrant (an estrogen receptor antagonist) or anastrozole (an aromatase inhibitor). However, endocrine therapy eventually fails to halt the progression of advanced breast cancer. Resistance to endocrine therapy can be related to mutations in the PIK3CA gene. These mutations result in overactivity of a kinase (PI3K) which results in cell proliferation. Inhibiting this kinase may therefore slow tumour growth.

Alpelisib is an inhibitor of PI3K. Preliminary studies confirmed that alpelisib had antitumour activity, particularly if given in combination with fulvestrant.

The once-daily dose is taken immediately after a meal as food improves absorption. Most of the dose is metabolised. As cytochrome P450 (CYP) 3A4 is responsible for only a small part of this metabolism, clinically significant interactions with CYP3A4 inducers or inhibitors are unlikely. Although data are limited, no dose adjustments are recommended for patients with liver or kidney impairment. Most of the dose is excreted from the gut.

The approval of alpelisib is mainly based on the phase III SOLAR-1 trial.[1] This randomised 571 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer that had relapsed or progressed despite treatment with an aromatase inhibitor. Most of the patients had metastases. The patients were divided into two cohorts according to the presence of the PIK3CA mutation. They were treated with either oral alpelisib 300 mg daily and injections of fulvestrant, or fulvestrant and a placebo.

The 341 patients with PIK3CA mutations were followed up for a median of 20 months. There was a response to treatment in 26.6% (45/169) of the patients given alpelisib and fulvestrant, and 12.8% (22/172) of those given fulvestrant alone. The median progression-free survival was 11 months with alpelisib and fulvestrant, and 5.7 months with fulvestrant. In the 231 women without a PIK3CA mutation there was no advantage for alpelisib treatment. Median progression-free survival was 7.4 months compared with 5.6 months for fulvestrant alone.[1]

Adverse events led to 25% of the patients receiving alpelisib and fulvestrant stopping treatment. This compares with 4.2% of the patients given fulvestrant and a placebo. Adverse events that were more frequent in patients given alpelisib included hyperglycaemia, diarrhoea, nausea, vomiting, reduced appetite, weight loss, rashes and alopecia. Patients with type 1 or uncontrolled type 2 diabetes were excluded from the SOLAR-1 trial, but many patients needed antidiabetic drugs as 63.7% of those taking alpelisib developed hyperglycaemia.[1] Fatal ketoacidosis has been reported. The skin rashes associated with alpelisib include severe cutaneous reactions such as Stevens-Johnson syndrome. Toxicities such as rashes, diarrhoea or hyperglycaemia require treatment to be reduced or stopped.

Like most new anticancer drugs, it is going to take time to determine where alpelisib fits in therapy. It is clearly of no benefit to the majority of women as they do not have the PIK3CA mutation. In recent years, inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6), such as palbociclib, have become available for the treatment of hormone receptor-positive and HER2-negative advanced breast cancer. Only 20 of the patients with PIK3CA mutations in the SOLAR-1 trial had been treated with these drugs. A phase II trial has studied a cohort of 127 women who had previously been treated with an aromatase inhibitor and a CDK4/6 inhibitor. They were treated with alpelisib and fulvestrant, with a median follow-up of 11.7 months. Their median progression-free survival was 7.3 months with a median overall survival of 17.3 months.[2] An analysis of overall survival in the SOLAR-1 trial showed no statistical advantage for alpelisib and fulvestrant. Median overall survival was 39.3 months with the combination and 31.4 months with fulvestrant alone.[3]

In addition to postmenopausal women, alpelisib with fulvestrant has also been approved for the treatment of men with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer containing the PIK3CA mutation. However, only one man was involved in the SOLAR-1 trial.[1]

T manufacturer provided the product information

REFERENCES

1. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-40. https://doi.org/10.1056/NEJMoa1813904

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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.

NEW DRUGS

2. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol 2021;22:489-98. https://doi.org/10.1016/S1470-2045(21)00034-6 [Erratum in: Lancet Oncol 2022;22:e184]
3. André F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32:208-17. https://doi.org/10.1016/j.annonc.2020.11.011

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, the European Medicines Agency and the Therapeutic Goods Administration.