New drugs

Brigatinib

Approved indication: non-small cell lung cancer
Alunbrig (Takeda)
30 mg, 90 mg and 180 mg film-coated tablets

Some non-small cell lung cancers are driven by particular mutations or genetic rearrangements of the genes coding for tyrosine kinases. Examples include the anaplastic lymphoma receptor kinase (ALK) and the ROS1 tyrosine kinase. About 3–5% of non-small cell lung cancers are ALK-positive. If one of these driver mutations is present, the patient can be treated with a tyrosine kinase inhibitor, such as crizotinib. A problem with crizotinib is that the cancer eventually becomes resistant to treatment. This has led to the development of so-called ‘second-generation’ tyrosine kinase inhibitors, such as alectinib, ceritinib and now brigatinib.

For patients with ALK-positive non-small cell lung cancer, brigatinib treatment begins with a daily dose of 90 mg. If this is tolerated for a week, the dose is increased to 180 mg once a day. The peak concentration is reached within four hours, but the absolute bioavailability of the tablets is unknown. Brigatinib is partly metabolised and partly excreted unchanged with an elimination half-life of 25 hours. Liver disease may increase concentrations of brigatinib, but it has not been studied in patients with moderate or severe hepatic impairment. Similarly, patients with severe renal impairment were not included in the trials.

As the metabolism of brigatinib includes cytochrome P450 (CYP) 2C8 and 3A4, there is a potential for interactions with inducers or inhibitors of these enzymes. Strong inhibitors of CYP3A, such as antifungals and macrolide antibiotics, should be avoided. Grapefruit juice should also be avoided. Inducers to avoid include carbamazepine, phenytoin and St John’s wort. As brigatinib can induce CYP3A, it could reduce the effectiveness of substrates such as hormonal contraceptives. Although pregnancy is very rare in women with lung cancer, there is probably an increased risk of fetal abnormalities with brigatinib.

An open-label phase II trial studied daily doses of 90 mg or 180 mg in 222 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer. The cancers had progressed during previous treatment with crizotinib with 69% of the patients having brain metastases. During a median follow-up of eight months, the investigators considered that there was an objective response in 45% of the patients given brigatinib 90 mg and 54% of those given brigatinib 180 mg. At the higher dose, progression-free survival was 12.9 months, with an 80% probability of the patients being alive at one year. An independent assessment considered that the size of the intracranial lesions had decreased in 67% (12/18) of the patients, with measurable brain metastases at baseline, who received brigatinib 180 mg.1

An open-label phase III trial compared crizotinib with brigatinib 180 mg in 275 patients who had not previously been treated with an ALK inhibitor. Brain metastases were present in 29% of the patients. The median duration of treatment was 7.4 months with crizotinib and 9.2 months with brigatinib. There was an objective response in 71% of the 137 patients randomised to receive brigatinib, compared with 60% in the crizotinib group. The estimated 12-month progression-free survival was 67% with brigatinib and 43% with crizotinib. In patients with measurable brain metastases, there was a response in 78% (14/18) of the brigatinib group and 29% (6/21) of the crizotinib group.2

The most common adverse reactions to brigatinib are gastrointestinal effects. While nausea, vomiting and diarrhoea were common in the phase III trial, they were less frequent than with crizotinib. Adverse events that were more frequent with brigatinib included cough, hypertension and rash. There were also more frequent increases in creatine kinase, lipase and amylase.3 Serious adverse reactions include interstitial lung disease, bradycardia, hyperglycaemia and visual disturbances. It may be necessary to withhold or stop treatment with brigatinib. In the phase III trial, 29% of patients had a dose reduction and 12% had to discontinue.2

The Australian approved indication for brigatinib is for the treatment of ALK-positive advanced non-small cell lung cancer in patients who have previously been treated with crizotinib. However, the evidence from the phase III trial suggests that brigatinib could be a better first-line option. While 85–86% of the patients treated with brigatinib and crizotinib were still alive after a year, there was a significant difference in progression-free survival, particularly in patients with brain metastases.2 Obviously, any difference in overall survival will emerge with longer term data. This will help to guide what sequence to use the
New drugs in. An indirect comparison of alectinib, brigatinib and ceritinib evaluated patients who had cancer that was refractory to crizotinib. It calculated that median overall survival was similar with brigatinib and alectinib (27.6 vs 22.7–26 months) but significantly longer than with ceritinib (27.6 vs 14.9 months).³

Manufacturer did not supply data

REFERENCES

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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.