New drugs

Crizotinib

Approved indication: non-small cell lung cancer
Xalkori (Pfizer)
200 mg and 250 mg capsules
Australian Medicines Handbook section 14.2.3

Along with erlotinib (Aust Prescr 2006;29:53-5) and gefitinib (Aust Prescr 2003;26:94-5), crizotinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer – it is indicated for people with anaplastic lymphoma kinase (ALK)-positive advanced disease. Rearrangements in this gene lead to continuous activation of the kinase which promotes cell proliferation and inhibits apoptosis. Up to 5% of people with non-small cell lung cancer will have mutated ALK. These are mainly adenocarcinomas and are more likely to occur in non-smokers.

Following an oral dose, peak concentrations are reached after 4–6 hours. Steady state is reached after 15 days with twice-daily dosing. After extensive metabolism in the liver, most of the dose is eliminated in the faeces (63%) and urine (22%). The terminal half-life is 42 hours. Drug concentrations are likely to increase in hepatic impairment so caution is urged in these patients. Dose reduction is needed in people with severe renal impairment (creatinine clearance <30 mL/min).

After showing antitumour activity in two single-arm trials[1,2], a phase III trial compared oral crizotinib to intravenous chemotherapy. Patients with locally advanced or metastatic ALK-positive disease despite platinum-based chemotherapy were enrolled. More people responded to crizotinib than to chemotherapy and progression-free survival was significantly longer (see Table). This trend was not reflected in overall survival time which was slightly shorter in people receiving crizotinib. However, people in the chemotherapy group were allowed to cross over to the crizotinib group once their disease progressed.[3]

The most common adverse events with crizotinib were vision disturbances (60% of patients), diarrhoea (60%), nausea (55%), vomiting (47%), constipation (42%), oedema (31%), fatigue (27%), upper respiratory tract infection (26%), dysgeusia (26%), dizziness (22%), neuropathy (19%), dyspnoea (13%), rash (9%) and alopecia (8%).[3] Some patients with vision problems had to have their dose reduced or interrupted.

Hepatotoxicity and interstitial lung disease have occurred with this drug, often in the first two months of treatment. In the phase III trial, 16% of patients had severe elevations in liver enzymes (grade 3 or 4). Two patients had to stop treatment and one patient died of hepatic failure.[3] Liver function should be monitored every month and dose reduction is recommended if elevations occur. Two patients taking crizotinib died from interstitial lung disease/pneumonitis.[3] Treatment should be discontinued permanently if symptoms develop.

QTc prolongation has been observed with crizotinib and ECG monitoring should be considered in patients who have or may develop a prolonged QT interval. Symptomatic bradycardia can also develop after several weeks of treatment so pulse and blood pressure should be measured each month. Avoid using crizotinib with drugs that slow the heart rate, including beta blockers, verapamil, diltiazem or digoxin. Crizotinib may need to be permanently stopped if severe QTc prolongation or severe bradycardia occur.

Severe neutropenia (13% of patients) and leucopenia (5% of patients) occurred with crizotinib.[3] White blood cell counts should be measured and dose reduction or interruption is recommended if these abnormalities occur.

Table **Efficacy of crizotinib in a comparative phase III trial** [3]

	Crizotinib (250 mg twice daily)	Chemotherapy (pemetrexed 500 mg/m² body surface or docetaxel 75 mg/m² body surface every 3 weeks)
Number of patients	173	174
Progression-free survival	7.7 months	3 months
Treatment response	1 complete response 112 partial responses	0 complete responses 34 partial responses
Median overall survival	20.3 months	22.8 months

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

Crizotinib is a substrate and a moderate inhibitor of cytochrome (CYP) P450 3A4/5 so has numerous potential drug interactions. Concomitant use of strong CYP3A inhibitors (some protease inhibitors and azole antifungals, grapefruit juice) or inducers (carbamazepine, rifampicin and St John's wort) may affect plasma concentrations of crizotinib and should be avoided.

Co-administration of drugs with a narrow therapeutic index that are mainly metabolised by CYP3A4 (including cyclosporin, fentanyl and sirolimus) is not recommended. Also avoid CYP3A substrates with a narrow therapeutic index and the potential to cause fatal arrhythmias (dihydroergotamine, ergotamine).

Crizotinib seems to significantly prolong progression-free survival in patients with non-small cell lung cancer, but its effect on overall survival is unclear. Confirmation that a patient has ALK-positive disease is needed before treatment can start. Prescribers and patients should be aware of the life-threatening adverse events that can occur with this treatment.

T manufacturer provided the AusPAR and the product information

REFERENCES *†A

1. Camidge DR, Bang Y-J, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-8.
2. Crino LL, Kim D, Riely GJ, Janne PA, Blackhall FH, Camidge DR, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005 [conference abstract]. J Clin Oncol 2011;29 (Suppl, abstr 7514).
3. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crino L, Ahn M-J, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.

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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).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)