NEW DRUGS

New drugs

Cobimetinib

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Approved indication: metastatic melanoma

Cotellic (Roche)
20 mg film-coated tablets
Australian Medicines Handbook section 14.2.5

Cobimetinib is another targeted drug for inoperable or metastatic melanoma. It should be used in combination with vemurafenib,[1] a BRAF inhibitor, and is indicated for patients with BRAF V600 mutations. About half of patients with metastatic melanoma carry these mutations.

Like trametinib,[2] cobimetinib is a MEK inhibitor. MEK1 and MEK2 are tyrosine kinases that interact with BRAF and lead to uncontrolled growth of melanoma cells. Adding a MEK inhibitor to a BRAF inhibitor has been shown to improve progression-free survival.[3]

The approval of cobimetinib is mainly based on a phase III trial of 495 previously untreated patients with advanced melanoma. The combination of cobimetinib and vemurafenib was compared to vemurafenib alone. Those with abnormal liver function, a recent history of acute coronary syndrome, congestive heart failure, active central nervous system tumours or retinal pathology were excluded from the trial. After a median follow-up of 7.3 months, median progression-free survival was significantly longer with cobimetinib and vemurafenib than with vemurafenib alone, and more people responded to the combination than to monotherapy (see Table).[4] Median overall survival was also significantly longer with the combination. After a median follow-up of 14.2 months, 48% of patients in the cobimetinib and vemurafenib arm were still alive compared with 38% in the vemurafenib arm.[5]

An earlier open-label, phase 1b, safety and dose-finding study of 129 patients with advanced melanoma found that people who had progressed on a BRAF inhibitor were less likely to respond to the combination of cobimetinib and vemurafenib compared with those who had never received a BRAF inhibitor (15% vs 87% had a complete or partial response).[6]

Serious adverse events (grade 3 or more) were common in the main trial and occurred in 71% of those taking the cobimetinib and vemurafenib combination and 59% of those taking vemurafenib monotherapy. Discontinuation because of an adverse event was similar between groups (13% vs 12%).[4]

Diarrhoea, nausea, elevated creatine kinase, decreased ejection fraction and retinal detachment were more common with cobimetinib and vemurafenib than with vemurafenib alone and are thought to be class effects of MEK inhibitors. Elevated liver enzymes, photosensitivity, fatigue, fever, bleeding and chorioretinopathy were also more frequently reported. Rash was very common in both treatment arms and was serious in 5–6% of patients. There were nine deaths from adverse events in the trial. Six of these were in the cobimetinib and vemurafenib group.[4]

Left ventricular ejection fraction may decrease during treatment therefore it should be evaluated at baseline and monitored regularly during therapy. Liver function tests should also be performed at baseline and monitored regularly. Creatine kinase may need to be checked during treatment. Patients with new or worsening visual disturbances should have an

Table **Efficacy of cobimetinib and vemurafenib in previously untreated patients with BRAF-mutated metastatic melanoma**

	Cobimetinib and vemurafenib	Placebo and vemurafenib
Number of patients	247	248
Median progression-free survival[4]	9.9 months	6.2 months
Response[4]		
complete	25 (10%)	11 (4%)
partial	142 (57%)	100 (40%)
Median overall survival[5]	22.3 months	17.4 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.

ophthalmologic examination as serous retinopathy can develop. Avoiding sun exposure and wearing sunblock when outdoors is also advised to reduce the risk of photosensitivity.

Adding cobimetinib to vemurafenib was associated with less cutaneous squamous cell carcinoma, keratoacanthoma and hyperkeratosis than vemurafenib alone.[4]

The recommended dose of cobimetinib is 60 mg taken every day for 21 days of a 28-day cycle. Following oral administration, the drug is extensively metabolised by cytochrome P450 (CYP) 3A and excreted in the faeces. Potent CYP3A inhibitors or inducers can affect cobimetinib concentrations and should not be co-administered.

Adding cobimetinib to vemurafenib improved progression-free survival by almost four months in patients with previously untreated inoperable or metastatic melanoma. Patients who had already progressed after taking a BRAF inhibitor were less responsive to this combination. Adverse effects were very common and some were serious so patient monitoring is important. Only patients with the BRAF V600 mutation qualify for this treatment.

T T manufacturer provided additional useful information

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.