NEW DRUGS

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Aust Prescr 2012;35:128–35

Vemurafenib

Approved indication: metastatic melanoma
Zelboraf (Roche)
240 mg film-coated tablets
Australian Medicines Handbook section 14.2

The prognosis for patients with metastatic melanoma is poor. Apart from the recently approved ipilimumab (Aust Prescr 2011;34:153-9), treatment options are limited. Vemurafenib offers another alternative for patients whose melanoma carries a specific mutation called BRAF V600. This is found in 40–60% of melanomas. The abnormal BRAF protein kinase stimulates cell proliferation and cell survival. Vemurafenib blocks BRAF and slows tumour growth.

The approval of vemurafenib for patients with unresectable or metastatic BRAF V600-positive melanoma is based on results from two trials (Table). These were a phase III trial comparing vemurafenib with dacarbazine in 672 previously untreated patients[1] and a single-arm phase II trial in 132 previously treated patients[2]. Overall, 92% of people in the trials had the BRAF V600E mutation. The remaining 8% mainly had the BRAF V600K mutation. Patients with untreated brain metastases were excluded from both trials.

In the phase III trial, more patients responded to vemurafenib than to dacarbazine and progression-free survival was longer (Table). After an interim analysis, it was recommended that patients receiving dacarbazine cross over to vemurafenib.[1] Outcomes with vemurafenib were similar in the phase II trial.[2] Median overall survival was calculated to be 13.2–15.9 months.[1,2] It is unclear if vemurafenib is effective against melanomas which have BRAF V600 non-E mutations.

Adverse events in the trials were common. In the comparative trial, 38% of patients taking vemurafenib had their dose modified or stopped because of an adverse event compared with only 16% of those receiving dacarbazine.[1] Arthralgia, rash, alopecia, fatigue, nausea, pruritus and skin papilloma were frequently reported with vemurafenib. Photosensitivity reactions were also common and patients should be advised to avoid the sun and cover up or wear sunscreen outdoors. The dose may need to be reduced for severe cases. Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis and uveitis have also been reported.

Between 18% and 26% of patients in the trials developed cutaneous squamous cell carcinoma or keratoacanthoma.[1,2] These occurred after a median of 7–8 weeks and some patients had more than one lesion. New primary melanomas were also reported. Both of these malignancies are not a contraindication to treatment and can usually be excised. Rare cases of non-cutaneous squamous cell carcinoma of the head and neck also occurred in the trials. It is important that patients are examined for new malignancies at baseline and during treatment.

Vemurafenib can prolong the QT interval so it is not recommended for patients with uncorrected electrolyte abnormalities, long QT syndrome or who are taking other drugs that prolong the QT interval. ECG and electrolytes should be measured at baseline and after a dose change.

Liver abnormalities have occurred with vemurafenib so liver enzymes and bilirubin should be monitored before and during treatment. Dose reduction or interruption may be necessary to manage elevations.

Following oral administration of vemurafenib, maximum plasma concentrations are reached after four hours. Most of the metabolites are recovered in the faeces and the elimination half-life is 57 hours. Vemurafenib is an inhibitor of P-glycoprotein and the cytochrome P450 (CYP) enzymes 1A2 and 2C9. It is also a substrate of CYP3A4 so there is a potential for many drug interactions.

Up to half of patients carrying the BRAF V600 mutation are expected to respond to vemurafenib

Table **Efficacy of vemurafenib in patients with BRAF V600-positive metastatic melanoma**

Clinical outcome	Phase III trial[1] (672 patients)		Phase II trial[2] (132 patients)
	vemurafenib	dacarbazine	vemurafenib
Response rate *	48% (2 complete responses, 104 partial responses)	5% (12 partial responses)	53% (8 complete responses, 62 partial responses)
Median progression-free survival	5.3 months	1.6 months	6.8 months
Survival rate at 6 months	84%	64%	77%
Median overall survival	13.2 months	9.6 months	15.9 months

* complete response – disappearance of all target lesions
partial response – at least 30% decrease in the sum of the diameters of target lesions

with a median overall survival of up to 16 months. However, adverse reactions may limit treatment and monitoring for new malignancies is important.

T manufacturer provided the product information

REFERENCES *†

1. Chapman PB, Hauschild A, Robert C, Haanaen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
2. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-14.

The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* 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).