New drugs

Trametinib

Approved indication: melanoma
Mekinist (GlaxoSmithKline)
0.5 mg and 2 mg tablets
Australian Medicines Handbook section 14.2.4

In 40–60% of melanomas there is a genetic mutation which results in an abnormal serine-threonine protein kinase (BRAF). This kinase is involved in the activation of mitogen-activated extracellular signal regulated kinases (MEK1 and 2) which are part of a pathway which regulates cell proliferation. Trametinib is a kinase inhibitor which reversibly blocks MEK1 and MEK2 in melanoma cells with the BRAF mutation. It therefore acts at a different point in the pathway from the BRAF inhibitors – vemurafenib (Aust Prescr 2012;35:128-35) and dabrafenib (Aust Prescr 2014;37:32-5).

A phase II trial studied trametinib in patients with metastatic melanoma. There were 40 patients who had previously been treated with a BRAF inhibitor (cohort A) and 57 who had received chemotherapy or immunotherapy (cohort B). Cohort A took 2 mg trametinib daily for a median of 56 days while cohort B took the drug for a median of 120 days. None of the patients in cohort A had a clinical response, but 25% of cohort B responded to treatment. The median progression-free survival was 1.8 months in cohort A and 4 months in cohort B.[1]

An open-label phase III trial compared trametinib against chemotherapy with dacarbazine or paclitaxel. The 326 patients in the trial had metastatic or stage IIIc melanomas containing BRAF mutations. Only 11 patients had a history of brain metastases and they were excluded from the primary efficacy analysis. There was a response to treatment in 47 of the 214 (22%) patients given trametinib and 9 of the 108 (8%) of those given chemotherapy.

Progression-free survival was 4.8 months with trametinib and 1.5 months with chemotherapy. By the end of the study 16% of the trametinib group and 27% of the chemotherapy group had died (see Table).[2]

The results for cohort A in the phase II trial suggested that patients who have been previously treated with a BRAF inhibitor develop a resistance to treatment with trametinib.[1] This led to another study which combined trametinib and dabrafenib for metastatic melanoma. After the pharmacokinetics of the combination had been assessed, 162 patients were randomised to take dabrafenib 150 mg twice daily as monotherapy, or in combination with trametinib 1 mg or 2 mg. After a median follow-up of 14.1 months, monotherapy had produced a response in 54% of patients while 50% of the trametinib 1 mg group and 76% of the trametinib 2 mg group responded. Progression-free survival was a median of 5.8 months with monotherapy, 9.2 months with the 1 mg combination and 9.4 months with the 2 mg combination. After one year 41% of the patients taking the 2 mg combination were alive and free of progression compared to just 9% of the monotherapy group.[3]

Adverse reactions to trametinib are common and may require the dose to be reduced or stopped. In the comparative study with chemotherapy 27% of patients had to reduce the dose of trametinib and 35% had to interrupt their treatment.[2] Adverse effects which require dose interruptions include rashes, reduced left ventricular function and retinal pigment epithelial detachment. Interstitial lung disease, congestive heart failure and retinal vein occlusion are indications for stopping trametinib. The most common adverse effects, which are more frequent with trametinib than with chemotherapy, are rashes (57% of patients), diarrhoea (43%) and peripheral oedema (26%).[2]

Patients taking trametinib in combination with dabrafenib will experience adverse effects from both drugs. Among the patients who took trametinib 2 mg

Table **Comparison of trametinib and chemotherapy for BRAF-mutated advanced melanoma** [2]

	Trametinib	Chemotherapy
Patients	214	108
Response rate	22%	8%
Progression-free survival	4.8 months	1.5 months
Overall survival rate at 6 months	81%	67%

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.

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with dabrafenib, common adverse events were fever (71%), chills (58%), fatigue (53%), nausea (44%) and vomiting (40%). Squamous cell carcinoma developed in 7% of these patients, but this was less than the 19% of patients affected by dabrafenib monotherapy.[3] The combination increases the risk of bleeding and fatal haemorrhages have occurred.

Trametinib is embryotoxic. If a woman of childbearing age is treated with this drug, pregnancy must be avoided.

Although trametinib is mainly metabolised there have been no studies of patients with moderate or severe hepatic impairment. As less than 20% of the dose is excreted in the urine, mild or moderate renal impairment is unlikely to affect the pharmacokinetics of trametinib. There are no studies in severe renal impairment. As the absorption of trametinib is reduced by food, it should not be taken with meals.

The overall five-year survival of patients with metastatic melanoma is 7–19%. While trametinib can increase progression-free survival, its effects on long-term survival are currently uncertain. The six-month overall survival rate was 81% with trametinib and 67% with chemotherapy.[2] Trametinib monotherapy is not effective if the melanoma has progressed despite treatment with a BRAF inhibitor.

 manufacturer did not supply data

REFERENCES *A

1. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 2013;31:482-9.
2. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107-14.
3. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694-703.

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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)

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)