Trametinib plus dabrafenib for unresectable or metastatic melanoma with BRAF V600E or V600K mutations

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On January 9, 2014, the combination of trametinib and dabrafenib was granted accelerated approval by the US Food and Drug Administration for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.[1,2] Approval of the combination is based on durable response rate observed in an open-label study.[2,3] Improvements in disease-related symptoms and overall survival have not yet been demonstrated for the combination. Both drugs were approved for use as single agents in this setting in May 2013.

Trametinib and dabrafenib target different tyrosine kinases in the RAS/RAF/MEK/ERK pathway. Trametinib is a reversible inhibitor of MEK1 and MEK2 activation and MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway, including MEK1 and MEK2. Dabrafenib is an inhibitor of some mutated forms of BRAF kinases; some mutations in the BRAF gene, including BRAF V600E, result in constitutively activated BRAF kinases that stimulate tumor cell growth. Both trametinib and dabrafenib inhibit BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo. The combination results in greater growth inhibition of BRAF V600 mutation-positive melanoma cell lines and prolonged inhibition of tumor growth in BRAF V600 mutation-positive melanoma xenografts compared with either drug alone.

Approval was based on findings in a trial in which 162 patients with no previous exposure to BRAF or MEK inhibitors were randomized to receive oral trametinib 2 mg (55 patients) or 1 mg (54 patients) once daily plus oral dabrafenib 150 mg twice daily or dabrafenib 150 mg alone (53 patients).[2,3] Patients had a median age of 53 years, 57% were male, almost of them were white, 66% had Eastern Cooperative Oncology Group performance status of 0 (ie, asymptomatic), 67% had M1c disease, 54% had normal lactate dehydrogenase levels, 8% had a history of brain metastases, and 81% had not received previous therapy for unresectable or metastatic disease. Overall, 85% had BRAF V600E mutations, and 15% had BRAF V600K mutations.

Median follow-up was 14 months. Investigator-assessed objective response rate (ORR), the primary endpoint, was 76% in patients receiving trametinib 2 mg plus dabrafenib, including complete response in 9%, compared with 54% in those receiving dabrafenib alone, including complete response in 4%. Median duration of response was 10.5 and 5.6 months, respectively. On independent radiology review committee assessment, ORR was 57% (complete response in 9%), compared with 46% (complete response in 7%), with median duration of response of 7.6 months in both groups. Outcomes were similar in patients with BRAF V600E mutations and BRAF V600K mutations.

Patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, current evidence of Class II or higher congestive heart failure (New York Heart Association), history of retinal pigment epithelial detachment or retinal vein occlusion, QTc interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, history of pneumonitis or interstitial lung disease, or a known history of glucose-6-phosphate dehydrogenase deficiency were excluded from the trial supporting approval of the combination.

The recommended dose of the combination is trametinib 2 mg once daily and dabrafenib 150 mg twice daily. The most common adverse events of any grade in patients receiving trametinib 2 mg or 1 mg in combination with dabrafenib in the trial supporting approval were pyrexia (71% and 69% vs 26% with dabrafenib alone), chills (58% and 50% vs 17%), fatigue (53% and 57% vs 40%), rash (45% and 43% vs 53%), nausea (44% and 46% vs 21%), and vomiting (40% and 43% vs 15%). The most common grade 3 or 4 adverse events were pyrexia (5% and 9% vs 0%), nausea (2% and 6% vs 0%), renal failure (7% and 0% vs 0%), back pain (5% and 0% vs 2%), and hemorrhage (5% and 0% vs 0%). The most common grade 3 or 4 laboratory abnormalities were lymphopenia (22% and 19% vs 6%), neutropenia (13% and 2% vs 6%)increased gamma glutamyltransferase (11% and 17% vs 2%), and hyponatremia (11% and 15% vs 2%).

Serious adverse events included bleeding, clot formation, heart failure, skin problems, and eye problems. The

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development of a new squamous cell carcinoma of the skin, which is a known adverse effect of dabrafenib, was reduced from 19% in the dabrafenib-alone group to 7% in the combination groups. Adverse events led to dose reduction in 49% of combination patients, with the most common reasons being pyrexia, chills, and nausea, and dose interruption in 67%, with the most common reasons being pyrexia, chills, and decreased ejection fraction. Adverse events led to permanent discontinuation of study treatment in 13% of combination patients, with the most common cause being pyrexia (4%). Fever was more common and more severe with the combination compared with dabrafenib alone. QTcF prolongation to > 500 msec occurred in 4% of patients receiving trametinib 2 mg plus dabrafenib and in 2% of dabrafenib-alone patients. QTcF increased by > 60 msec from baseline in 13% of the trametinib 2 mg plus dabrafenib group and in 2% of the dabrafenib group.

In the entire safety population of 202 patients considered for regulatory approval, clinically important adverse events that occurred with a frequency of < 10% in combination recipients included blurred vision, transient blindness, stomatitis, pancreatitis, asthenia, cellulitis, folliculitis, paronychia, pustular rash, skin papilloma, palmar-plantar erythrodysesthesia syndrome, hyperkeratosis, hyperhidrosis, and hypertension.

The combination of trametinib and dabrafenib carries warnings/precautions for new primary cutaneous and noncutaneous malignancies (during and after treatment), hemorrhage (including major hemorrhagic events), and venous thromboembolism (deep vein thrombosis and pulmonary embolism). Trametinib alone carries warnings/precautions for cardiomyopathy, ocular toxicities (including retinal vein occlusion), interstitial lung disease, serious febrile reactions, serious skin toxicity, hyperglycemia, and embryofetal toxicity. Dabrafenib alone carries warnings/precautions for tumor promotion in BRAF wild-type melanoma, cardiomyopathy, ocular toxicities, serious febrile reactions, serious skin toxicity, hyperglycemia, glucose-6-phosphate dehydrogenase deficiency, and embryofetal toxicity. Concurrent administration of trametinib/dabrafenib with strong CYP3A4 or CYP2C8 inhibitors or strong CYP3A4 or CYP2C8 inducers should be avoided. Concurrent use of the combination with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents.

Trametinib is marketed as Mekinist by GlaxoSmithKline, and dabrafenib as Tafinlar, by the same company.

References

1. Mekinist (trametinib) tablets prescribing information, GlaxoSmithKline, January 2014. http://us.gsk.com/products/assets/us_mekinist.pdf.
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3. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367:1694-1703.