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Trametinib: A Targeted Therapy in Metastatic Melanoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Trametinib is a MEK inhibitor approved both as a single agent and in combination with dabrafenib for the treatment of *BRAF* V600E or V600K mutated melanoma. It is a once-daily oral medication that was approved based on progression-free survival and overall survival advantage compared to chemotherapy. Most common side effects include rash, diarrhea, peripheral edema, and fatigue. When used in combination with dabrafenib, pyrexia and nausea are also common. Most side effects can be managed effectively with dose interruptions, supportive care, and/or dose reductions. Ongoing trials are investigating the use of targeted therapy in combination with immunotherapy for cutaneous melanoma and other malignancies. The treatment landscape for metastatic melanoma continues to evolve. However, targeted therapy with trametinib remains a fast-acting and efficacious option, particularly when used in combination with dabrafenib.

Melanoma accounts for just 1% of all skin cancers, but the majority of skin cancer deaths (American Cancer Society, 2018). The incidence of melanoma has increased significantly over the past 30 years, with a 3% increase per year between 2005 and 2014 among those age 50 and older (American Cancer Society, 2018). Fortunately, during this same time period, the 5-year overall survival rate increased as well (American Cancer Society, 2018). Several targeted therapies and immunotherapies have been approved by the US Food and Drug Administration (FDA) since 2011, including therapies targeting the MAP kinase pathway, anti–PD-1 antibodies, anti–CTLA-4 antibodies, and an oncolytic virus therapy. Although immunotherapy is now the mainstay of metastatic melanoma treatment, targeted therapies continue to have an important role. Approximately 50% of melanomas have activating mutations in serine/threonine-protein kinase B-Raf (BRAF), which is a constituent of the MAP kinase signal-transduction pathway and provides an actionable therapeutic target (Flaherty et al., 2012). The MEK inhibitor trametinib (Mekinist) was initially approved as a single agent and then as a combination therapy with dabrafenib (Tafinlar). Here

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we focus primarily on the mechanism of action, clinical trial data, adverse events, and patient management for single-agent trametinib.

INDICATION

In 2013, the FDA approved trametinib as a single agent for the treatment of *BRAF* V600E or *BRAF* V600K mutation–positive unresectable or metastatic melanoma. One year later, the FDA granted accelerated approval to trametinib plus dabrafenib (a BRAF inhibitor) for use in combination for the same indication. Presently, trametinib has both single-agent and combination-therapy approval in the metastatic setting; however, it is more commonly prescribed in combination due to improved efficacy. Of note, dabrafenib and trametinib are also approved in metastatic non–small cell lung cancer, anaplastic thyroid cancer, and most recently in 2018 for the adjuvant treatment of melanoma.

MECHANISM OF ACTION

The MAP kinase pathway regulates the proliferation and survival of tumor cells in many different cancers (Flaherty et al., 2012). The pathway progresses through the Ras/Raf/MEK/ERK kinases, providing multiple targetable mutations for cancer therapy. Activated BRAF phosphorylates and activates MEK, which then activates downstream targets. Trametinib is an orally available, reversible, selective inhibitor of MEK1/MEK2 activation and kinase activity (Kim et al., 2013). In vitro studies showed that trametinib decreases cell proliferation, causes G1 cell-cycle arrest, and induces apoptosis. However, MEK inhibitors suppress ERK signaling in both tumor and normal cells, and therefore on-target toxicities limit the doses that can be safely administered (Chapman, Solit, & Rosen, 2014).

ADMINISTRATION

Trametinib is administered orally as a 2-mg tablet once daily at the same time each day. Tablets are available in 2-mg or 0.5-mg strengths in the event that a patient requires a dose reduction. Medication can be ordered through specialty pharmacies and shipped directly to the patient's home. It should be kept refrigerated and taken on an empty stomach at least 1 hour before or 2 hours after a meal (Novartis Pharmaceuticals Corporation, 2018). Keeping medication refrigerated can be a challenge for patients who travel, but small, insulated coolers can serve as a portable solution. Oral medication adherence can be improved through patient education, counseling, and support. The Oncology Nursing Society offers an Oral Adherence Toolkit for nurses and providers on their website that includes strategies and resources to facilitate adherence (Oncology Nursing Society, 2009).

CLINICAL STUDIES

The phase II clinical trial of trametinib consisted of two cohorts including patients with metastatic *BRAF*-mutant melanoma previously treated with a BRAF inhibitor (cohort A) vs. those treated with chemotherapy and/or immunotherapy (BRAF inhibitor–naive; cohort B; Kim et al., 2013). There was significant clinical activity in the BRAF inhibitor–naive cohort, with 25% of patients achieving at least a partial response and 51% of patients with stable disease. There were no objective responses in cohort A, indicating that sequential monotherapy was not effective in patients who had developed resistance to BRAF inhibitors (Kim et al., 2013).

In the phase III open-label trial, patients with metastatic melanoma with a *BRAF* V600E or *BRAF* V600K mutation were randomized to receive either trametinib at 2 mg orally once daily or chemotherapy (dacarbazine or paclitaxel) every 3 weeks. Median progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (Flaherty et al., 2012). At 6 months, the overall survival was 81% in the trametinib group and 67% in the chemotherapy group (with crossover). Trametinib was approved based on the documented progression-free and overall survival.

ONGOING RESEARCH AND FUTURE STUDIES

Ongoing clinical trials seek to investigate the use of targeted therapies such as trametinib in combination with immunotherapies, including anti–PD-1 antibodies and anti–CTLA-4 antibodies. The challenges seen with these combination trials have included a significant increase in the rates and severity of known toxicities. Trametinib has also shown unique activity in uveal melanoma

and is under investigation in a study of trametinib alone vs. in combination with GSK2141795 (NCI #9445). Finally, trametinib is under investigation for use in other *BRAF*-mutant cancers, including colon cancer and multiple myeloma.

ADVERSE SIDE EFFECTS

In the phase III trial, at least 15% of patients reported adverse events. The most common side effects with single-agent trametinib include rash, diarrhea, peripheral edema, fatigue, and acneiform dermatitis. Decreased ejection fraction or ventricular dysfunction has been observed in approximately 7% of patients, with reports of grade 3 cardiac toxicities due to the drug. Ocular events have been reported in 9% of patients receiving trametinib, with the most prevalent symptom being blurred vision. Other observed ocular toxicities include chorioretinopathy, central serous retinopathy, and retinal vein occlusion (Infante et al., 2012). Dose interruptions due to adverse events occurred in 35% of patients, and dose reductions due to adverse events occurred in 27% of patients in the trametinib arm (Flaherty et al., 2012). It has been our experience that many toxicities are well managed with short dose interruptions, such as a 2- or 3-day hold. Dose reductions are also efficacious, but may require a new prescription for 0.5-mg tablets; this can cause a delay in therapy while waiting for prescription approval and delivery. Targeted symptom management, including doxycycline for acneiform dermatitis or compression stockings for peripheral edema, can improve tolerability (Tables 1–3).

Combination Dabrafenib and Trametinib Adverse Events

The combination of dabrafenib and trametinib compared to a single-agent BRAF inhibitor in randomized controlled trials for patients with *BRAF*-mutated metastatic melanoma demonstrated the improved efficacy of combination therapy. The most common side effects reported in the phase III open-label COMBI-v trial investigating dab-

Table 1. Special Monitoring and Dose Modification Recommendations

Adverse event	Monitoring	Severity	Trametinib
Cardiomyopathy	Assess LVEF at baseline, 1 month, and every 2–3 months while on treatment.	Asymptomatic decrease in LVEF of more than 10% from baseline and below normal limits	Withhold trametinib for up to 4 weeks. • If normal LVEF, resume at reduced dose. • If LVEF remains below normal, discontinue.
		Symptomatic congestive heart failure	Discontinue
		Decrease in LVEF more than 20% from baseline and below normal limits	Discontinue
Retinal pigment epithelial detachment	Routine ophthalmology exams and within 24 hours of visual disturbance		Withhold trametinib for up to 3 weeks. • If improved, resume trametinib at same or lower dose. • If not improved, discontinue or resume at lower dose.
Retinal vein occlusion			Discontinue
Febrile drug reaction		Fever higher than 104° F	Withhold until fever resolves. Then resume trametinib at same or lower dose level.
		Complicated by rigors, hypotension, dehydration, or renal failure	Withhold until fever resolves. Then resume trametinib at same or lower dose level.

Note. LVEF = left ventricular ejection fraction. Adapted from Novartis Pharmaceuticals Corporation (2018).

Table 2. Most Common Adverse Events of Trametinib (N = 211) of Any Grade and Grade 2 or 3

Adverse event	Any grade, number of patients (%)	Grade 2, number of patients (%)	Grade 3, number of patients (%)	Dose modification/management
Rash	121 (57)	40 (19)	16 (8)[a]	Grade 2 intolerable or grade 3 or 4 skin toxicity, hold trametinib for up to 3 weeks. Consider oral corticosteroids for grade 3 rash. If improved, resume at lower dose. If not improved, permanently discontinue.
Diarrhea	91 (43)	13 (6)	0	Loperamide and/or diphenoxylate/atropine, electrolyte-containing fluids, BRAT (bananas, rice, apples, and toast) diet. Rule out infection.
Fatigue	54 (26)	11 (5)	8 (4)	Manage contributing symptoms. Consider dose modification and/or low dose steroids.
Peripheral edema	54 (26)	8 (4)	2 (1)	Maintain nutrition, limit salt intake. Elevate extremities, consider compression stockings.
Acneiform dermatitis	40 (19)	20 (9)	2 (1)	Consider topical erythromycin gel or if widespread, oral doxycycline.
Nausea	38 (18)	5 (2)	2 (1)	Supportive care and antiemetics.
Alopecia	36 (17)	3 (1)	1 (< 1)	Provide support, resources for hairpieces.
Hypertension	32 (15)	6 (3)	26 (12)	Prompt treatment with antihypertensive.
Constipation	30 (14)	3 (1)	0	Increase fiber, fluids, and activity. Stool softeners if indicated.
Vomiting	27 (13)	3 (1)	2 (1)	Antiemetics, electrolyte-containing fluids. Maintain nutrition.
Other		Intolerable grade 2	Any grade 3	Hold trametinib. If improved to grade 0–1, restart at lower dose level. If not improved, discontinue. If recurrent grade 4, discontinue.

Note. Information from Dy & Adjei (2013); Flaherty et al. (2012); Welsh & Corrie (2015).
[a]One patient had grade 4 rash.

rafenib plus trametinib vs. vemurafenib (Zelboraf) were pyrexia, nausea, diarrhea, chills, fatigue, headache, and vomiting. Permanent treatment discontinuation due to adverse events was similar in both groups: 13% in the combination group vs. 12% in the vemurafenib arm. Pyrexia and decreased ejection fraction were the most common reasons for permanent treatment discontinuation in the combination arm (Lugowska, Kosela-Paterczyk, Kozak, & Rutkowski, 2015). However, pyrexia can be managed with dose interruptions, reductions, nonsteroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and supportive care (Dy & Adjei, 2013). Of note, there was a lower incidence of cutaneous squamous cell carcinoma and keratoacanthomas in the combination dabrafenib and trametinib group (1%) vs. the single-agent vemurafenib group (18%; Robert et al., 2015).

IMPLICATIONS FOR THE ADVANCED PRACTICE PROVIDER

Providers prescribing trametinib should be aware of the common and serious potential side effects of treatment and counsel patients on side-effect reporting and management. Pyrexia

Table 3. Recommended Trametinib Dose Reductions for Toxicity (Single-Agent Trametinib)

First dose reduction	1.5 mg once daily
Second dose reduction	1 mg once daily
Subsequent modification	Permanently discontinue if unable to tolerate 1-mg dose

Note. Information from Novartis Pharmaceuticals Corporation (2018).

seen with trametinib can be particularly concerning for patients accustomed to neutropenic fever protocols during chemotherapy. Additional education regarding fever management and differentiation between drug fever and neutropenic fever can prevent unnecessary emergency room visits. For many patients, brief treatment interruptions for 24 to 48 hours result in the resolution of fevers. Consider low-dose prednisone (10 mg daily) for pyrexia refractory to treatment interruption and NSAIDs. Ocular complaints should be evaluated immediately as retinal vein occlusion, while rare, can occur and can result in permanent vision loss.

Trametinib can cause both lower extremity edema as well as cardiomyopathy, and these two adverse events are not necessarily related. If a patient presents with lower extremity edema, that does not definitively portend cardiac causes. Follow prescribing information recommendations for monitoring ejection fraction. Providers should keep in mind the significant proportion of dose interruptions or reductions in the phase III trial and not hesitate to hold the drug and potentially dose reduce for intolerable adverse events.

The average monthly cost of trametinib is approximately $10,000, and the manufacturer does offer a co-pay assistance program (us.tafinlarmekinist.com/advanced-melanoma/patient-support/cost-support). Specialty pharmacies are generally adept at assisting in the insurance approval process.

SUMMARY

Metastatic melanoma remains an aggressive and difficult malignancy to treat. Within the rapidly evolving treatment landscape, targeted therapy with trametinib is a fast-acting and efficacious treatment option, particularly when combined with dabrafenib. Side effects are tolerable with proper monitoring and management. Although immunotherapy has offered exciting advances in the durability of response and overall response, these therapies do not work immediately. Time to response can be crucial, particularly in patients with significant disease burden, and trametinib may induce rapid therapeutic responses.

Disclosure

Ms. Hoffner has served as a consultant for Bristol-Myers Squibb and Merck. Ms. Benchich has no conflicts of interest to disclose.

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