Dabrafenib and Trametinib, Alone and in Combination for BRAF-Mutant Metastatic Melanoma

Alexander M. Menzies and Georgina V. Long

Abstract
Dabrafenib and trametinib were approved for use as monotherapies in BRAF-mutant metastatic melanoma by the U.S. Food and Drug Administration (FDA) in 2013, and most recently, their use in combination has received accelerated FDA approval. Both drugs target the mitogen-activated protein kinase (MAPK) pathway: dabrafenib selectively inhibits mutant BRAF that constitutively activates the pathway, and trametinib selectively inhibits MEK1 and MEK2 proteins activated by RAF kinases. The phase III study of dabrafenib in BRAFV600E metastatic melanoma reported rapid tumor regression in most patients and a 59% objective RECIST response rate. The median progression-free survival (PFS) and overall survival (OS) were improved compared with dacarbazine. Toxicities were well tolerated and different from those reported for vemurafenib, the first FDA-approved BRAF inhibitor. Efficacy has been demonstrated in other BRAF-mutant genotypes. The phase III study of trametinib in BRAF inhibitor-naïve patients with BRAFV600E or BRAFV600K also showed benefit with a prolonged median PFS and OS compared with chemotherapy. Trametinib is ineffective in patients who have progressed on BRAF inhibitors. A phase II trial of combined dabrafenib and trametinib demonstrated higher response rates and longer median PFS than dabrafenib monotherapy, with less cutaneous toxicity. Here, we review the clinical development of both drugs as monotherapies and in combination, and discuss their role in the management of BRAF-mutant melanoma. Clin Cancer Res; 20(8); 2035–43. ©2014 AACR.

Introduction
The mitogen-activated protein kinase (MAPK) pathway is constitutively activated in the majority of melanomas as a result of molecular alterations in genes encoding key components of the pathway (e.g., BRAF and NRAS mutations) or upstream cell-surface receptors (e.g., KIT), resulting in uncontrolled tumor proliferation and survival (1). Approximately 40% to 50% of cutaneous melanomas harbor mutations in BRAF (2). Mutations most commonly occur in exon 15, at codon 600 (BRAFV600), with more than 75% characterized by substitution of valine by glutamic acid at residue 600 (BRAFV600E). Less-frequent mutations include BRAFV600K (valine by lysine, 10% to 30%), BRAFV600R (valine by arginine, 1% to 7%), and BRAFK601E (lysine by glutamic acid at residue 601, 1% to 4%; ref. 3).

In 2011, two drugs were approved by the U.S. Food and Drug Administration (FDA) for American Joint Committee on Cancer (AJCC) stage IIIC unresectable and IV melanoma—ipilimumab, for all melanoma, regardless of BRAF mutation status of the tumor, and vemurafenib, for BRAFV600E melanoma. In 2013, the approval of dabrafenib and trametinib for BRAF-mutant metastatic melanoma in the United States (BRAFV600E for dabrafenib, BRAFV600E/K for trametinib) increased the number of available effective systemic treatments for BRAF-mutant metastatic melanoma to four. In early 2014, the combination of dabrafenib and trametinib was approved for BRAFV600E/K melanoma. This review outlines the development of dabrafenib and trametinib as monotherapies and in combination, and places these new drugs in context with approved treatments.

Dabrafenib
Drug design and preclinical activity
Dabrafenib (GSK2118436) is a reversible and potent ATP-competitive inhibitor that selectively inhibits the BRAFV600E kinase. The drug concentration required for 50% inhibition of BRAFV600E kinase activity (IC50) is 5-times lower than that for BRAFV600E or CRAF (4). Preclinical data demonstrated that dabrafenib inhibited the MAPK pathway in BRAFV600E melanoma cells, leading to decreased proliferation and regression in xenograft mouse models (4).

Clinical trials
Phase I trial (BREAK-1). Clinical trials of dabrafenib began in 2009. Initial results were presented in 2010, with final results published in 2012 (5). The trial began with dose titration from 12 mg daily until the recommended phase II dose (RP2D) of 150 mg twice a day was defined. After establishment of the dosage, expanded cohorts were added,
including a metastatic melanoma cohort and a cohort of patients with asymptomatic untreated melanoma brain metastases (≥3 mm size). Of 156 patients with melanoma enrolled in the study, 131 were BRAFV600E, 18 BRAFV600K, 2 BRAFV600K, 1 BRAFV600E_K601E, 3 BRAFhet, and 1 had an uncharacterized BRAF mutation (Table 1).

The most common toxicities were fatigue, cutaneous effects (including palmar-plantar hyperkeratosis, actinic keratosis, and rash), and arthralgia. Rarely were these severe (Table 1). Notable toxicities included cutaneous squamous cell carcinoma (cuSCC) or cutaneous actinica (11%) and pyrexia (20%, 4% grade 3). Dose reductions occurred in 7% of patients. The maximum tolerated dose (MTD) was not reached at doses of up to 300 mg twice a day; however, a minority of patients developed dose-limiting effects at 300 mg twice a day (2 of 10 patients) and 200 mg twice a day (3 of 20 patients). A RP2D of 150 mg twice a day was selected, as patients on 200 mg twice a day showed minimum increase in drug exposure (AUC) with no increase in the proportion of patients with RECIST response, PET metabolic response, or MAPK inhibition (measured by pERK expression on biopsy), and the development of some dose-limiting events.

Of the 36 patients with BRAFV600E melanoma treated at the RP2D, 25 (69%) had a RECIST response, and in 18 (50%) this was confirmed on a subsequent scan. The response rate was higher in BRAFV600E patients (78%), than BRAFV600K patients (22%), but the median PFS was similar (approximately 5.5 months; Table 1). Nine of 10 patients with BRAFV600E melanoma and previously untreated brain metastases showed a decrease in the size of their brain tumors, and 4 patients achieved a complete response in the brain. This was the first evidence that BRAF inhibitors were active in melanoma brain metastases. No responses were seen in patients with BRAFV600E_K601E or BRAFV600E_K601E mutations or those with wild-type BRAF.

**Phase II trial (BREAK-2).** The single arm, open label, Phase II trial recruited MAPK inhibitor–naive patients with BRAFV600E or BRAFV600K metastatic melanoma (6). Patients with current or previous brain metastases were excluded. Ninety-two patients were enrolled (76 BRAFV600E, 16 BRAFV600K). Adverse events were similar to those seen in the phase I study, with arthralgia, cutaneous effects, pyrexia, and fatigue being the most prevalent (Table 1). Most were mild, but led to dose reduction due in 22% of patients.

Response rates were impressive in BRAFV600E patients (52%), but less so in BRAFV600K patients (13%), and only a minority of patients (16% BRAFV600E, 31% BRAFV600K) had progressive disease at first assessment. Median PFS (6.3 months in BRAFV600E and 4.5 months in BRAFV600K patients) and median OS (13.1 months in BRAFV600E and 12.9 months in BRAFV600K patients) was longer than reported for standard chemotherapies. Patients with M1a/b disease appeared to have a greater degree of tumor shrinkage and longer PFS than M1c disease, and the baseline circulating free DNA (cfDNA) BRAFV600E mutation fraction, which correlated with baseline tumor burden, inversely correlated with the response rate and PFS.

**Phase II brain metastases trial (BREAK-MB).** Following the efficacy seen in 10 patients in the phase I trial with previously untreated brain metastases, a dedicated phase II study was conducted to further examine the effect of dabrafenib in those with untreated, or previously treated but progressed, brain metastases, i.e., active brain metastases (7). This trial enrolled patients with BRAFV600E or BRAFV600K melanoma with asymptomatic brain metastases. At least one brain metastasis needed to be ≥0.5 cm and <4.0 cm to be a measurable target lesion, and leptomeningeal disease was excluded.

One hundred and seventy-two patients were enrolled in two cohorts: (i) those without prior local treatment for brain metastases (N = 89) and (ii) those with brain metastases previously treated with local therapy (surgery, stereotactic radiosurgery, and/or whole brain radiotherapy) but with subsequent intracranial progression (N = 83).

Dabrafenib toxicity was similar to that seen in the earlier trials, with the exception of intracranial hemorrhage, which occurred in 6% of patients, in both cohorts, in both responding and progressive lesions, and did not seem higher than the background rate; thus, it was attributed to the patient population rather than to the drug.

Treatment responses were seen in both cohorts, and in both BRAFV600E and BRAFV600K genotypes (Table 1). In patients with BRAFV600E melanoma, the intracranial response rates in untreated patients and in previously treated patients were 39% and 31%, respectively, higher than in BRAFV600K patients (7% and 22%, respectively). The intracranial disease control rate (i.e., including RECIST-defined stable disease, partial response, and complete response) was 80% to 90% in BRAFV600E and 50% in BRAFV600K patients. In untreated BRAFV600E patients, the median PFS and OS was 3.7 and 7.6 months, respectively, and in untreated BRAFV600K patients, 1.8 months and 3.7 months, respectively (Table 1). Activity was also seen in patients with previously treated and progressed brain metastases. No data were available about the nature of disease progression, but a single institution substudy of 23 patients reported that progression occurred in extracranial sites with ongoing intracranial disease control in 30% (8).

The results of this trial were impressive when compared with studies of other systemic agents, which reported response rates of less than 10%, PFS of less than 2 months and OS of 3 to 5 months (9). The findings suggest that dabrafenib may be an effective adjunct for treatment of brain metastases (alongsid surgery and radiotherapy), and that it warrants consideration as first-line therapy in patients with brain metastases, particularly if they are multiple or concurrent with rapidly progressing extracranial disease.

**Phase III trial (BREAK-3).** The phase III trial recruited patients with stage IV or unresectable stage IIIC BRAFV600E melanoma (excluding BRAFV600K), with no prior therapy for advanced disease [apart from interleukin (IL)-2 in 1 patient], and Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 (10). Patients with a history of brain metastases required demonstration of...
Table 1. Summary of dabrafenib and trametinib clinical trial results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabrafenib</th>
<th>Dabrafenib</th>
<th>Dabrafenib</th>
<th>Dabrafenib</th>
<th>Trametinib</th>
<th>Trametinib</th>
<th>Trametinib</th>
<th>Trametinib</th>
<th>Dabrafenib + trametinib (150/2)</th>
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<td>Phase</td>
<td>1</td>
<td>2</td>
<td>2 active&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3</td>
<td>1</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>2</td>
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<tr>
<td>No. of melanoma patients</td>
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<td>92</td>
<td>172</td>
<td>187</td>
<td>97</td>
<td>57</td>
<td>214&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54</td>
<td></td>
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<tr>
<td>V600E</td>
<td>130</td>
<td>76</td>
<td>139</td>
<td>187</td>
<td>19</td>
<td>46</td>
<td>NR</td>
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<td>33</td>
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<td>6</td>
<td>8</td>
<td>NR</td>
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<td>0</td>
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<td>1 V600R</td>
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<td>Response rate (%)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>untreated</td>
<td>78 V600E</td>
<td>59 V600E</td>
<td>39 V600E&lt;sup&gt;d&lt;/sup&gt;</td>
<td>31 V600E&lt;sup&gt;d&lt;/sup&gt;</td>
<td>59</td>
<td>40</td>
<td>25</td>
<td>22</td>
<td>76</td>
</tr>
<tr>
<td>previously treated</td>
<td>22 V600K</td>
<td>13 V600K</td>
<td>7 V600K&lt;sup&gt;d&lt;/sup&gt;</td>
<td>22 V600K&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>PFS (mo)</td>
<td>5.5 V600E</td>
<td>6.3 V600E</td>
<td>3.7 V600E</td>
<td>3.8 V600E</td>
<td>6.9</td>
<td>5.7</td>
<td>4.0</td>
<td>4.8</td>
<td>9.4</td>
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<td>OS (mo)</td>
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<td>4.5 V600K</td>
<td>1.8 V600K</td>
<td>3.7 V600K</td>
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<td>23.8</td>
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<td>Toxicity% (all grades; G3)</td>
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<td></td>
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<tr>
<td>cutaneous keratoacanthoma</td>
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<td>10</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pyrexia</td>
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<td>24 (3)</td>
<td>26 (6)</td>
<td>16 (3)</td>
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<td>NR</td>
<td>NR</td>
<td>71 (5)</td>
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<td>33 (1)</td>
<td>(1)</td>
<td>19 (1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Fatigue</td>
<td>33 (2)</td>
<td>22 (1)</td>
<td>(&lt;1)</td>
<td>18 (1)</td>
<td>31 (4)</td>
<td>26 (2)</td>
<td>26 (4)</td>
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<td>Rash&lt;sup&gt;*&lt;/sup&gt;</td>
<td>30 (0)</td>
<td>27 (1)</td>
<td>(3)</td>
<td>30 (0)</td>
<td>88 (8)</td>
<td>75 (9)</td>
<td>57 (8)</td>
<td>27 (0)</td>
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<tr>
<td>Diarrhoea</td>
<td>21 (0)</td>
<td>11 (1)</td>
<td>(1)</td>
<td>NR</td>
<td>45 (0)</td>
<td>52 (4)</td>
<td>43 (0)</td>
<td>36 (2)</td>
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<tr>
<td>Serous retinopathy&lt;sup&gt;f&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>2 (0)</td>
<td>9 (&lt;1)</td>
<td>2 (2)</td>
<td></td>
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<tr>
<td>Cardiac</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>7 (0)</td>
<td>(3)</td>
<td>7 (1)</td>
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<tr>
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<td>NR</td>
<td>NR</td>
<td>35 (0)</td>
<td>29 (3)</td>
<td>28 (1)</td>
<td>29 (3)</td>
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<tr>
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<td>22</td>
<td>32</td>
<td>28</td>
<td>12</td>
<td>15</td>
<td>27</td>
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<td>Permanent discontinuation</td>
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<td>2</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9%</td>
<td></td>
</tr>
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</table>

NOTE: For phase I trials, toxicity data are from all doing cohorts.
Abbreviations: G3, grade 3 or greater; KA, cutaneous keratoacanthoma; mets, metastases; NR, not reported.
<sup>a</sup>Active indicates untreated, or previously treated but progressed brain metastases.
<sup>b</sup>Data from the <i>BRAF</i> inhibitor-naïve cohort.
<sup>c</sup>Number receiving drug.
<sup>d</sup>Investigator-assessed intracranial response rate.
<sup>e</sup>Nonspecific term for any skin rash, and includes hyperkeratosis (dabrafenib) and acneiform dermatitis (trametinib).
<sup>f</sup>No cases of retinal vein occlusion were reported in any patients with melanoma on the phase I to III trials of trametinib.
stability for 3 months after local treatment (surgery or stereotactic radiotherapy only).

Initial results were reported in mid 2012 (10), and updated in 2013 (11). Of note, 250 BRAF\textsuperscript{V600E} patients were enrolled and randomized 3:1 to dabrafenib (n = 187) or dacarbazine (n = 63). Cross-over to dabrafenib upon progression was permitted in the dacarbazine arm. Most patients receiving dabrafenib had ECOG performance status of 0 (66%), AJCC M1c disease (66%), and a normal serum lactate dehydrogenase (LDH; 64%), which was similar to the baseline characteristics of patients in the phase III trial of vemurafenib (12).

The investigator-assessed response rate to dabrafenib was 59%, and median PFS in the dabrafenib arm was 6.9 months, compared with 2.7 months in the dacarbazine arm. The median OS was 18.2 months in the dabrafenib arm, and 15.6 months in the dacarbazine arm (Table 1). The improved survival in the dacarbazine arm compared with historic studies was attributed to the benefit of cross-over to dabrafenib (59%) or treatment with vemurafenib (10%). Twenty-five percent of patients on the dabrafenib arm received ongoing BRAF inhibitor treatment after RECIST progression, potentially improving OS compared with the phase III vemurafenib trial (13).

Toxicities were similar to those seen in the early-phase trials, the most common being cutaneous manifestations, pyrexia, fatigue, and arthralgia. Dose reductions occurred in 28% of patients, and 3% permanently discontinued dabrafenib due to toxicity (Table 1).

**Comparisons with vemurafenib**

Dabrafenib and vemurafenib are both selective type 1 BRAF inhibitors, with proven efficacy in BRAF\textsuperscript{V600E} metastatic melanoma. Unlike dabrafenib, which is more selective for BRAF\textsuperscript{V600E} than wild-type RAF kinases, vemurafenib has similar potency for CRAF, wild-type BRAF, and BRAF\textsuperscript{V600E} (14). Furthermore, unlike dabrafenib, vemurafenib reached the MTD in the phase I trial. Despite these differences, the reported efficacy is similar in BRAF\textsuperscript{V600E} patients, with response rates of approximately 55% to 60%, and median PFS of 6 to 7 months. The differences in median OS reported between vemurafenib (13.6 months) and dabrafenib (18.2 months) are likely influenced by the availability and use of treatments received after disease progression, such as ongoing treatment with BRAF inhibitors “beyond progression,” ipilimumab, and trials of highly active PD-1 antibodies, rather than true differences in efficacy. The two drugs also have similar intracranial activity, as vemurafenib has a response rate of 29% in untreated patients, disease control rate of 73%, median PFS of 3.7 months, and OS of 6.5 months (15, 16).

Vemurafenib was codeveloped with the Cobas 4800 V600 mutation test, designed to accurately detect the BRAF\textsuperscript{V600E} mutation, but it can also detect a proportion of BRAF\textsuperscript{V600K} mutations. Initially, it was thought that almost all patients on the phase III trial of vemurafenib were BRAF\textsuperscript{V600E} (12). The phase III dabrafenib trial was thus designed to only include BRAF\textsuperscript{V600E}, such that results could then be compared. Retrospective analysis of the vemurafenib phase III trial demonstrated that 57 (8.6%) BRAF\textsuperscript{V600K} patients had been enrolled, with response rates and survival similar to those reported in the phase II trial of dabrafenib (17). Neither drug has, therefore, been prospectively studied in patients with BRAF\textsuperscript{V600K} melanoma in a randomized trial, but sufficient data exist to suggest that both drugs are active, and likely equally active, in BRAF\textsuperscript{V600E} melanoma. Both drugs are also active in patients with BRAF\textsuperscript{V600R} melanoma and there is a case report of response to vemurafenib in BRAF\textsuperscript{E597K} melanoma (18, 19). It, therefore, seems that patients with all forms of BRAF\textsuperscript{V600} mutations are likely to benefit from BRAF inhibition.

Toxicity is the main difference between dabrafenib and vemurafenib, although the drugs have not been compared head-to-head in a clinical trial. Cutaneous toxicities, including rash, hyperkeratosis, cuSCC, and cutaneous keratoacanthoma, occur with both drugs, but have been reported to occur less frequently in the dabrafenib trials. Of note, cuSCCs were reported to occur in 19% of patients treated with vemurafenib (12), and only in 5% with dabrafenib (10). Whether this difference was due to the drugs themselves, or differences in trial design and clinical assessment is unknown (20). Other toxicities such as arthralgia and fatigue also seem to occur at a higher rate and grade with vemurafenib. Photosensitivity (related to the chemical structure of the molecule and UVA exposure rather than RAF inhibition) and hepatitis occur with vemurafenib but seldomly with dabrafenib, whereas pyrexia occurs more frequently and severely with dabrafenib than vemurafenib (10, 12, 21). The need for dose reduction or interruption due to toxicity is approximately 30% to 40% for both drugs, but only a minimal number of patients treated with either drug permanently discontinue therapy due to toxicity.

Another BRAF inhibitor, LGX818, is also in development (22). Initial data from a phase I trial (n = 54) suggest that it is active, and may have a more favourable toxicity profile than vemurafenib or dabrafenib, with photosensitivity and pyrexia reported in less than 10% of patients, and cuSCC in less than 5% thus far.

**Trametinib**

**Drug design and preclinical activity**

Trametinib (GSK1120212) is a reversible allosteric inhibitor of MEK1 and MEK2 activation and kinase activity, with preclinical evidence of MAPK inhibition and growth inhibition in BRAF\textsuperscript{V600E} melanoma cell lines and xenografts (23).

**Clinical trials**

**Phase I trial.** The phase I trial commenced in 2008, and of 206 patients, 97 had metastatic melanoma with no restriction of eligibility by somatic mutations, for example BRAF mutations. Thirty-six patients had BRAF-mutant melanoma and 39 had wild-type BRAF melanoma (7 of whom had an NRAS-mutant melanoma), 6 had unknown BRAF status, and 16 patients had uveal melanoma (24, 25). Dose titration commenced at 0.125 mg, with dose-limiting...
toxicities observed at total daily doses of 3 mg and 4 mg, and the RP2D was 2 mg once daily. At this dose, analysis of biopsies taken early during treatment and compared with baseline samples showed that there was effective inhibition of MAPK signaling as measured by phosphorylated extracellular signal–regulated kinase (ERK: 60% reduction), effective inhibition of proliferation (Ki67 reduced by 80%), and an increase in cell-cycle inhibition (p27 increased by 170%). The frequent toxicities included MEK inhibitor class-like toxicities such as an acneiform rash (88%), diarrhea, peripheral oedema, and fatigue (Table 1). In the trial of 206 patients with solid tumors, ocular toxicities occurred in 15% (n = 31) of patients, including reversible central serous retinopathy (n = 3) and rarely irreversible retinal vein occlusion (n = 1). Transient left ventricular dysfunction was noted in 8% (n = 16) of patients. Twelve percent of patients treated at 2 mg required dose reductions, most commonly due to rash.

The RECIST-defined response rate was 40% in the 30 patients with BRAF inhibitor–naive metastatic melanoma, but only 17% in those with prior BRAF inhibitor treatment (n = 6) and 10% in wild-type BRAF patients (n = 39). None of 7 NRAS-mutant patients or 16 patients with uveal melanoma had a response (25). One patient with BRAFV600E melanoma had a confirmed partial response and remained on treatment for more than 2 years.

Phase II trial. A phase II study in 97 patients with BRAFV600E/K metastatic melanoma with or without prior BRAF inhibitor treatment demonstrated a response rate of 25% (n = 57) in BRAF inhibitor–naive and 0% (n = 36) in those treated after BRAF inhibitor failure (the 2 patients who responded had not progressed on prior BRAF inhibitor, but ceased due to toxicity; ref. 26). In BRAF inhibitor–naive patients, the median PFS was 4.0 months, and median OS was 14.2 months. In contrast, in those with prior BRAF inhibitor treatment, the median PFS was only 1.8 months, and median OS 5.8 was months, indicating that sequencing of treatment from BRAF inhibitor to trametinib was not effective. One patient had BRAFV600E melanoma, and had a partial response to trametinib, and a PFS of 32 weeks. As in the phase I trial, adverse events were common and usually mild, with skin toxicity (acneiform rash, pruritis), diarrhea, and peripheral edema being the most common. Ocular toxicity was rare, 2% of patients had reversible central serous retinopathy, no patients developed retinal vein occlusion, and 3% of patients had grade 3 reversible reduction in left ventricular function.

Phase III trial (METRIC). The phase III trial recruited patients with stage IV or unresectable stage IIIC BRAFV600E/K melanoma, with up to one prior therapy for advanced disease (excluding MAPK inhibitors and ipilimumab), and ECOG performance score of 0 or 1 (27). Patients with stable brain metastases were eligible, but those with a history of retinal vein occlusion or central serous retinopathy were excluded.

Initial results were presented in 2012 (27), with an update in 2013 (28). Of note, 281 BRAFV600E and 40 BRAFV600K patients were enrolled and randomized 2:1 to trametinib 2 mg daily (n = 214) or chemotherapy (dacarbazine or paclitaxel, n = 108). Cross-over to trametinib upon progression was permitted in the chemotherapy arm. Most patients receiving trametinib had ECOG performance status of 0 (64%), AJCC M1c disease (67%), and a normal serum LDH (63%). Thirty-three percent had received one prior line of chemotherapy, and 4% had a history of treated and stable brain metastases.

The response rate to trametinib was 22%, and median PFS in the trametinib arm was 4.8 months, compared with 1.4 months of PFS in the chemotherapy arm. The median OS was 15.6 months in the trametinib arm, and 11.3 months in the chemotherapy arm (in which 65% crossed over to trametinib upon progression). On both arms, most patients received additional therapy after trametinib progression, including a vemurafenib (20%–30%, for a median of 15–18 weeks) and ipilimumab (10%–20%, for a median of 9 weeks).

Toxicities were similar to those in the earlier trials, including MEK inhibitor class-like effects such as rash, diarrhea, peripheral oedema, hypertension, and transient mild cardiac dysfunction. Chorioretinopathy was rare (<1% grade 3), and no cases of retinal vein occlusion were reported. Most toxicities were mild and did not require drug discontinuation; however, 27% of patients underwent dose reduction.

Other MEK inhibitors in development
Several other MEK inhibitors are in clinical development for metastatic melanoma, including selumetinib, MEK162, GDC-0973, and pimasertib. Trametinib is the only drug that has undergone phase III trials as monotherapy in patients with BRAF-mutant metastatic melanoma, but monotherapy phase II trials of selumetinib and MEK162 have been reported (29–31). As with trametinib, most drugs are being investigated in combination with other targeted drugs (outlined below), and a randomized phase II trial of selumetinib in combination with dacarbazine reported improved median PFS (5.6 months) than dacarbazine monotherapy (3.0 months; ref. 32).

The Current Treatment Approach for BRAF-Mutant Metastatic Melanoma
Two classes of treatments are currently available for patients with BRAF-mutant melanoma, MAPK inhibitors and ipilimumab. Ipilimumab can induce tumor regression and provide durable benefit in only a subset of patients, with data from the phase III trial suggesting greatest efficacy in patients with lower disease burden (33). Conversely, BRAF inhibitors induce rapid tumor regression in the majority of patients, but subsequent resistance is near universal, and the majority of patients progress after 6 to 7 months. Retrospective studies suggest that there is little benefit from ipilimumab treatment after BRAF inhibitor disease progression (34, 35). For patients with rapidly progressive symptomatic disease, there is little debate that BRAF inhibitors are the current approved treatment of
choice; however, it can be argued that in patients with low volume asymptomatic disease, ipilimumab therapy should be considered first-line, despite the fact that these patients may also derive the most benefit from BRAF inhibitors (6, 36). No studies to date have prospectively assessed the best sequence of therapy, and the first phase I trial of combined ipilimumab and vemurafenib was terminated because of excessive toxicity (37).

Among MAPK inhibitors, despite not being studied head-to-head, trametinib does not seem to be as effective as dabrafenib or vemurafenib in BRAFV600E-mutant metastatic melanoma. The phase II trametinib trial demonstrated that treatment with trametinib after BRAF inhibitor progression is not effective (38). In contrast, BRAF inhibitors may have benefit after trametinib, as observed in a subgroup of patients on the phase III trametinib study who received vemurafenib for several months after trametinib progression, as well as data from 23 patients at a single institution (39). Dabrafenib and vemurafenib resistance mechanisms are similar (40), therefore, treatment with one drug after progression on the other is unlikely to result in tumor regression, but there are data to suggest that ongoing BRAF inhibitor treatment beyond disease progression may be beneficial in certain scenarios (41). The best approach, however, may be combined BRAF and MEK inhibition therapy up front (discussed below). Currently, the main role for trametinib is limited to patients who are intolerant of BRAF inhibitors (and have not yet progressed on them), or those with non-V600 exon 15 BRAF mutations such as BRAFV601E and BRAFK597V (25, 42), although the latter may also be responsive to BRAF inhibitors (19).

Combined Dabrafenib and Trametinib

Preclinical studies demonstrated that the combination of a BRAF and MEK inhibitor delayed the onset of resistance and increased apoptosis compared with BRAF inhibitor monotherapy (43). As both drugs target the MAPK pathway, the aim of combined blockade was to (i) circumvent or delay acquired resistance that occurs due to reactivation of the MAPK pathway and (ii) reduce the toxicities seen with monotherapy, especially the cutaneous toxicity from BRAF inhibitors that occur due to paradoxical activation of the MAPK pathway in BRAF wild-type keratinocytes (20).

Dabrafenib and trametinib (CombiDT) was the first combination of a BRAF and MEK inhibitor to be tested in clinical trials. Data were first published in 2012 (44) with updates presented in 2013 (45, 46). In the randomized phase II trial (part C), MAPK inhibitor–naive patients with BRAF-mutant melanoma (n = 54) on *full dose* CombiDT 150/2 (dabrafenib at 150 mg twice daily and trametinib at 2 mg daily) had improved outcomes compared with those with dabrafenib monotherapy. The response rate was significantly higher at 76% versus 54%, no patients had
progressive disease as best response, the median PFS was significantly longer at 9.4 months versus 5.8 months, and median OS was an impressive 23.8 months on the CombiDT arm (Table 1; ref. 46). The response rate to combination treatment in those who crossed over after progressing on dabrafenib monotherapy was only 9%, suggesting that patients are best suited to combination treatment up front (45).

BRAF inhibitor class toxicities were less frequent, including hyperkeratosis, alopecia, arthralgia, and rash. Notably, the rate of cuSCC with CombiDT was one third that of dabrafenib monotherapy (7% vs. 19%, respectively). The most common toxicity was pyrexia, which occurred in 71% of patients (5% grade 3/4) treated with CombiDT 150/2 (44). Fifty-eight percent of patients underwent dose reductions, many temporary with subsequent dose reescalation, and the majority were due to pyrexia. The pathogenesis of pyrexia is incompletely understood, but one study suggested that it generally occurs early, is often repetitive, can be managed with brief dose interruption and corticosteroid prophylaxis (in recurrent cases), and may not necessitate dose reduction (47).

Two phase III trials of CombiDT have completed recruitment and results are expected shortly, comparing CombiDT 150/2 with dabrafenib (NCT01584648) and vemurafenib (NCT01597708) monotherapy, and an adjuvant trial in high-risk stage III melanoma is underway (NCT016582083). In the interim, the FDA has approved CombiDT for patients with BRAF V600E/K melanoma based upon the impressive phase II data. Other BRAF and MEK inhibitor combinations are concurrently in phase III trials [vemurafenib and cobimetinib (NCT01689519), and LGX818 and MEK162 (NCT01909453)]. Preliminary phase I results of these combinations suggest higher efficacy than BRAF inhibitor monotherapy, little efficacy in BRAF inhibitor-resistant patients, and different toxicity profiles to CombiDT (48, 49).

Conclusions and Future Directions

Dabrafenib and vemurafenib are currently the standard BRAF inhibitors for BRAF-mutant metastatic melanoma, distinguished mainly through their toxicity profiles rather than clinical efficacy. Trametinib is less effective, and is most suitable for patients intolerant to BRAF inhibitors or those with L597 or K601 BRAF mutations. Use of trametinib after BRAF inhibitor progression is not effective, and although there is some efficacy of BRAF inhibitors after trametinib failure, and CombiDT after BRAF inhibitor failure, the best approach is up-front combination therapy (Fig. 1). The recent FDA approval of CombiDT now means that this is the current standard MAPK inhibitor treatment of choice. Several emerging treatments, including other BRAF and MEK inhibitor combinations, inhibitors of the PD-1/PD-L1 immune axis, and other cell signaling pathway inhibitors, used alone and in combination with current drugs, will no doubt change the treatment paradigm further in the near future. Until then, there are now several standard treatment options for patients with melanoma, with a vast array of clinical trials also available that hope to improve outcomes further.

Disclosure of Potential Conflicts of Interest

A.M. Menzies reports receiving speakers bureau honoraria from Roche and has provided expert testimony for GlaxoSmithKline. G.V. Long reports receiving speakers bureau honoraria from GlaxoSmithKline and Roche and is a consultant/advisory board member for GlaxoSmithKline, Roche, Bristol-Myers Squibb, Novartis, and Amgen.

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Dabrafenib and Trametinib, Alone and in Combination for \textit{BRAF}-Mutant Metastatic Melanoma

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