Dabrafenib and Trametinib, alone and in combination for BRAF-mutant metastatic melanoma

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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 MAPK pathway: dabrafenib selectively inhibits mutant BRAF which constitutively activates the pathway, and trametinib selectively inhibits MEK1 and MEK2 proteins activated by RAF kinases. The phase 3 study of dabrafenib in BRAFV600E metastatic melanoma reported rapid tumour 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 3 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 2 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.
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 40-50% of cutaneous melanomas harbor mutations in BRAF (2). Mutations most commonly occur in exon 15, at codon 600 (BRAF<sup>V600</sup>), with over 75% characterized by substitution of valine by glutamic acid at residue 600 (BRAF<sup>V600E</sup>). Less frequent mutations include BRAF<sup>V600K</sup> (valine by lysine, 10-30%), BRAF<sup>V600R</sup> (valine by arginine, 1-7%), and BRAF<sup>K601E</sup> (lysine by glutamic acid at residue 601, 1%-4%) (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 tumour, and vemurafenib, for BRAF<sup>V600E</sup> melanoma. In 2013, the approval of dabrafenib and trametinib for BRAF-mutant metastatic melanoma in the USA (BRAF<sup>V600E</sup> for dabrafenib, BRAF<sup>V600E/K</sup> 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 BRAF<sup>V600E/K</sup> 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 BRAF<sup>V600E</sup> kinase. The drug concentration required for 50% inhibition of BRAF<sup>V600E</sup> kinase activity (IC50) is five times lower than that for BRAF<sup>wt</sup> or CRAF (4). Preclinical data demonstrated that dabrafenib inhibited the MAPK pathway in BRAF<sup>V600E</sup> 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 12mg daily
until the recommended phase two dose (RP2D) of 150mg BID 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 (≥3mm size). Of 156 melanoma patients enrolled in the study, 131 were BRAF<sup>V600E</sup>, 18 BRAF<sup>V600K</sup>, two BRAF<sup>K601E</sup>, one BRAF<sup>V600_K601E</sup>, three BRAF<sup>wt</sup>, and one 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 keratoacanthoma (KA) (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 300mg BID, however a minority of patients developed dose-limiting effects at 300mg BID (2/10 patients) and 200mg BID (3/20 patients). A RP2D of 150mg BID was selected, as patients on 200mg BID 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 BRAF<sup>V600</sup> melanoma patients 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 BRAF<sup>V600E</sup> patients (78%), than BRAF<sup>V600K</sup> patients (22%), but the median PFS was similar (approximately 5.5 months) (Table 1). Nine of ten patients with BRAF<sup>V600</sup> melanoma and previously untreated brain metastases showed a decrease in the size of their brain tumors, and four 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 BRAF<sup>K601E</sup> or BRAF<sup>V600_K601E</sup> mutations or those with wild-type BRAF.

**Phase 2 Trial (BREAK-2)**

The single arm, open label, phase 2 trial recruited MAPK inhibitor naïve patients with BRAF<sup>V600E</sup> or BRAF<sup>V600K</sup> metastatic melanoma (6). Patients with current or previous brain metastases were excluded. 92 patients were enrolled (76 BRAF<sup>V600E</sup>, 16 BRAF<sup>V600K</sup>). Adverse events were similar to those seen in the phase 1 study, with arthralgia, cutaneous effects, pyrexia and fatigue most prevalent (Table 1). Most were mild, but led to dose reduction due in 22% of patients.

Response rates were impressive in BRAF<sup>V600E</sup> patients (52%), but less so in BRAF<sup>V600K</sup> patients (13%), and only a minority of patients (16% BRAF<sup>V600E</sup>, 31%
BRAF\textsuperscript{V600K} had progressive disease at first assessment. Median PFS (6.3 months in BRAF\textsuperscript{V600E} and 4.5 months in BRAF\textsuperscript{V600K} patients) and median OS (13.1 months in BRAF\textsuperscript{V600E} and 12.9 months in BRAF\textsuperscript{V600K} patients) was longer than reported for standard chemotherapies. Patients with M1a/b disease appeared to have a greater degree of tumor shrinkage and longer progression-free survival than M1c disease, and the baseline circulating free DNA (cfDNA) BRAF\textsuperscript{V600E} mutation fraction, which correlated with baseline tumor burden, inversely correlated with the response rate and PFS.

**Phase 2 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 2 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 BRAF\textsuperscript{V600E} or BRAF\textsuperscript{V600K} melanoma with asymptomatic brain metastases. At least one brain metastasis needed to be \( \geq 0.5\text{cm} \) and \( \leq 4.0\text{cm} \) to be a measurable target lesion, and leptomeningeal disease was excluded.

172 patients were enrolled in two cohorts: A) those without prior local treatment for brain metastases (N=89); B) 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 appear 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 BRAF\textsuperscript{V600E} and BRAF\textsuperscript{V600K} genotypes (Table 1). In BRAF\textsuperscript{V600E} melanoma patients, the intracranial response rates in untreated patients and in previously treated patients were 39% and 31%, respectively, higher than in BRAF\textsuperscript{V600K} patients (7% and 22%, respectively). The intracranial disease control rate (i.e. including RECIST-defined stable disease, partial response and complete response) was 80-90% in BRAF\textsuperscript{V600E} and 50% in BRAF\textsuperscript{V600K} patients. In untreated BRAF\textsuperscript{V600E} patients, the median PFS and OS was 3.7 and 7.6 months, respectively, and in untreated BRAF\textsuperscript{V600K} 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 was available regarding the nature of disease progression, but a single institution sub-study 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 3-5 months (9). The findings suggest that dabrafenib may be an effective adjunct for treatment of brain metastases (alongside 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 3 Trial (BREAK-3)**

The phase 3 trial recruited patients with stage IV or unresectable stage IIIC BRAFV600E melanoma (excluding BRAFV600K), with no prior therapy for advanced disease (apart from IL-2 in one patient), and ECOG performance score of 0 or 1 (10). Patients with a history of brain metastases required demonstration of 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). 250 BRAFV600E patients were enrolled and randomized 3:1 to dabrafenib (n=187) or dacarbazine (n=63). Crossover 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 LDH (64%), which was similar to the baseline characteristics of patients in the phase 3 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 DTIC arm. The median overall survival (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 to historical studies was attributed to the benefit of crossover to dabrafenib (59%) or treatment with vemurafenib (10%). 25% of patients on the dabrafenib arm received ongoing BRAF inhibitor treatment after RECIST progression, potentially improving overall survival compared to the phase 3 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 BRAFV600 metastatic melanoma. Unlike dabrafenib, which is more selective for BRAFV600E than wild-type RAF kinases, vemurafenib has similar potency for CRAF, wild-type BRAF, and BRAFV600E (14). Furthermore, unlike dabrafenib, vemurafenib reached the MTD in the phase 1 trial. Despite these differences, the reported efficacy is similar in BRAFV600E patients, with response rates of approximately 55-60%, and median PFS of 6-7 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 co-developed with the Cobas® 4800 V600 mutation test, designed to accurately detect the BRAFV600E mutation, but it can also detect a proportion of BRAFV600K mutations. Initially, it was thought that almost all patients on the phase 3 trial of vemurafenib were BRAFV600E (12). The phase 3 dabrafenib trial was thus designed to only include BRAFV600E, such that results could then be compared. Retrospective analysis of the vemurafenib phase 3 trial demonstrated that 57 (8.6%) BRAFV600K patients had been enrolled, with response rates and survival similar to those reported in the phase 2 trial of dabrafenib (17). Neither drug has therefore been prospectively studied in BRAFV600K melanoma patients in a randomized trial, but sufficient data exists to suggest that both drugs are active, and likely equally active, in BRAFV600K melanoma. Both drugs are also active in patients with BRAFV600R melanoma and there is a case report of response to vemurafenib in BRAFV597R melanoma (18, 19). It therefore appears that patients with all forms of BRAFV600 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 KA, 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 appear 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 30-40% for both drugs, but only a minimal number of patients treated with either drug permanently discontinuing therapy due to toxicity.

Another BRAF inhibitor, LGX818, is also in development (22). Initial data from a phase 1 trial (n=54) suggests 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 BRAFV600E melanoma cell lines and xenografts (23).

Clinical Trials
Phase 1 Trial
The phase I trial commenced in 2008, and of 206 pts, 97 had metastatic melanoma with no restriction of eligibility by somatic mutations e.g. BRAF mutations. 36 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 0.125mg, with dose-limiting toxicities observed at total daily doses of 3mg and 4mg, and the RP2D was 2mg once daily. At this dose, analysis of biopsies taken early during treatment and compared with baseline samples showed there was effective inhibition of MAPK signaling as measured by phosphorylated ERK (60% reduction), effective inhibition of proliferation (Ki67 reduced by 80%), and an increase in cell cycle inhibition (p27 increased by 170%).

The most frequent toxicities included MEK inhibitor class-like toxicities such as an acneiform rash (88%), diarrhoea, 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. 12% of patients treated at 2mg required dose reductions, most
commonly due to rash.

The RECIST-defined response rate was 40% in the 30 patients with BRAF
inhibitor-naïve 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 uveal melanoma patients had a response (25). One patient with a
BRAF<sup>L597V</sup> mutation had a confirmed partial response and remained on treatment for
over 2 years.

Phase 2 Trial
A phase 2 study in 97 patients with BRAF<sup>V600E/K</sup> metastatic melanoma with or
without prior BRAF inhibitor treatment demonstrated a response rate of 25% (n=57) in BRAF
inhibitor naïve 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) (26). In BRAF inhibitor naïve patients, the median PFS was 4.0 months,
and median OS 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 months, indicating that
sequencing of treatment from BRAF inhibitor to trametinib was not effective. One
patient had BRAF<sup>K601E</sup> melanoma, and had a partial response to trametinib, and a
PFS of 32 weeks.

As in the phase 1 trial, adverse events were common and usually mild, with
skin toxicity (acneiform rash, pruritis), diarrhoea and peripheral odema 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 3 Trial (METRIC)
The phase 3 trial recruited patients with stage IV or unresectable stage IIIC
BRAF<sup>V600E/K</sup> 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). 281
BRAF<sup>V600E</sup> and 40 BRAF<sup>V600K</sup> patients were enrolled and randomized 2:1 to
trametinib 2mg daily (n=214) or chemotherapy (dacarbazine or paclitaxel, n=108).
Crossover 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%). 33% 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 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 15-18 weeks) and ipilimumab (10-20%, for a median 9 weeks).

Toxicities were similar to those in the earlier trials, including MEK inhibitor class-like effects such as rash, diarrhoea, peripheral oedema, hypertension, 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 3 trials as monotherapy in BRAF-mutant metastatic melanoma patients, but monotherapy phase 2 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 2 trial of selumetinib in combination with dacarbazine reported improved median PFS (5.6 months) than dacarbazine monotherapy (3.0 months) (32).

THE CURRENT TREATMENT APPROACH FOR BRAF-MUTANT METASTATIC MELANOMA
Two classes of treatments are currently available for BRAF-mutant melanoma patients, MAPK inhibitors and ipilimumab. Ipilimumab can induce tumor regression and provide durable benefit in only a subset of patients, with data from the phase 3 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 6-7 months. Retrospective studies suggest 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 1 trial of combined ipilimumab and vemurafenib was terminated due to excessive toxicity (37).

Amongst MAPK inhibitors, despite not being studied head-to-head, trametinib does not appear to be as effective as dabrafenib or vemurafenib in BRAF<sup>V600</sup>-mutant metastatic melanoma. The phase 2 trametinib trial demonstrated that treatment with trametinib treatment 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 3 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 is 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 BRAF<sup>K601E</sup> and BRAF<sup>L597V</sup> (25, 42) although the latter may also be responsive to BRAF inhibitors (19).

**COMBINED DABRAFENIB AND TRAMETINIB**

Pre-clinical studies demonstrated that the combination of a BRAF and MEK inhibitor delayed the onset of resistance and increased apoptosis compared to BRAF inhibitor monotherapy (43). As both drugs target the MAPK pathway, the aim of combined blockade was to: a) circumvent or delay acquired resistance that occurs due to reactivation of the MAPK pathway, b) reduce the toxicities seen with monotherapy, especially the cutaneous toxicity from BRAF inhibitors which 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 was first published in 2012 (44) with updates presented in 2013 (45, 46). In the randomized phase 2 trial (Part C), MAPK inhibitor-naïve BRAF-mutant melanoma patients (n=54) on “full dose” CombiDT 150/2 (dabrafenib at 150mg twice daily and trametinib at 2mg daily) had improved outcomes compared to 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 overall survival was an impressive 23.8 months on
the CombiDT arm (Table 1) (46). The response rate to combination treatment in
those who crossed-over after progressing on dabrafenib monotherapy was only 9%,
suggesting 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% versus 19% respectively). The most
common toxicity was pyrexia, which occurred in 71% of patients (5% grade 3/4)
treated with CombiDT 150/2 (44). 58% of patients underwent dose reductions, many
temporary with subsequent dose re-escalation, 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 3 trials of CombiDT have completed recruitment and results are
expected shortly, comparing CombiDT 150/2 with dabrafenib (NCT01584648) and
vemurafenib (NCT01597908) monotherapy, and an adjuvant trial in high-risk stage III
melanoma is underway (NCT01682083). In the interim, the FDA has approved
CombiDT for BRAF<sup>V600E/K</sup> melanoma patients based upon the impressive phase 2
data. Other BRAF and MEK inhibitor combinations are concurrently in phase 3 trials
(vemurafenib and cobimetinib [NCT01689519], LGX818 and MEK162
[NCT01909453]). Preliminary phase 1 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 (Figure 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 melanoma patients, with a vast array of clinical trials also available that hope to improve outcomes further.
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## Table 1. Summary of dabrafenib and trametinib clinical trial results

<table>
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<th>Dabrafenib</th>
<th>Dabrafenib</th>
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<th>Dabrafenib</th>
<th>Trametinib</th>
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### Efficacy

| Response rate (%) | Untreated | Previously Treated & Progressed | | | | | | |
|-------------------|-----------|---------------------------------| | | | | | |
| untreated         | untreated | untreated | untreated | untreated | untreated | untreated | untreated | untreated |
| V600E             | 78 V600E 22 V600K | 59 V600E 13 V600K | 39 V600E^ 7 V600K^ | 31 V600E^ 22 V600K^ | 59 | 40 | 25 | 22 | 76 |
| V600K             | 5.5 V600E 5.6 V600K | 6.3 V600E 4.5 V600K | 3.7 V600E 1.8 V600K | 3.8 V600E 3.7 V600K | 6.9 | 5.7 | 4.0 | 4.8 | 9.4 |
| OS (months)       | NR        | 13.1 V600E 12.9 V600K | 7.6 V600E 3.7 V600K | 7.2 V600E 5.0 V600K | 18.2 | NR | 14.2 | 15.6 | 23.8 |

### Toxicity % (all grades) [G3]

| cuSCC/KA | 11 | 10 | 6 | 10 | 0 | 0 | 0 | 7 |
| Serous retinopathy# | NR | NR | NR | NR | 10 [0] | 2 [0] | 9 [<1] | 2 [2] |
| Cardiac | NR | NR | NR | NR | 7 [0] | [3] | 7 [1] | 0 |
For phase 1 trials, toxicity data is from all doing cohorts.

Legend:
* Active = untreated, or previously treated but progressed brain metastases
† Data from the BRAF inhibitor naïve cohort.
‡ Number receiving drug.
^ Investigator-assessed intracranial response rate
§ non-specific term for any skin rash, and includes hyperkeratosis (dabrafenib), acneiform dermatitis (trametinib)
# No cases of retinal vein occlusion were reported in any melanoma patients on the phase 1-3 trials of trametinib.

Abbreviations: mets, metastases; PFS, median progression-free survival; OS, median overall survival; G3, grade 3 or greater; cuSCC, cutaneous squamous cell carcinoma; KA, cutaneous keratoacanthoma; NR, not reported

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<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9%</td>
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Data from the BRAF inhibitor naïve cohort.
FIGURES

Figure 1. Response rate and median progression-free survival of MAPK inhibitors for BRAF-mutant melanoma.

* These data are derived from a subgroup of patients who progressed on a BRAF inhibitor (BRAFi) and were still well enough to receive second-line targeted therapy. The addition of the median PFS for this treatment to the dabrafenib median PFS is not accurate.
Figure 1:

- **CombiDT (76%)**
  - Drug (response rate): 9.4 months

- **Dabrafenib (59%)**
  - Median PFS (months): 6.9

- **Vemurafenib (57%)**
  - Median PFS (months): 6.9

- **Trametinib (22%)**
  - Median PFS (months): 4.0

- **CombiDT after dabrafenib (9%)**
  - Median PFS (months): 3.6

- **Trametinib after BRAFi (0%)**
  - Median PFS (months): 1.8
Dabrafenib and Trametinib, alone and in combination for BRAF-mutant metastatic melanoma

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