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Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy

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***Abstract*:** Treatment with BRAF inhibitors such as vemurafenib or dabrafenib in patients with advanced BRAFV600 mutated melanoma has shown objective tumor responses in approximately half of the patients. However, the duration of responses is limited in a majority of these patients, with progression-free survival rates around 6 months due to tumor progression from development of acquired resistance. Preclinical studies have suggested that concurrent inhibition of the BRAF kinases and MEK of the mitogen-activated protein kinase (MAPK) pathway could decrease MAPK-driven acquired resistance, resulting in longer duration of responses, higher rate of tumor responses, and a decrease in the cutaneous toxicities observed from paradoxical MAPK pathway activation with BRAF inhibitor monotherapy. This review provides an overview of the currently available clinical trial data on BRAF and MEK inhibitors together and in combinations with other therapeutic agents.

Keywords: BRAF inhibitors, MEK inhibitors, melanoma

Introduction

Nearly half of the patients with advanced melanomas harbor a valine to glutamine substitution (V600E) in codon 600 of the serine-threonine kinase BRAF [Davies *et al.* 2002]; less common BRAF mutations such as lysine (V600K) or arginine substitutions (V600R) have also been reported. In the past 4 years, two BRAF inhibitors that target these mutations, vemurafenib and dabrafenib, have been approved by the US Food and Drug Administration (FDA). These drugs have shown high rates of rapid response not previously seen in melanoma patients, with response rates ranging from 48% to 59% in phase II and III trials of vemurafenib and dabrafenib [Chapman *et al.* 2011; Ascierto *et al.* 2013; Hauschild *et al.* 2012]. However, the duration of responses is limited in the majority of patients, with median progression-free survival (PFS) in these patients ranging from 5.1 to 6.8 months [Sosman *et al.* 2012; Hauschild *et al.* 2012]. Treatment with the MEK inhibitor trametinib has also shown similar PFS (4.8 months) and response rates (48%) when administered as first-line therapy in this patient population [Flaherty *et al.* 2012b].

The rapid antitumor responses observed with BRAF or MEK inhibitor monotherapy are not long lasting in most cases (although in a minority can last for over 5 years) due to the development of acquired resistance with progression after a period of objective tumor response. Drivers of acquired resistance to BRAF inhibitor therapy are diverse and include mechanisms leading to reactivation of the mitogen-activated protein kinase (MAPK) pathway in over two-thirds of tumors (such as activating mutations in upstream NRAS, BRAF amplification or truncation, overexpression of genes such as COT, or mutations in the downstream kinase MEK1), along with promotion of parallel signaling networks such as the PI3K–PTEN–AKT pathway [Shi *et al.* 2014; Rizos *et al.* 2014; Wagle *et al.* 2011]. Sequential therapy with a MEK inhibitor following progression on a BRAF inhibitor has also not shown benefit, as no responses and a PFS of only 1.8 months was observed in a study of 40 patients, suggesting

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that resistance to BRAF inhibitors also confers resistance to MEK inhibitors [Kim *et al.* 2013]. Therefore, the premise behind the subsequent clinical trials combining inhibitors of both MEK and mutant BRAF kinase was that they would help to delay this MAPK-driven acquired resistance and result in longer duration of responses, higher rate of tumor responses, and decrease the toxicities observed from paradoxical MAPK pathway activation with BRAF inhibitor monotherapy. In this review, we discuss existing clinical trial data on BRAF and MEK inhibitors together and in combinations with other therapeutic agents.

Dabrafenib and trametinib

Dabrafenib and trametinib were in the first BRAF and MEK inhibitor combination in clinical trials, and currently the FDA approved combination in patients with advanced BRAFV600 mutated melanoma. In the first phase I/II study (BRF113220), 8 patients received repeated doses of trametinib and a single dose of dabrafenib to confirm absence of a drug–drug interaction, and 77 patients received escalating doses of dabrafenib [75 and 150 mg twice daily (BID)] in combination with trametinib [1, 1.5 and 2 mg every day (QD)] to determine toxicity profile and pharmacokinetic activity [Flaherty *et al.* 2012a].

In the phase II portion of this study, 162 patients with BRAFV600 mutated advanced melanoma with no prior BRAF targeted therapy were assigned 1:1:1 to receive combination therapy with dabrafenib (150 mg QD) and trametinib (either 1 or 2 mg daily) or dabrafenib (150 mg) monotherapy. For these patients, median (PFS for those in the combination 150/2 group was 9.4 months *versus* 5.8 months for patients who received dabrafenib monotherapy [hazard ratio (HR) for progression or death, 0.39; $p < 0.001$) A 1-year PFS rate of 41% was observed in the combination 150/2 group *versus* 9% in the monotherapy group ($p < 0.001$). Table 1 shows key findings from several BRAF/MEK inhibitor combination clinical trials.

In the combination 150/2 group, an objective response rate (ORR) of 76% *versus* 54% with dabrafenib monotherapy was observed ($p = 0.03$). The 1-year overall survival (OS) rate was 79% in the combination 150/2 group and 70% in the monotherapy group, even though 80% of patients in the monotherapy group crossed over to the combination at the time of disease progression. Updated data showed a median OS of 25 months with the combination with a 3-year OS rate of 38%, and normal lactate dehydrogenase (LDH) and <3 sites of metastases were associated with longer survival [Daud *et al.* 2015b]. (Another analysis of BRAF inhibitor treated patients, which included 31 treated with dabrafenib and trametinib combination, also found that normal LDH was associated with improved PFS and OS [Menzies *et al.* 2015]). The most frequent adverse events (AEs) observed in the 150/2 group were pyrexia (all grades, 71%; grade 3, 5%) and chills (all grades, 58%; grade 3, 2%); the most frequently occurring grade 3 or 4 toxicity in the 150/2 group was neutropenia (in 11% of patients), with one case of febrile neutropenia.

Skin toxicities such as cutaneous squamous cell carcinoma with BRAF inhibitor monotherapy had been linked to paradoxical activation of the MAPK pathway activation during BRAF inhibition, while a mouse model had shown blockage of this effect with the addition of a MEK inhibitor [Su *et al.* 2012]. The trial results also supported these findings, as cutaneous squamous cell carcinoma was observed in 19% of patients treated with dabrafenib alone, but only in 2% of combination 150/1 and 7% of combination 150/2 patients ($p = 0.004$ and $p = 0.09$, respectively).

The 45 patients who had disease progression on this study while receiving dabrafenib monotherapy could cross over to receive combination 150 mg/2 mg dosing regimen, which was reported in a subsequent analysis, along with another cohort of 25 patients who received the combination after disease progression with single agent BRAF inhibitor [Johnson *et al.* 2014]. For these patients who received dabrafenib and trametinib after progression on BRAF inhibitor monotherapy, an ORR of only 13% [95% confidence interval (CI): 5–27%) to 15% (95% CI: 4–35%) was reported. Median PFS was only 3.6 months (95% CI: 2–4), and median OS was 11.8 months (95% CI: 8–25) for the 45 crossover patients. Patients who previously received dabrafenib for at least 6 months had better outcomes with the combination compared with those treated for <6 months, with median PFS of 3.9 *versus* 1.8 months (HR, 0.49; $p = 0.02$) and ORR of 26% *versus* 0%.

Two phase III trials were subsequently conducted with dabrafenib and trametinib therapy. A randomized phase III study (COMBI-d) compared combination of first-line therapy with dabrafenib

Table 1. Results from BRAF and MEK inhibitor combination trials.

Trial	Treatment arms	Median PFS	Median OS/OS rates	ORR	Grade 3/4 AE %
BRF113220 [ClinicalTrials.gov identifier: NCT0107217]	Phase II section with dabrafenib (150 mg BID) and trametinib (2 mg QD) *versus* dabrafenib	9.4 months with combo *versus* 5.8 months with dabrafenib	25 months with combo, 2-year OS rate of 51%, 3-year OS rate of 38% with combo	76% with combo *versus* 54% with dabrafenib	58% with combo *versus* 43% with dabrafenib
COMBI-d [ClinicalTrials.gov identifier: NCT01584648]	Phase III dabrafenib and trametinib *versus* dabrafenib	11 months with combo *versus* 8.8 months with dabrafenib	25.1 months with combo *versus* 18.7 months dabrafenib, 2-year OS rate of 51% *versus* 42%	69% with combo *versus* 53% with dabrafenib	35% with combo *versus* 37% with dabrafenib
COMBI-v [ClinicalTrials.gov identifier: NCT0159790]	Phase III dabrafenib and trametinib *versus* vemurafenib	11.4 months with combo *versus* 7.3 months with vemurafenib	Not reached for combo, 17.2 months for vemurafenib	64% with combo *versus* 51% with vemurafenib	52% with combo *versus* 63% with vemurafenib
BRIM7 [ClinicalTrials.gov identifier: NCT01271803]	Phase Ib vemurafenib and cobimetinib (BRAF inhibitor naïve patient group)	13.7 months	28.5 months, 2-year OS rate of 61%	87%	62% for all patients
coBRIM [ClinicalTrials.gov identifier: NCT01689519]	Phase III vemurafenib and cobimetinib *versus* vemurafenib	12.3 months with combo *versus* 7.3 months with vemurafenib	Not available yet	70% with combo *versus* 50% with vemurafenib	65% with combo *versus* 59% with vemurafenib
CMEK162X210	Phase Ib/2 encorafenib and binimetinib	11.3 months	Not available yet	74.5%	67% for 600 mg dose of encorafenib

AE, adverse event; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

(150 mg BID) and trametinib (2 mg QD) in 211 patients to dabrafenib and placebo in 212 patients. Patients with unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations were eligible and stratified according to baseline LDH concentration and BRAF genotype, with PFS as the primary endpoint [Long *et al.* 2014b]. Median PFS was 9.3 months in the combination arm and 8.8 months in the dabrafenib monotherapy arm (HR 0.75; $p=0.03$); an ORR of 67% in the dabrafenib–trametinib group and 51% in the dabrafenib-only group ($p=0.002$) was observed. Congruent with the phase II findings, frequency of cutaneous squamous cell carcinoma was lower in the dabrafenib and trametinib combination than dabrafenib alone (2% *versus* 9%), while pyrexia was more frequent in the combination arm (51% *versus* 28%) *versus* dabrafenib alone. A health-related quality of life analysis of the COMBI-d study patients was also conducted using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 which included questions on functional status and symptoms. Improved preservation of quality of life in physical, social and cognitive functioning, and pain were observed in the patients treated with the combination compared with dabrafenib alone [Schadendorf *et al.* 2015].

While statistically significant, the small absolute difference in PFS between the two arms of the COMBI-d study was initially surprising; however, updated results from the trial were published earlier this year with an additional 17 months of follow up [Long *et al.* 2015]. Median PFS was now reported at 11.0 months (95% CI: 8.0–13.9) *versus* 8.8 months (95% CI: 5.9–9.3), with an HR of 0.67 ($p=0.0004$). Median OS was also reported in this update,

observed at 25.1 months (95% CI: 19.2 to not reached) for the dabrafenib and trametinib combination arm, and 18.7 months (95% CI: 15.2–23.7) for dabrafenib monotherapy. Forty-seven percent of 211 patients in the dabrafenib and trametinib group had died *versus* 58% of 212 in the dabrafenib only group, with an HR of 0.71 ($p = 0.0107$). The survival benefit was present in all of the subgroup analyses, including patients with elevated LDH concentrations and regardless of the BRAF V600 mutation subtype.

A second phase III trial (COMBI-v) compared the dabrafenib-trametinib combination to vemurafenib monotherapy [Robert *et al.* 2015a]. The median PFS of the 352 patients who received the combination regimen was similar to the COMBI-d trial at 11.4 months *versus* 7.3 months with vemurafenib therapy (HR 0.56; $p < 0.001$) and ORR of 64% with the combination compared with 51% with vemurafenib alone ($p < 0.001$). Median OS for the combination had not been reached, while it was 17.2 months for the vemurafenib arm (HR 0.69, $p = .005$). The prespecified stopping boundary of the trial was crossed, and it was stopped for efficacy and amended to allow patients to crossover to the combination arm. Cutaneous squamous cell carcinoma and keratoacanthoma were observed in only 1% of patients in the combination arm and in 18% of those in the vemurafenib arm.

Vemurafenib and cobimetinib

Similar results in responses rates, PFS and OS have been reported with the combination clinical trials of the BRAF inhibitor vemurafenib and MEK inhibitor cobimetinib. Patients with advanced BRAFV600 mutated melanoma who were either BRAF inhibitor naïve ($n = 63$) or had either recently progressed on vemurafenib ($n = 66$) were included in the phase Ib BRIM7 trial [Ribas *et al.* 2014]. In the dose escalation phase, patients received vemurafenib 720 or 960 mg BID continuously and cobimetinib 60, 80 or 100 mg QD for 14 days on and 14 days off, or 21 days on and 7 days off, or continuously. The maximum tolerated dose was established as vemurafenib 960 mg BID in combination with cobimetinib 60 mg for 21 days on, 7 days off. The ORR rate was 87% in the 63 BRAF inhibitor naïve patients, with a median PFS of 13.7 months (95% CI: 10·1–17·5). Comparable with the ORR and PFS results in the dabrafenib/trametinib patients after they had progressed on dabrafenib alone, the ORR was only 15% in the 66 patients who had already progressed on vemurafenib, with a median PFS of 2.8 months (95% CI: 2·6–3·4). The study results were updated recently with an additional 11 months of follow up; a median OS of 28.5 months in the vemurafenib-naïve and 8.4 months in the vemurafenib-progressing patients was reported, with 2-year OS rates of 61.1% and 15.1% respectively [Pavlick *et al.* 2015].

Survival and ORR findings of the phase III coBRIM trial with vemurafenib and cobimetinib were also analogous to the COMBI-d and COMBI-v phase III trials of dabrafenib and trametinib discussed earlier. In the coBRIM trial, addition of cobimetinib (60 mg QD for 21 of 28 days) to vemurafenib (960 mg BID) led to an improvement in median PFS of 9.9 in the 247 patients *versus* 6.2 months in the 248 patients who received vemurafenib with placebo, with HR for death or disease progression of 0.51 ($p < 0.001$) [Larkin *et al.* 2014]. The ORR was 68% in the combination arm compared to 45% in the control arm.

The combination was associated with a nonsignificant higher incidence of grade 3 or 4 AEs compared with vemurafenib and placebo (65% *versus* 59%) and there was no significant difference in the rate of study drug discontinuation. Toxicities observed more frequently with the combination compared with single agent vemurafenib included central serous retinopathy, diarrhea, nausea or vomiting, photosensitivity, elevated aminotransferase levels and an increased creatine kinase level. As expected, the incidence of secondary cutaneous squamous cell cancers decreased with the combination therapy compared with vemurafenib alone (down to 2% compared with 11%). Study results were updated with an 8 months additional follow up, with a PFS of 12.3 months for the combination arm compared with 7.3 for monotherapy, HR 0.58, and ORR of 70% *versus* 50% respectively [Larkin *et al.* 2015]. Co-existing baseline activating RAS/RAF/RTK mutations together with BRAFV600 mutation were not associated with worse PFS or ORR. OS analysis data from the coBRIM trial are not yet available.

Encorafenib and binimetinib

The third BRAF and MEK inhibitor combination in clinical trials is encorafenib and binimetinib. In a phase Ib/II trial (CMEK162X2110) of patients with advanced BRAFV600 melanoma, patients were treated with 400, 450 or 600 mg

QD of encorafenib and 45 mg BID of binimetinib [Sullivan *et al*. 2015]. For the 55 patients without prior BRAF inhibitor therapy, the combined ORR was 74.5%, with a median PFS of 11.3 months (95% CI: 7.4–14.6) for all of the BRAF inhibitor naïve patients. A 64% frequency of grade 3/4 toxicities was observed in patients treated with 600 mg encorafenib, such as increased alanine aminotransferase (ALT) (18%), lipase (15%), aspartate transaminase (AST) (13%), and creatine phosphokinase (13%). A phase III trial (COLUMBUS) is ongoing with 3 arms: encorafenib 450 mg daily with 45 mg BID of binimetinib, encorafenib alone at 300 mg daily, and vemurafenib alone [ClinicalTrials.gov identifier: NCT01909453].

Intermittent dosing and sequencing of therapies

Preclinical studies have demonstrated that intermittent as opposed to continuous therapy with a BRAF inhibitor may delay the development of acquired resistance [Thakur and Stuart, 2013]. Acquired resistance to BRAF and MEK inhibitor therapy combination is also of significant concern with these drugs, and resistance mechanism are similar to mechanisms of resistance to BRAF inhibitors alone, except in greater magnitudes or in combinations such as BRAF ultra-amplification [Long *et al*. 2014a]. Melanoma clones resistant to BRAF and MEK inhibitor therapy also appear to display increased drug addiction compared with those resistant to BRAF inhibitors alone [Moriceau *et al*. 2015].

Therefore, studies examining sequential or intermittent dosing of BRAF and MEK inhibitors are ongoing. In the phase II randomized COMBAT study [ClinicalTrials.gov identifier: NCT02224781], patients are randomized to the combination of dabrafenib and trametinib *versus* their combination after 8 weeks of monotherapy with dabrafenib or trametinib. Biopsies are taken at randomization, week 2, week 8, week 10, and at progression to assess biomarkers linked to treatment response and resistance [Mateus *et al*. 2014]. The SWOG study S1320 [ClinicalTrials.gov identifier: NCT02196181] is looking at an intermittent dosing schedule, with patients treated with dabrafenib at 150 mg BID and trametinib 2 mg QD during an 8-week lead in period, and randomizing patients without disease progression at the end of the lead in period to either continuous dosing or to intermittent dosing with a 5 weeks on, 3 weeks off schedule [Algazi *et al*. 2015]. Serial biopsies are used to determine mechanisms associated with disease progression.

BRAF and MEK inhibitors in combination with other targeted therapies

Besides intermittent therapy, other drugs have been combined with BRAF and MEK inhibitors in an attempt to overcome acquired resistance. Preclinical studies have demonstrated that heat shock protein 90 (HSP90) inhibitors such as XL888 can overcome the onset of BRAF inhibitor resistance [Paraiso *et al*. 2012]. HSP90 is a chaperone protein involved in resistance mechanisms to BRAF targeted therapies and inhibition of HSP90 was shown to degrade proteins critical for vemurafenib resistance such as IGF1R, PDGFRβ, CRAF and cyclin D1 and to inhibit AKT, extracellular-signal-regulated kinase (ERK) and S6 signaling. There is an ongoing phase I study of vemurafenib with XL888 in patients with advanced BRAF V600-mutant melanoma [ClinicalTrials.gov identifier: NCT01657591], with plans for a triple combination with BRAF and MEK inhibitor therapy. PI3K–PTEN–AKT–upregulating genetic alterations have also been observed as a resistance mechanism to BRAF targeted therapies [Shi *et al*. 2014] and AKT inhibitors are undergoing clinical trials including in a triple combination of GSK2141795 with dabrafenib and trametinib in the SWOG study S1221 [ClinicalTrials.gov identifier: NCT01902173]. MDM2 is an oncogene that is a major negative regulator of the tumor suppressor p53; AMG 232 is a small molecule inhibitor of MDM2 designed to block the MDM2–p53 interaction and is currently under investigation in a phase I/II trial with dabrafenib and trametinib [ClinicalTrials.gov identifier: NCT02110355].

BRAF and MEK inhibitors in combination with immunotherapy

While response rates up to 70% have been observed with BRAF and MEK inhibitors in clinical trials, given the limited durability of responses, there has been interest in combination with checkpoint inhibitors such as anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) and anti-programed death 1 (anti-PD-1)/programmed death-ligand 1 (PD-L1) antibodies. These therapies offer less frequent objective responses compared with targeted therapies (10–15% range with the anti-CTLA-4

antibodies ipilimumab or tremelimumab, up to 30–40% with the anti-PD-1 antibodies nivolumab or pembrolizumab in patients with advanced melanoma), but with significant durability of responses compared with BRAF and MEK inhibitor therapies; a 2-year OS rate of 60% with first-line pembrolizumab and 4-year OS rate of 32% with first-line nivolumab have been reported [Schadendorf *et al.* 2015; Robert *et al.* 2015b; Ribas *et al.* 2013; Hodi *et al.* 2010, 2014; Daud *et al.* 2015a]. BRAF and MEK inhibition have been shown in tumor biopsies to modulate the immune microenvironment and increase CD8 positive T cells and melanoma differentiation antigens like MART-1 and gp100, which may have role in T-cell recognition [Frederick *et al.* 2013; Wilmott *et al.* 2012; Wargo *et al.* 2014] and animal studies have demonstrated improved survival with BRAF/MEK inhibitors when combined with anti-PD1 therapy [Hu-Lieskovan *et al.* 2015]. Subsequently clinical trials have been undertaken to determine if the combination of BRAF and MEK targeted therapies with immunotherapy would indeed result in higher frequency of long-lasting responses in patients with advanced BRAF mutated melanoma.

In a study undertaken to determine the safety of dabrafenib with and without trametinib and ipilimumab at the doses of dabrafenib 100 mg BID, trametinib 1 mg QD and ipilimumab at the FDA-approved dose of 3 mg/kg every 3 weeks for 4 doses, 2 out of 7 advanced melanoma patients developed grade 3 colitis complicated by perforation [Puzanov, 2015]. Therefore, enrollment to the triple combination arm was stopped, although the dabrafenib and ipilimumab combination arm is ongoing. Another ongoing trial is looking at the combination of the anti-PD-L1 antibody MEDI4736 at 10 mg/kg every 2 weeks, together with dabrafenib 150 mg BID and trametinib 2 mg QD [Ribas *et al.* 2015]. Tumor biopsies from the patients have revealed evidence of immune activation post-treatment, with frequency of tumor-infiltrating CD8+ T cells and levels of interferon-γ increased post-treatment. For the 26 BRAF mutated advanced melanoma patients treated with the triple combination, an ORR of 69% was obtained and 16 out of 18 patients have ongoing responses. There was no exacerbation of immune-related AEs. While an ORR of 69% does not appear to be higher than the ORR of BRAF and MEK inhibitor combinations alone, some of the responses may not have declared yet during the short follow up presented for this study; more importantly, further follow up will determine how durable the tumor responses of these patients will be. Another ongoing phase I/II trial KEYNOTE-022 [ClinicalTrials.gov identifier: NCT02130466] is looking at the combination of pembrolizumab with dabrafenib and trametinib.

Patients with brain metastases

There has been a special focus in patients with brain metastases in metastatic melanoma. While animal studies have suggested that BRAF inhibitors may have limited brain distribution due to efflux from transporters such as P-glycoprotein, activity has been seen clinical trials [Mittapalli *et al.* 2013]. In the BREAK-MB trial of 171 patients with at least one asymptomatic brain metastasis treated with 150 mg dabrafenib BID, there was an ORR of 39.2% in patients with melanoma brain metastases without previous local (brain) therapy, with a 39.2% intracranial response rate which went down to 30.8% in patients with prior local therapy [Long *et al.* 2012]. In a small study of 24 patients with unresectable and previously treated brain metastases, a 42% ORR was observed at both intracranial and extracranial sies of disease with vemurafenib treatment [Dummer *et al.* 2014]. Limited data have been reported on low cerebrospinal fluid (CSF) concentrations of vemurafenib in patients, although CSF drug concentration may not necessarily be the optimum surrogate marker for concentration of a drug in brain tumor tissue [Sakji-Dupré *et al.* 2015]; there have also been case reports of melanoma patients with leptomeningeal disease who have had responses to vemurafenib [Schäfer *et al.* 2013; Kim *et al.* 2015]. There is an ongoing phase II study of the dabrafenib and trametinib combination in patients with BRAF mutation-positive melanoma that has metastasized to the brain; cohorts will include patients with symptomatic and asymptomatic brain metastases, and with or without prior therapy to the brain [Davies *et al.* 2014]. Another study, coBRIM-B, is focusing on vemurafenib and cobimetinib therapy in patients with active melanoma brain metastases with the primary objective of determining the objective intracranial response rate [Yee *et al.* 2015].

Conclusion

In comparison with single agent BRAF inhibitors, the combination of BRAF and MEK inhibitors have shown significant improvement in response

rates, PFS and OS in addition to fewer side effects related to paradoxical activation of the MAPK pathway; the combination has now become the standard of care in patients with BRAFV600 mutated advanced melanoma for whom targeted therapy is used. While there has not yet been direct comparison of the three different BRAF–MEK inhibitor combinations in clinical trials, they have shown similar clinical efficacy. There are some differences in the toxicity profiles of the combinations, such as much more frequent pyrexia with dabrafenib and trametinib compared with vemurafenib/cobimetinib and encorafenib/binimetinib, and vice versa with photosensitivity much more common with vemurafenib/cobimetinib; hepatic enzyme elevations were reported more frequently with encorafenib/binimetinib in comparison with the other two combinations.

However, the decision about whether to use targeted therapy or immunotherapy first in these patients is still not fully delineated. While response rates of up to 70% have been observed with first-line BRAF/MEK targeted therapy, the duration of responses is still only about a year. Although anti-PD-1 inhibitors are now FDA approved for BRAF mutated melanoma only after progression on targeted therapy and ipilimumab, it is expected that anti-PD-1 inhibitors will soon gain approval for upfront systemic therapy in advanced melanoma. Perhaps not all patients with BRAF mutated melanoma should be treated with BRAF–MEK inhibitor therapy in the first line, although it is it not yet clear which patients would benefit from upfront targeted *versus* immune therapy. Clinical trials are ongoing to answer this question, such as looking at sequence of BRAF/MEK inhibitor therapy followed by the ipilimumab and nivolumab combination after progression, and vice versa. [ClinicalTrials.gov identifier: NCT02224781]. Further studies to determine which patients may be more likely to respond to immunotherapy are also continuing, and perhaps in the future, patients with BRAFV600 mutations who are determined to be less likely to respond to upfront checkpoint inhibitor therapy can be considered for BRAF/MEK therapy, whereas those with features more likely for response may be treated with upfront immunotherapy, with targeted therapy reserved for progression. In addition, initial results from triple combinations of BRAF–MEK inhibitors with anti-PD-L1 antibodies appear promising and may provide an additional treatment option for patients with BRAF mutated advanced melanoma.

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