Review Article

Treatment of BRAF-mutated advanced cutaneous melanoma

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Abstract: The field of melanoma oncology has recently awakened with groundbreaking scientific advances and innovative therapeutic strategies. New groups of small-molecule kinase inhibitors targeting the aberrant mitogen-activated protein kinase (MAPK) pathway activation mediating tumor growth and survival have revolutionized the therapeutic approach to advanced melanoma. BRAF and MEK inhibitors are the first groups of agents that improved all clinical efficacy endpoints, including response rate, progression-free survival (PFS) and overall survival (OS), in patients with BRAF-mutated advanced melanoma when compared with standard chemotherapy in randomized phase III studies. However, despite the impressive clinical responses in patients with BRAF mutant advanced melanoma, duration of response to MAPK pathway-targeted therapy remains limited, implicating rapid emergence of drug resistance. Diverse strategies to overcome tumor resistance to MAPK inhibitors, the focus of today's translational and clinical research, will further improve the clinical outcome for patients with BRAF-mutated advanced melanoma in the near future.

Keywords: Advanced melanoma; BRAF mutation; vemurafenib; dabrafenib; LGX818; BRAF inhibitor; selumetinib; trametinib; cobimetinib; MEK162; MEK inhibitor; dual mitogen-activated protein kinase (MAPK) blockade; BRAF inhibitor resistance

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Introduction

The most important reason for the dismal prognosis faced by patients with advanced melanoma has been lack of effective therapies (1). About a decade ago, melanoma tumors were found to harbor several driver mutations in various components of the mitogen-activated protein kinase (MAPK) signaling transduction pathway, an important signaling pathway regulating cell growth, differentiation and survival (2). Mutation in the *BRAF* gene is the most common event, occurring in approximately 50% of melanomas. This molecular insight has propelled drug development for advanced melanoma into the realm of genomic medicine. This chapter will focus on the targeted therapies that have been approved by regulatory agencies or are under investigation for the treatment of BRAF-mutated advanced melanoma.

BRAF mutations in melanoma

The most common oncogenic BRAF mutations in melanoma are $BRAF^{V600E}$ and $BRAF^{V600K}$, representing 80-90% and 10-20% of all BRAF mutations, respectively (3,4). $BRAF^{V600E}$ and $BRAF^{V600K}$ are point mutations corresponding to the valine-to-glutamic acid and valine-to-lysine substitutions at amino acid 600, respectively. $BRAF^{V600E}$ and $BRAF^{V600K}$ kinases are constitutively active, sustaining MAPK signaling and perpetuating cell growth. Phenotypically, $BRAF^{V600E}$ and $BRAF^{V600K}$ confer aggressive behavior to melanoma cells (5,6) and have been correlated with unfavorable disease survival in patients with metastatic melanoma (4). There is also evidence to indicate an association between BRAF mutations and the frequency of central nervous system metastases at the time of stage IV diagnosis (3).

Identification of constitutively activating BRAF mutations

in melanoma tumors has led to the development of MAPK-pathway targeted small molecule kinase inhibitors, specifically BRAF and MEK inhibitors, for the treatment of advanced melanoma. Blocking the mutation-driven constitutive activation of MAPK pathway, these agents have significantly improved antitumor response and survival for patients with $BRAF^{V600}$ mutant advanced melanoma in randomized phase III studies, leading to the approval of vemurafenib in 2011, and of dabrafenib and trametinib in 2013 in the US (7-9).

MAPK pathway targeted therapies

Selective BRAF inhibitors

Vemurafenib

Vemurafenib is an orally active, selective small-molecule inhibitor of mutant BRAF kinase with marked anti-tumor activity in melanoma cell lines harboring the $BRAF^{V600E}$ mutation. Vemurafenib also inhibits other kinases such as CRAF and wild-type BRAF *in vitro*. The *in vitro* half-maximal inhibitory concentration (IC_{50}) values of vemurafenib for $BRAF^{V600E}$, wild-type BRAF and CRAF are 31, 100 and 48 nM, respectively (10). Based on the impressive clinical activity of vemurafenib in phase I and II studies (11,12), BRIM 3, a randomized phase III trial, was conducted to compare vemurafenib to dacarbazine in patients with unresectable stage III or IV melanoma (13). In this trial, 675 previously untreated patients with $BRAF^{V600E}$-positive advanced melanoma were randomly assigned to vemurafenib 960 mg orally twice a day or dacarbazine 1 gm/m^2 intravenously every 3 weeks. Progression-free survival (PFS) and overall survival (OS) were the co-primary endpoints of the study. At a median follow-up of 3.8 months for the vemurafenib-treated patients and 2.3 months for those given dacarbazine, vemurafenib was associated with a 63% relative reduction in the risk of death and 74% relative reduction in the risk of disease progression compared to dacarbazine (P<0.001). Other clinical benefits of vemurafenib included more rapid disease control and higher response rate. Considering the striking clinical benefit of vemurafenib, the independent data and monitoring board recommended allowing patients to cross over from the dacarbazine group to receive vemurafenib at disease progression (13).

Safety and efficacy results of this phase III study were recently updated at a median follow-up of 12.5 and 9.5 months on vemurafenib and dacarbazine, respectively. The median OS was 13.6 months in the vemurafenib arm versus 9.7 months in the dacarbazine group, with hazard ratio (HR) for death of 0.70 (95% CI: 0.57-0.87; P=0.0008) favoring vemurafenib (14). Median PFS was significantly longer in the vemurafenib group than in the dacarbazine group [6.9 *vs.* 1.6 months; HR 0.38 (95% CI: 0.32-0.46); P<0.0001]. The updated analysis also assessed the relative impact of vemurafenib with respect to BRAF mutation subtypes, demonstrating similar efficacy and toxicity profile in patients with $BRAF^{V600E}$ and $BRAF^{V600K}$ mutation (14).

Vemurafenib is generally well tolerated, with common adverse events including arthralgia, fatigue, nausea, rash, photosensitivity and cutaneous squamous cell carcinoma (cSCC) or keratoacanthoma (KA) (14). The most frequently observed grade 3 or 4 adverse events were cSCC/KA, transaminitis and rash (14). In the BRIM 3, 38% of vemurafenib-treated patients required dose modification or interruption due to adverse events (13); however, permanent discontinuation of vemurafenib occurred in only 7% of the study population (14). Vemurafenib was the first targeted therapy approved by the US Food and Drug Administration (FDA) for patients with $BRAF^{V600E}$ mutated advanced melanoma in 2011 (7).

Dabrafenib

Dabrafenib is a potent inhibitor against mutant $BRAF^{V600E}$, $BRAF^{V600K}$ and $BRAF^{V600D}$ kinases, with IC50 values of 0.65, 0.5 and 1.84 nM, respectively (8). It also has activity against wild type BRAF and CRAF kinases at higher IC50 values of 3.2 and 5.0 nM, respectively (8). Dabrafenib has been shown to inhibit growth of $BRAF^{V600}$ mutant melanoma cells *in vitro* and *in vivo* (8). The significant antitumor activity of dabrafenib in BRAF-mutated advanced melanoma noted in phase I and II studies (15,16) has led to the BREAK-3 study, the registration trial that later earned the licensing of dabrafenib for $BRAF^{V600E}$ mutant advanced melanoma in the US in 2013 (17).

In this trial, 250 patients with $BRAF^{V600E}$-mutated unresectable stage III or stage IV melanoma were randomly assigned 3:1 to receive dabrafenib 150 mg orally twice a day continuously (n=187) or dacarbazine 1 gm/m^2 intravenously every 3 weeks (n=63). Previous therapy, except for interleukin-2, was not allowed. Patients initially assigned to receive dacarbazine were able to crossover to receive dabrafenib upon disease progression. The primary endpoint of the study was investigator-assessed PFS. Secondary endpoints included PFS as assessed by an independent review committee, OS, objective response rate, duration of response and safety (17).

At a median follow-up of 5.1 and 3.5 months for those treated with dabrafenib or dacarbazine, respectively, 44% of the dacarbazine-treated patients had crossed over to the dabrafenib arm. Per investigators' assessment, the median PFS was 5.1 months in the dabrafenib group and 2.7 months in the dacarbazine group, with HR for progression of 0.30 (95% CI: 0.18-0.51; P<0.0001) favoring dabrafenib. The evaluation by the independent review panel revealed similar results, with median PFS of 6.7 months for the dabrafenib group and 2.9 months for the dacarbazine group (HR 0.35; 95% CI: 0.20-0.61). Objective response rate with dabrafenib was 53%, superior to 19% with dacarbazine (17).

Updated survival data were presented at the 2013 ASCO annual meeting, confirming the PFS advantage of dabrafenib (18). The updated median PFS was 6.9 months in the dabrafenib arm and 2.7 months in the dacarbazine arm, with HR for disease progression of 0.37 (95 % CI: 0.23-0.57) favoring dabrafenib. OS results were difficult to interpret due to the crossover effect. Median OS was 18.2 and 15.6 months in the patients treated with dabrafenib and dacarbazine, respectively (HR 0.76; 95% CI: 0.48-1.21) (18).

Dabrafenib was well tolerated. Dose reduction for toxicities was required in 28% of patients, and permanent discontinuation of dabrafenib occurred in 3% of the study population (17). The most frequently reported adverse effects of dabrafenib include hyperkeratosis, pyrexia, fatigue, headache, and arthralgia. However, the most common reasons for dabrafenib dose reduction in the BREAK-3 were pyrexia, palmar-plantar erythrodysesthesia syndrome, chills, fatigue and headache. KA and cSCC, the unique class effect of the selective BRAF inhibitors, were documented in 6% of patients (17). The toxicity profile of dabrafenib appeared different than that of vemurafenib. The incidence of arthralgia, photosensitivity and transaminitis seemed lower with dabrafenib at the expense of increased pyrexia, hyperglycemia and hypophosphatemia when compared with vemurafenib (13,17).

LGX818

LGX818 is a highly potent BRAF inhibitor under development for BRAF-mutated advanced melanoma. Compared to vemurafenib and dabrafenib, LGX818 has a much longer half-life of dissociation from $BRAF^{V600E}$ kinase, resulting in sustained MAPK pathway inhibition (19). The results of a phase I dose-finding study of LGX818 conducted in 54 BRAF inhibitor-naïve or refractory patients with $BRAF^{V600}$ mutant advanced melanoma were reported at the 2013 ASCO annual meeting (20). In this study, LGX818 dose ranged from 50-700 mg daily to 75-150 mg twice daily. LGX818 plasma concentration increased proportionally to dose, with a mean half-life of 4 hours. The maximum tolerated dose (MTD) or recommended phase II dose (RP2D) was 450 mg once daily, which appeared well tolerated. LGX818's toxicity profile mimicked those of vemurafenib and dabrafenib, with cutaneous manifestations, arthralgia and fatigue being most common. cSCC was seen in two patients. The preliminary efficacy data also appeared similar to other selective BRAF inhibitors, with overall response rates at all dose levels of 67% and 8.3% in the BRAF inhibitor-naïve and BRAF inhibitor-exposed groups, respectively. The ongoing COLUMBUS trial is a randomized, open label, 3-arm phase III study comparing the efficacy and safety of LGX818-MEK162 combination or LGX818 monotherapy to vemurafenib in patients with unresectable or metastatic melanoma with BRAF V600 mutation (NCT01909453).

MEK inhibitors

Selumetinib (AZD6244, ARRY-142886)

Selumetinib is an orally available allosteric inhibitor of MEK1 and MEK2 kinases with demonstrated anti-proliferative activity in $BRAF^{V600E}$-mutant cell lines (21). Early clinical trials of selumetinib were carried out with the free-base formulation at the RP2D of 100 mg orally twice a day (22). In a phase II study by Kirkwood and colleagues, 200 patients with treatment-naïve advanced melanoma were randomized to selumetinib 100 mg twice daily continuously or temozolomide 200 mg/m^2 daily for 5 days every 28 days (23). Patients with advanced mucosal or uveal melanoma were allowed to participate. BRAF mutation positivity was not required for enrollment; however, correlation of treatment effect to BRAF or NRAS mutation status was prospectively planned. Patients in the temozolomide arm were able to crossover to receive selumetinib at disease progression.

PFS did not differ significantly between selumetinib and temozolomide (median time to progression 78 and 80 days, respectively; HR 1.07; 80% CI: 0.86-1.32; 1-sided P=0.65; 2-sided P=0.699). There was also no significant difference in PFS between the 2 groups in the BRAF- and/or NRAS-mutant subsets. Partial response was observed in 5.8% and 9.4% in the selumetinib and temozolomide arms, respectively. Among patients with BRAF mutations, objective responses were similar between selumetinib and temozolomide groups (11.1% and 10.7%, respectively). However, 5 of the 6 selumetinib partial responders were

BRAF-mutated. The low level of clinical activity of selumetinib was attributed to unselected patient population and poor bioavailability of the free-base formulation. Selumetinib was fairly well tolerated. The most common adverse events were acneiform dermatitis, diarrhea, nausea, vomiting, peripheral edema and fatigue.

Hint of selumetinib's anti-tumor activity in patients with BRAF-mutant melanoma in the above study and preclinical evidence of synergy between MEK inhibitor and cytotoxic chemotherapy (24) provided the rationale for the randomized phase II trial by Robert and colleagues comparing dacarbazine plus selumetinib versus dacarbazine plus placebo in 91 previously untreated patients with advanced BRAF-mutated cutaneous melanoma (25). This study utilized selumetinib hydrogen sulfate salt in capsule at the MTD of 75 mg twice daily, which was shown to increase drug exposure by 2-fold when compared to the free base suspension (22). Dacarbazine was administered at 1 gm/m^2 every 3 weeks for up to eight cycles. Crossover at disease progression was not allowed. At a median follow-up of 12.3 months, there was no difference between the two arms in the primary endpoint of OS. Median OS was 13.9 months in the selumetinib-dacarbazine group versus 10.5 months in the placebo-dacarbazine arm (HR 0.93; 80% CI: 0.67-1.28; 1-sided P=0.39).The addition of selumetinib to dacarbazine did not improve survival outcome in patients with BRAF-mutated advanced melanoma. However, PFS was significantly improved in the selumetinib plus dacarbazine group versus the placebo plus dacarbazine group (HR 0.63, 80% CI: 0.47-0.84, one-sided P=0.021), with a median of 5.6 months (80% CI: 4.9-5.9) versus 3.0 months (2.8-4.6), respectively. The limited clinical activity of selumetinib has curbed enthusiasm for its utility in BRAF-mutated cutaneous melanoma; however, it continues to be evaluated for metastatic uveal melanoma.

Trametinib (GSK1120212)

Trametinib is another orally available allosteric inhibitor of MEK1 and MEK2 kinases. Phase I study of trametinib demonstrated a favorable pharmacokinetic profile with small peak-to-trough ratio, long half-life and low interpatient variability, which may improve its therapeutic index in comparison to other MEK inhibitors (26). In 2013, trametinib became the first MEK inhibitor licensed in the US as monotherapy for BRAF^{V600E} or BRAF^{V600K} advanced melanoma based on its survival benefit evident in the phase III METRIC trial (27).

In this study, 322 patients with BRAF^{V600E}- or BRAF^{V600K}-mutated advanced melanoma who had failed one prior chemotherapy regimen were randomized in 2:1 ratio to trametinib 2 mg orally daily or chemotherapy. For chemotherapy, investigators could choose dacarbazine 1 gm/m^2 or paclitaxel 175 mg/m^2 administered intravenously every 21 days. Patients who had disease progression on chemotherapy were allowed to cross over to receive trametinib (27).

Trametinib and chemotherapy produced an overall response rate of 22% and 8%, respectively. Median PFS, the primary endpoint of the trial, was 4.8 months in the trametinib arm and 1.5 months in the chemotherapy group, with HR for progression or death of 0.45 (95% CI: 0.33-0.63; P<0.001) favoring trametinib. At 6 months, the rate of OS was 81% in the trametinib group and 67% in the chemotherapy group (HR for death 0.54; 95% CI: 0.32-0.92; P=0.01), despite the fact that 47% patients in the chemotherapy arm had crossed over at the primary analysis (27). Updated survival data were presented at the Society for Melanoma Research Meeting in November 2013. Median OS was 15.6 and 11.3 months in the groups treated with trametinib and chemotherapy, respectively (HR 0.78; 95% CI: 0.57-1.06). In this analysis, 65% patients in the chemotherapy arm had crossed over to receive trametinib (28).

Rash, diarrhea, peripheral edema, and fatigue were the most common toxicities of trametinib and were managed with dose interruption and dose reduction; asymptomatic reduction in the cardiac ejection fraction and reversible ocular toxic effects occurred infrequently (27). Interestingly, hyperproliferative skin lesions such as cSCC or KA were not observed with trametinib. In the METRIC study, 35% and 27% of trametinib-treated patients required dose interruption and reduction due to adverse events, respectively (27).

Cobimetinib (GDC-0973)

Cobimetinib is an ATP noncompetitive inhibitor highly specific for MEK1 and 2 kinases. A phase I trial in 87 previously treated patients with advanced solid tumors established the MTD of cobimetinib at 60 mg orally daily for 3 weeks of a 28-day cycle or 100 mg orally daily for 2 weeks followed by 2 weeks of rest (29). Six patients with advanced melanoma achieved partial response, 5 of whom had documented BRAF mutation. Common adverse events were rash, diarrhea, nausea, vomiting, fatigue and edema. Central serous retinopathy, a class effect of MEK inhibitor, was infrequently observed. Currently, cobimetinib is being evaluated in combination with vemurafenib in patients with

advanced BRAF V600-mutant melanoma (NCT01689519).

MEK162 (ARRY-438162)

MEK162 is an oral, ATP noncompetitive, highly selective inhibitor of MEK1 and 2 kinases with promising activity against NRAS- and $BRAF^{V600E}$-mutated melanoma in preclinical models. A phase I study in patients with advanced solid tumors established the MTD at 60 mg orally twice a day (30). Promising clinical activity in patients with NRAS- or BRAF-mutant advanced melanoma has been noted in an open-label phase II trial conducted by Ascierto and colleagues (31).

In this study, previously-treated patients with NRAS- or BRAF-mutated advanced melanoma were assigned to one of three treatment cohorts. The NRAS-mutated cohort received MEK162 at 45 mg twice daily, whereas those with BRAF-mutated melanoma could be treated in one of 2 cohorts: 45 or 60 mg twice a day. At data cutoff, there were too few patients in the 60-mg cohort to analyze results. Thirty and 41 patients with NRAS- and BRAF-mutated melanoma, respectively, were treated with 45 mg twice daily. At a median follow-up of 3.3 months, 20% patients in each group achieved partial response (31). MEK162 is the first targeted therapy to show activity in patients with NRAS-mutated melanoma.

MEK162 was fairly well tolerated, with 13% and 27% of patients in the NRAS- and BRAF-mutated groups discontinuing treatment due to adverse events, respectively. The most frequent adverse events were acneiform dermatitis, rash, peripheral edema, facial edema, diarrhea, and elevated creatine phosphokinase. Central serous retinopathy-like events, all grade 1 or 2, were observed in 18% patients. Currently, in addition to the combination trial with LGX818 in BRAF-mutated melanoma (NCT01909453), MEK162 is also being evaluated against dacarbazine in a phase III trial in patients with NRAS-mutated advanced melanoma (NCT01763164).

Combined BRAF and MEK inhibitors

Despite the striking clinical benefit in patients with BRAF-mutated advanced melanoma, duration of response to MAPK pathway-targeted therapy is relatively short, implicating rapid emergence of drug resistance. Since MAPK reactivation is a common theme of tumor resistance mechanisms (32,33), dual MAPK pathway blockade with combined BRAF and MEK inhibitors may be advantageous in deterring resistance and limiting the development of squamo-proliferative skin lesions mediated by BRAF inhibitor-induced paradoxical MAPK pathway activation in BRAF wild-type cells (34).

Dabrafenib-trametinib

The concept of a dual MAPK pathway blockade was originally tested in a phase I/II study by Flaherty and colleagues (35). This study comprised four parts: part A examined drug-drug interaction between dabrafenib and trametinib, part B was the dose escalation portion to define the MTD/RP2D for the combination, part C was the randomized phase II study comparing the combination against dabrafenib monotherapy, and part D evaluated a new formulation of dabrafenib capsule.

In part C, 162 patients with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutated advanced melanoma were randomized 1:1:1 to receive dabrafenib 150 mg twice daily with trametinib 2 mg daily (150/2), dabrafenib 150 mg twice daily plus trametinib 1 mg daily (150/1), and dabrafenib monotherapy. Patients could have up to one prior systemic therapy for advanced disease except for BRAF and/or MEK inhibitors. Primary endpoints for part C included the incidence of cSCC, PFS and response rate. Patients who had disease progression on single-agent dabrafenib were allowed to cross over to the 150/2 arm (35).

At a median follow-up of 14.1 months, median PFS was 9.4 months in the 150/2 arm and 5.8 months in the dabrafenib alone group, with HR for progression or death of 0.39 (95% CI: 0.25-0.62; P<0.001) favoring the combination (35). Overall response rate was also higher in the 150/2 arm than that observed in the dabrafenib alone group, 76% *vs.* 54%, respectively (P=0.03). Interestingly, cutaneous adverse events, including the development of cSCC, were lower with the combination (7% *vs.* 19%, P=0.09) at the expense of increased pyrexia and gastrointestinal side effects (35). The safety and efficacy of this combination are being confirmed in two randomized phase III trials in patients with $BRAF^{V600E}$- or $BRAF^{V600K}$-mutated advanced melanoma: the COMBI-D (NCT01584648) compares the combination to single-agent dabrafenib while the COMBI-V (NCT01597908) evaluates the combination against vemurafenib monotherapy.

Despite the remarkable clinical activity of dual BRAF and MEK inhibitors in BRAF inhibitor-naïve patients, the combination appears to have limited efficacy in those patients whose disease progressed after prior BRAF inhibitor therapy (36). In part B of the above study, full dose of dabrafenib-trametinib generated a response rate of 15% and a median PFS of 3.6 months in 26 BRAF

inhibitor-refractory patients with BRAF-mutated advanced melanoma. Similar results were noted in part C of the study in 43 patients who had crossed over from dabrafenib monotherapy to the combination 150/2 at disease progression. This group of patients achieved a response rate of 9% and a median PFS of 3.6 months with dual BRAF and MEK inhibitors (36).

Vemurafenib-cobimetinib

The preliminary safety and efficacy data of BRIM7, an ongoing phase Ib study evaluating vemurafenib-cobimetinib in BRAF inhibitor-naïve or vemurafenib-refractory patients, were presented at the European Cancer Congress 2013 (37). Dose-escalation schema involved ten dose cohorts, with vemurafenib 720 or 960 mg twice daily continuously combined with cobimetinib 60, 80, 100 mg daily for 2 weeks or 60 mg daily for 3 weeks or 60 mg daily continuously on a 28-day cycle. Dose-limiting toxicities, manifested as mucositis and arthralgia, were noted in the cohort receiving vemurafenib 960 mg twice daily plus cobimetinib 60 mg daily continuously (37).

The combination was fairly tolerable at the respective MTD for each agent, vemurafenib 960 mg twice daily continuously and cobimetinib 60 mg daily for 3 weeks followed by 1 week of rest. The most common toxicities included rash, diarrhea, fatigue, photosensitivity, and elevated liver function tests. Preliminary efficacy results in 108 evaluable patients appeared promising, with overall response rates of 73% in BRAF inhibitor-naïve and 14% in vemurafenib-refractory patients (37). Median PFS had not been reached due to short follow-up duration. The coBRIM trial, a randomized, double-blind, placebo-controlled phase III study comparing the combination to single-agent vemurafenib in previously untreated patients with V600-mutated advanced melanoma, is in progress (NCT01689519).

LGX818 + MEK162

Preliminary results of a phase Ib/II dose-finding study of this combination were reported at ASCO 2013 (38). The trial began with a dose-escalation phase in BRAF inhibitor-naïve or -pretreated patients with BRAF-mutant advanced solid tumors to define the safety profile and to establish the MTD or RP2D of the combination. Increasing dose of LGX818, 50-600 mg daily, was administered in combination with a fixed dose of MEK162, 45 mg BID. The MTD was not achieved in the evaluated dose range. Two RP2Ds, 450/45 and 600/45, were declared, and the phase II portion of the trial will begin with 600/45 with the objective of evaluating the efficacy of the combination (38).

No drug-drug interaction was observed. There was no significant increase in toxicity compared to respective monotherapy. The most common adverse events included grade 1 or 2 gastrointestinal symptoms, headache and fatigue. Cutaneous toxicities commonly observed with BRAF inhibitor monotherapy were not observed. No pyrexia or photosensitivity reactions have been reported to date. At the data cut-off point of the phase Ib portion, the response rate was 88% in BRAF inhibitor-naïve and 18% in BRAF inhibitor-exposed patients with BRAF-mutated advanced melanoma (38). COLUMBUS, a randomized, open label, 3-arm phase III study comparing the efficacy and safety of LGX818-MEK162 combination or LGX818 monotherapy to vemurafenib in patients with unresectable or metastatic melanoma with BRAFV600 mutation, is underway (NCT01909453).

The roles of MAPK pathway-targeted therapy in the management of BRAF-mutant advanced melanoma

In advanced disease

V600-mutated and BRAF inhibitor-naïve

The integration of MAPK pathway-targeted agents into the treatment algorithm of advanced cutaneous melanoma is discussed in depth in the article by Buzaid and colleagues in this special issue. If MAPK pathway-targeted agents are selected, current data appear to favor co-targeting BRAF and MEK due to improved response rate, prolonged PFS, and decreased likelihood of on-target adverse events secondary to paradoxical pathway activation by BRAF inhibitor monotherapy. However, until confirmatory data are available from various randomized phase III trials comparing dual MAPK pathway blockade to single-agent BRAF inhibitor, BRAF inhibitor monotherapy remains an appropriate option, especially in those patients who cannot tolerate the combination. With lower response rate and shorter PFS, trametinib monotherapy does not seem to play a significant role in the overall treatment schema, except in those patients who discontinue BRAF inhibitor monotherapy due to intolerable toxicities.

The toxicity profiles of BRAF inhibitors and management guidelines are reviewed in detail in the article by McArthur and colleagues in this special issue. Rash, diarrhea, peripheral edema, and fatigue are the most common toxicities of MEK inhibitors, and can be managed with symptom support,

dose interruption and dose reduction (23,25-27,29-31). Unlike the maculopapular rash seen with BRAF inhibitors, acneiform dermatitis is the typical cutaneous eruption with MEK inhibitors and can be treated with topical or systemic steroids in addition to topical and oral antibiotics (39). Rare class effects of MEK inhibitors are cardiac dysfunction and central serous retinopathy, requiring routine left ventricular ejection fraction monitoring and prompt ophthalmologic exam at development of visual disturbances (23,25-27,29-31). Generally, these serious adverse events are reversible with therapy interruption.

V600-mutated and BRAF inhibitor-refractory

Currently, whether or not to continue BRAF inhibitor at disease progression is an evidence-free zone. Considering the clinical benefits of continuing targeted therapies beyond progression in other oncogene-driven malignancies, such as HER2-positive breast cancer, EGFR-mutant non-small cell lung cancer or gastrointestinal stromal tumor (40-42), a randomized study comparing continuation versus discontinuation of BRAF inhibitor upon progression should be conducted to unravel this issue.

Since MAPK reactivation is the common theme of tumor resistance mechanisms, interrupting the pathway at the level of MEK represents a logical notion. MEK inhibition with trametinib 2 mg orally daily was explored as sequential therapy after BRAF inhibitor failure in a phase II study by Kim and colleagues (43). Previously treated patients with BRAF-mutant advanced melanoma were enrolled in two treatment cohorts based on their BRAF inhibitor exposure status. The primary endpoint was overall response rate. At data cutoff, no response was noted in 40 patients who had formerly been treated with a BRAF inhibitor (43). Of note, 2 patients who later achieved partial responses had previously discontinued BRAF inhibitor because of adverse events. MEK inhibitor monotherapy should not be used as sequential therapy after BRAF inhibitor failure. Despite the impressive efficacy of dual BRAF and MEK inhibition in BRAF inhibitor-naïve patients, the combination appears to have limited activity in patients whose disease progressed after BRAF inhibitor. The therapeutic role of co-targeting BRAF and MEK once BRAF inhibitor resistance has already occurred requires further investigation (43).

Non-V600-mutated

In addition to V600E and V600K subtypes, atypical BRAF mutations, such as K601E, G466E, G466V, G596R, etc., have been identified (44). Recently, *BRAF* gene fusions like PAPSS1-BRAF or TRIM24-BRAF have been isolated in melanoma tumors (45). At present, little is known about their oncogenic potential, nor the implication for MAPK pathway-targeted therapies. Future studies in these genetically defined subsets are needed.

In advanced disease with active brain metastases

Vemurafenib

Despite confirmed clinical activity against extracranial melanoma, data regarding the intracranial activity of vemurafenib are currently limited to a pilot study conducted by Dummer and colleagues (46). In this study, 24 patients with V600 mutated advanced melanoma and active brain metastases were treated with vemurafenib 960 mg orally twice a day. At enrollment, all patients required corticosteroid support and had failed at least one prior therapeutic modality for brain metastases. Half of the patients had four or more brain lesions, and 63% of them exhibited central nervous system-related symptoms at baseline (46).

The primary endpoint of the study was to assess the safety of vemurafenib in patients with active brain metastases. Secondary efficacy endpoints included best overall response rate (BORR), duration of response, PFS and OS, with BORR calculated separately for intracranial, extracranial, and whole body disease. Confirmed intracranial partial response to vemurafenib was 16% (95% CI: 3.4-39.6%), with intracranial disease stabilization observed in 68% of patients (95% CI: 43.4-87.4%). Median duration of tumor regression in the brain lasted 4.4 months (95% CI: 2.1-4.6). Overall response rate, based on tumor response when both intra- and extra-cranial disease were assessed, was 42% (95% CI: 22.1-63.4%). Median PFS and OS were 3.9 months (95% CI: 3.0-5.5) and 5.3 months (95% CI: 3.9-6.6), respectively. Corresponding to clinical response, patients' symptomatology also improved, as evident by reduction in corticosteroid requirement, decrease in pain score and improvement in performance status compared to baseline assessment. The safety profile of vemurafenib in this study was similar to previous experience from the BRIM 3. One patient died of ileus occlusion; however, it was not deemed treatment-related (46). A phase II study evaluating vemurafenib in a larger group of patients with BRAF-mutated advanced melanoma and active brain metastases is underway (NCT01378975).

Dabrafenib

Dabrafenib-induced intracranial tumor response observed in a phase I trial provided the rationale for BREAK-MB,

a large phase II study evaluating the safety and efficacy of dabrafenib 150 mg orally twice daily in melanoma patients with active brain metastases (47). A total of 172 patients with $BRAF^{V600E}$- or $BRAF^{V600K}$-mutated advanced melanoma with at least one asymptomatic brain metastasis measuring 5-40 mm in diameter were assigned to one of two cohorts: patients who had not received local therapy for brain metastases were assigned to cohort A, whereas those with progressive intracranial disease despite local therapy went to cohort B. Half of the patients had 2-4 brain lesions, and 81% of them had V600E mutation (47).

The primary endpoint of the study was the proportion of patients with V600E mutated melanoma who achieved an overall intracranial response assessed with a modified form of Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Secondary efficacy endpoints included intracranial response in patients with V600K-mutated melanoma, overall response, duration of intracranial and overall response, PFS and OS grouped by mutation subtype. Intracranial response to dabrafenib was 39.2% and 30.8% in patients with V600E mutation in cohort A and cohort B, respectively. Response rate in the brain was lower in patients with V600K-mutated tumor, 6.7% in cohort A and 22.2% in cohort B. Median durations of intracranial tumor regression lasted 20.1 and 28.1 weeks in cohort A and B for individuals with V600E-mutated melanoma, respectively. Median durations of response in the brain were shorter for patients with V600K-mutated tumor, 12.4 weeks in cohort A and 16.6 weeks in cohort B. Overall response rates, based on tumor response when both intra- and extra-cranial disease was assessed, were 37.8% (95% CI: 26.8-49.9) and 30.8% (95% CI: 19.9-43.5) in patients with V600E-mutated melanoma in cohort A and cohort B, respectively. Overall response rates were lower in those with V600K-mutated melanoma, 0% (95% CI: 0-21.8) in cohort A and 27.8% (95% CI: 9.7-53.5) in cohort B (47). Median OS was 31.4-33.1 weeks for those with V600E-positive tumor. Median OS was shorter for those with V600K-positive melanoma, ranging 16.3-21.9 weeks. The safety profile of dabrafenib in this study was similar to previous experience from the BREAK 3. Intracranial hemorrhages occurred in 10 patients, and 1 was treatment-related (47).

Dabrafenib-trametinib

Targeted therapy for melanoma brain metastases has also shifted towards dual MAPK blockade. COMBI-MB, an open-label, phase 2 study evaluating dabrafenib-trametinib combination in patients with V600-mutant melanoma and active brain metastases, has started enrolling patients (NCT02039947).

Median OS achieved with BRAF inhibitors in patients with BRAF-mutant melanoma involving the brain appeared favorable when compared to historical controls, whose median OS was approximately 4 months in published data (48-51). This suggests that both vemurafenib and dabrafenib produce meaningful intracranial response, expanding the pharmacologic options for this patient subset. This is particularly important when intracranial disease burden precludes neuro- or radio-surgery. Whether dual BRAF and MEK inhibition is safe and effective in patients with brain metastases remains to be determined.

Tumor resistance to MAPK inhibitors and future directions

Strategies to overcome tumor resistance to MAPK inhibitors

Despite the unprecedented high response rate seen with MAPK-targeted therapy, the duration of disease control is disappointingly short, implicating rapid emergence of drug resistance. The heterogeneous mechanisms of tumor resistance to MAPK-targeted therapy appear to arise from the complex interface between expansion of de novo resistant clones and acquisition of secondary bypass mechanisms (32,33,52). Unlike other oncogene-addicted tumors, gatekeeper mutation in the *BRAF* gene has not been identified in patient-derived tumor biopsy at disease progression. Most melanomas escape drug pressure by reactivating the MAPK pathway, whereas a few of them do so by signaling through the PI3K/Akt pathway (32,33).

MAPK reactivation can be achieved at multiple levels along the pathway. Up-regulation of receptor tyrosine kinases such as fibroblast growth factor receptor (FGFR) (53), increased secretion of growth factors like hepatocyte growth factor from stromal cells in the tumor microenvironment (54,55), acquisition of activating NRAS or MEK mutations (32,33), and alterations of *BRAF* gene by amplification or truncation (33) are among the common tactics tumor cells use to restore MAPK signaling.

Thus, the mission to overcome drug resistance to MAPK pathway-targeted therapy should be tackled from various angles and guided by tumors' genotypes at disease progression. To avoid selecting out de novo resistant clones, an intermittent dosing schedule has been proposed to deter the emergence of drug resistance (56) based on the observation

that tumor sensitivity to BRAF inhibitor was restored after a drug-free period in 2 patients with $BRAF^{V600E}$-mutated advanced melanoma refractory to BRAF inhibitor (NCT01894672) (57). With emerging data indicating that MAPK pathway reactivation also mediates tumor escape from dual BRAF and MEK inhibition, ERK inhibitors such as MK-8353 have been developed and entered phase I trial (NCT01358331). Rational combinations of BRAF inhibitor with another targeted therapy directing at the predominant mechanism of tumor resistance identified from tumor tissue sample at disease progression are being actively pursued. Based on the current knowledge of tumor escape from MAPK pathway blockade, the second targeted agent can be an inhibitor of MEK, PI3K, FGFR, CDK4/6 or c-met (NCT01820364).

Another strategy to improve efficacy and overcome drug resistance is to combine BRAF inhibitors with immunotherapy such as ipilimumab. Theoretically, rapid tumor antigens released after MAPK inhibitor-induced tumor apoptosis can effectively stimulate antigen-specific cytotoxic T-lymphocyte responses, of which activation and proliferation are augmented by concurrent immunotherapy. An additional rationale for this approach stems from preclinical data suggesting that increased MAPK signaling can decrease melanoma antigen expression in tumor cells (58,59). Unfortunately, the phase I study examining the concurrent administration of ipilimumab with vemurafenib was terminated early due to unacceptable hepatotoxicity (60). Investigators are now assessing the toxicity profile of sequencing vemurafenib and ipilimumab in a phase II study (NCT01673854). The low incidence of hepatic adverse events with dabrafenib makes it an ideal candidate for combination therapy with ipilimumab. Ipilimumab with dabrafenib plus or minus a MEK inhibitor is currently being investigated in a phase I dose-finding study in patients with BRAF V600-mutant advanced melanoma (NCT01767454).

MAPK-targeted therapy in the adjuvant or neoadjuvant setting

Expansion of MAPK-targeted therapy utility into the neoadjuvant and adjuvant setting is ongoing. BRIM 8, a large phase III trial, is underway to explore the safety and efficacy of single-agent vemurafenib as adjuvant therapy in patients with BRAF-mutant resected high-risk melanoma (NCT01667419). Dabrafenib-trametinib combination is currently being tested against matching placebos in the COMBI-AD trial, a randomized double-blind phase III study, in patients with resected V600E- or V600K-positive stage III melanoma (NCT01682083). Various phase II trials are also being conducted to explore the safety and efficacy of BRAF inhibitors with or without MEK inhibitors as neoadjuvant therapy in patients with BRAF mutation-positive resectable regionally advanced disease (NCT02036086, NCT01701037, and NCT01972347).

After 20 years of dormancy, the field of melanoma oncology has awakened with groundbreaking scientific advances and innovative therapeutic strategies. A new family of small-molecule kinase inhibitors targeting the aberrant MAPK pathway activation mediating growth and survival of melanoma tumors has revolutionized the therapeutic approach to advanced melanoma. BRAF and MEK inhibitors are the first agents that improved all clinical efficacy endpoints, including response rate, PFS and OS, in patients with BRAF-mutated advanced melanoma when compared with chemotherapy in randomized phase III studies. Despite the impressive clinical responses in patients with BRAF mutant advanced melanoma, duration of response to MAPK pathway-targeted therapy remains short, implicating rapid emergence of drug resistance. Diverse strategies to overcome tumor resistance to MAPK inhibitors, the focus of today's translational and clinical research, will further improve the clinical outcome for patients with BRAF-mutated advanced melanoma in the near future.

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