Chapter 4
Clinical Utility of BRAF-Targeted Therapy in Melanoma

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Abstract The identification of $BRAF^{V600}$ mutations in melanoma rapidly translated into a search for strategies to exploit this recurrent genetic alteration. The selective BRAF inhibitors, vemurafenib and dabrafenib have demonstrated impressive antitumor activity with objective response rates of approximately 50 % and improved progression-free and/or overall survival compared to cytotoxic chemotherapy. The MEK inhibitor trametinib also subsequently demonstrated improved survival compared to chemotherapy. Acquired resistance, however, has limited the long-term antitumor efficacy of these therapies. Combined BRAF and MEK inhibition represents one strategy to delay the onset of resistance and potentially extend survival. Additional BRAF and MEK inhibitors and combinations are being developed with a goal of improving outcomes further. In this chapter, we review the development of approved BRAF and MEK inhibitors, the experience with combination therapy, and special clinical situations for BRAF-targeted therapy.

Keywords BRAF inhibitor · MEK inhibitor · Melanoma · BRAF-mutant · Vemurafenib · Dabrafenib · Trametinib

4.1 Introduction

Constitutive activation of the mitogen activated protein-kinase (MAPK) pathway drives growth and progression in most melanomas of which 40–50 % harbor $BRAF^{V600}$ mutations. The discovery of small molecule inhibitors which suppress MAPK signaling has represented a major step forward in melanoma therapeutics. Pathway inhibition has now been achieved by targeting different levels of the pathway and has efficacy in advanced melanoma through direct targeting of mutant BRAF and blockade of its downstream signaling partner, MEK. Two selective

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inhibitors of BRAF (vemurafenib, dabrafenib) and one MEK inhibitor (trametinib) are now approved for clinical use and several other agents are advancing in the developmental pipeline. These targeted therapies induce rapid tumor regressions in many patients and improve clinical outcomes in comparison to cytotoxic chemotherapy based on progression-free and overall survival. Acquired resistance remains the significant problem, although progression can be forestalled by combination therapy. In this chapter, we will review the clinical utility of these small molecule inhibitors in $BRAF^{V600}$ mutant melanoma, focusing on approved agents but also briefly discussing an early BRAF inhibitor and newer, experimental agents.

4.2 BRAF Inhibitors

4.2.1 Sorafenib

The identification of recurrent mutations in the 600^{th} codon of BRAF in nearly half of melanomas in 2002 by Davies et al. represented a major therapeutic opportunity [1]. Sorafenib (Nexavar, Bayer), a putative BRAF inhibitor, was the first agent to show pre-clinical activity in BRAF mutant melanomas, partially inhibiting ERK signaling and inducing cell death [2]. The clinical experience with this agent, however, was disappointing. In an early study, 37 unselected patients with advanced melanoma received sorafenib, with only one patient experiencing a partial response and 19% achieving temporary stable disease [3]. Moreover, there was no correlation between disease stability and BRAF mutation status. Subsequent trials combined sorafenib with cytotoxic chemotherapy but demonstrated no advantage over chemotherapy alone and no genotype-specific effect for those patients with BRAF mutant melanoma was observed [4, 5]. The modest activity of sorafenib is now generally attributed to its anti-angiogenic properties rather than to specific inhibition of mutant BRAF. Additional clinical development of sorafenib in melanoma is not ongoing since more effective BRAF inhibitors have now been approved.

4.2.2 Vemurafenib

4.2.2.1 Early Phase Studies

Vemurafenib (Zelboraf®, PLX4032, RG7204, Roche/Genentech, Basel) was the first selective inhibitor of mutant BRAF developed. Pre-clinical studies demonstrated exquisite sensitivity of most cell lines harboring $BRAF^{V600E}$ mutations [6], leading to further clinical development. In the phase I trial, patients were initially treated with a crystalline formulation of vemurafenib, which was found to have minimal efficacy and poor bioavailability. The drug was reformulated to a microprecipitated bulk-powder formulation and dose escalation was performed, with a recommended phase two dose (RP2D) of 960 mg twice daily. An expansion cohort

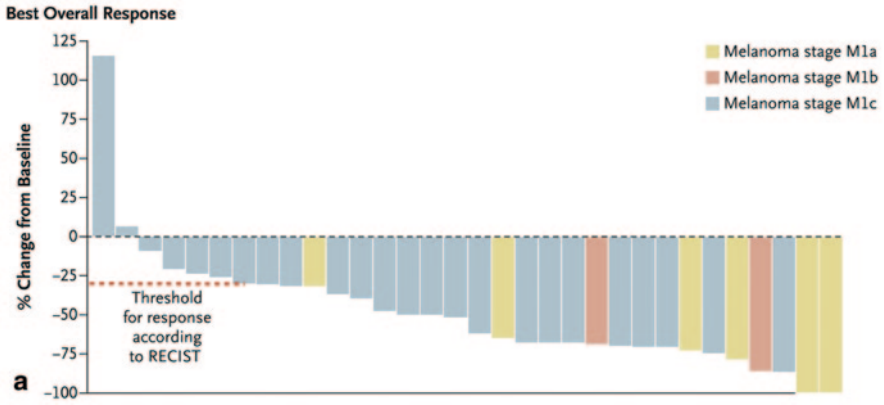

Fig. 4.1 Best overall response for 32 patients treated at the recommended phase II dose of vemurafenib in the phase I study (960 mg twice daily), measured as the change from baseline in the sum of the largest diameter of each target lesion

of 32 patients with BRAF mutant melanoma were treated at this dose, of which 24 (80%) experienced a partial response (investigator assessed, including both confirmed and unconfirmed), often with rapid and dramatic regression of disease. This trial demonstrated that almost all patients experience at least some disease regression with vemurafenib with the exception of two patients with primary disease progression (Fig. 4.1) [7]. The median progression-free survival (PFS) was approximately 7 months; nearly all patients eventually developed disease progression. The drug was relatively well tolerated although 41% of patients required a dose reduction to 720 mg twice daily for chronic toxicity.

4.2.2.2 Phase II/III Studies and Subsequent Experience

The follow-up non-randomized phase II study, BRIM-2, enrolled 132 patients with $BRAF^{V600E}$ mutant melanoma ($BRAF^{V600K}$ mutations were excluded). The overall response rate was 53% (6% with complete responses) with a median PFS of 6.7 months and a median overall survival (OS) of 15.9 months [8]. These results were observed despite unfavorable baseline patient characteristics: 61% had AJCC stage M1c disease and nearly half had elevated lactate dehydrogenase (LDH). The most common toxicities observed were cutaneous, including rash (52%), pruritis (29%), skin papilloma (29%), skin cutaneous squamous cell carcinoma (cSCC; 26%), and palmar-plantar erythrodysesthesia (10%). Cutaneous SCCs were generally limited with one or two lesions managed with surgical resection although a few patients had multiple and recurrent SCCs eventually limiting therapy. Arthralgia was common but not severe (78%); elevated liver function tests were also observed (17%) and managed with dose reduction.

BRIM-3 was a randomized trial comparing vemurafenib with dacarbazine, enrolling 675 patients with a 1:1 randomization between arms. At the first interim analysis (3.8 months median follow up for the vemurafenib arm, performed soon after

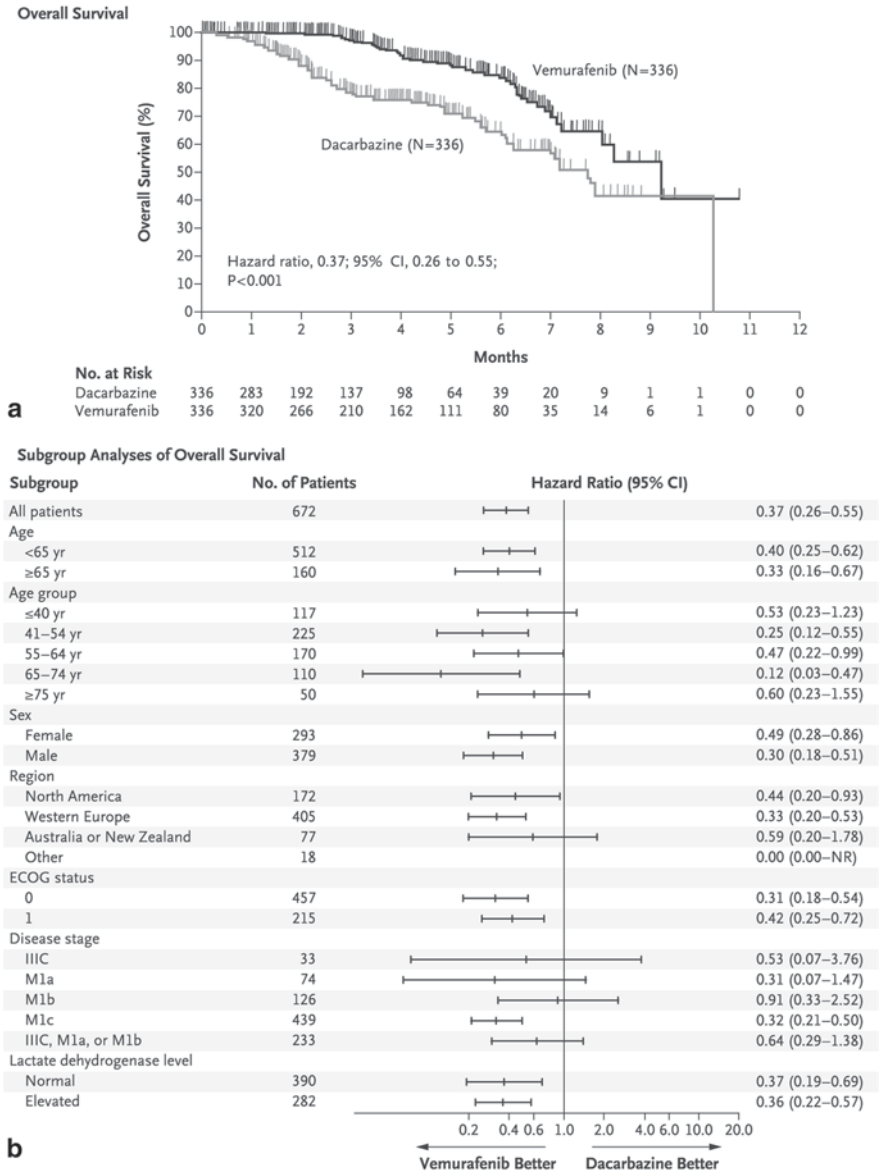

Fig. 4.2 Kaplan-Meier estimates of survival in patients with $BRAF^{V600E}$ mutant melanoma treated with vemurafenib or dacarbazine in the phase III study of vemurafenib

enrollment was completed) the OS and PFS endpoints had been met and patients on dacarbazine were allowed to cross over [9]. Vemurafenib-treated patients had a decreased hazard of death (hazard ratio 0.37, 95% CI 0.26–0.55, $p<0.01$), and progression (hazard ratio 0.26, 95% CI, 0.20–0.33; $p<0.001$), and an overall response rate was 48% (Fig. 4.2). Toxicities were observed in similar incidence to

BRIM-2; photosensitivity was also described in this trial which could be prevented with sunblock in many cases. Notably, 2.4% of patients also developed a second primary melanoma. Vemurafenib received regulatory approval in the United States for treatment of advanced melanoma in August of 2011 and is now widely used in first-line and previously treated advanced or metastatic melanoma.

Following approval, pre-clinical studies suggested that the intermittent administration of BRAF inhibitors delay the onset of acquired resistance [10]. This has not yet been verified in the clinical setting, therefore this strategy should not be recommended for patients. However, when patients develop intolerable chronic toxicities, we prefer a strategy of intermittent dosing (i.e. 2 weeks on and 1 week off) over dose reduction below 720 mg twice daily. This approach has not yet been evaluated in a clinical trial.

4.2.3 Dabrafenib

4.2.3.1 Early Phase Trials

Dabrafenib (Tafinlar®, GSK2118436, GlaxoSmithKline, London) is a selective BRAF inhibitor developed after vemurafenib. A phase I/II study of dabrafenib was conducted in Australia and the United States between May 2009 and March of 2011 [11]. The phase I component initially permitted entry regardless of BRAF mutation status but subsequently restricted enrollment to $BRAF^{V600E}$ or $BRAF^{V600K}$ mutant melanoma after several patients lacking BRAF mutations failed to respond. In contrast to the vemurafenib trials, patients with $BRAF^{V600K}$ mutant melanoma were allowed to enroll, including nine patients in this study. While dose-limiting toxicity was not found, the phase II recommended dose (RP2D) was determined to be 150 mg twice daily; 46 patients received this dose. Disease characteristics were unfavorable including 91% with AJCC stage M1c melanoma and 22 % with brain metastases (see "Special Clinical Situations" below). Of the 36 patients with only extracranial metastases treated with the RP2D, 69% experienced partial or complete responses (50% confirmed) with median PFS of 5.5 months. Elevated LDH and worse baseline performance status predicted for more rapid disease progression. Cutaneous squamous cell carcinomas developed in 11% of patients who received at least 50 mg twice daily. Additional cutaneous toxicities were similar to vemurafenib, although photosensitivity was not observed. The most prevalent distinct non-cutaneous toxicity was pyrexia (20%, grade 3–4 in 4%).

4.2.3.2 Phase III Clinical Trial

This encouraging clinical activity led to the initiation of a multicenter, phase III trial of dabrafenib compared to cytotoxic chemotherapy [12]. Two-hundred fifty patients were randomized 3:1 to dabrafenib 150 mg twice daily or dacarbazine; enrollment in this trial was limited to $BRAF^{V600E}$ mutant melanoma and to patients

without brain metastases. The primary endpoint was PFS; crossover was allowed from dacarbazine to dabrafenib at disease progression. Baseline characteristics included 67% with ECOG performance status of 0, 65% with AJCC stage IVc disease, 34% with elevated LDH, and 98% with any previous therapy. Median PFS was 5.1 months with dabrafenib compared to 2.7 months with dacarbazine (hazard ratio for progression 0.30, 95% CI 0.18–0.51; $p<0.0001$). An independent review determined median PFS durations of 6.7 months and 2.9 months for dabrafenib and dacarbazine, respectively. This trial was not powered for overall survival, although a trend to improved OS with dabrafenib was observed (hazard ratio 0.61, 95% CI 0.25–1.48). Confirmed objective responses were seen in 53% of patients on dabrafenib (3% CR). As with vemurafenib, the vast majority of patients had some degree of tumor shrinkage with primary disease progression occurring only rarely. Adverse events were similar and included cSCCs/keratocanthomas (6%) and 11% with pyrexia (3% with≥grade 3). Arthralgias, asthenia, headaches, and fatigue also occurred in >5% of patients but were rarely severe. Notably, two patients developed second primary melanomas and four developed basal cell carcinomas. Dabrafenib received regulatory approval in the United States in May of 2013.

4.2.4 Encorafenib (LGX818)

Encorafenib (LGX818; Novartis) is a selective BRAF inhibitor currently undergoing phase II and III testing. This agent has a longer dissociation time compared to available BRAF inhibitors which may confer additional activity. In a phase I trial, 16 of 24 (67%) BRAF inhibitor naïve patients experienced partial responses [13]. Among patients pre-treated with other BRAF inhibitors, the response rate was <10%. Toxicities were similar to vemurafenib and dabrafenib although palmar-plantar erythrodysesthesia was observed more frequently and only two patients developed cSCCs. Ongoing development is focused on monotherapy across malignancies harboring BRAF mutations and on combination therapy with other agents in advanced melanoma.

4.2.5 Secondary Malignancies and Rare Toxicities

The incidence of cSCCs is strongly increased with both vemurafenib and dabrafenib (6–26%). This led to concerns that selective BRAF inhibitors may induce secondary cancers. After further study, it appears that these agents promote progression of existing cancers (or pre-malignant conditions) by paradoxically promoting MAPK pathway activity. This effect appears to primarily occur in neoplasia with RAS mutations. For example, 60% of secondary cSCCs harbor activating mutations in RAS [14]. Additional primary melanomas appear to occur more frequently in patients previously diagnosed with melanoma although it has not been determined whether BRAF inhibitors contribute to this increased incidence. Patients receiving BRAF

inhibitors should be evaluated by a dermatologist if suspicious lesions occur during therapy.

Diagnoses of new non-cutaneous malignancies have been uncommon during BRAF inhibitor therapy. A case of chronic myelomonocytic leukemia (CMML) was diagnosed by rapidly rising white blood cell (WBC) count in a patient on vemurafenib [15]. Periodic drug cessation and rechallenge induced clear regression and progression of the CMML as measured by fluctuating WBC counts. The development of colon adenomas and gastric polyps have also been identified during BRAF inhibitor therapy [16]. The incidence of visceral, RAS-mutant carcinomas (e.g. lung, pancreas, colon etc.) appears to be rare, although these remain a potential concern.

Other severe toxicities are relatively rare with these agents. Bilateral peripheral facial nerve palsy has been observed with vemurafenib (in a patient who achieved a complete remission) [17]. Also in two patients who had previously received agents targeting the programmed cell death-1 (PD-1) receptor, a syndrome of rash, hepatic and renal injury, and hypotension occurred when they received vemurafenib [18]. Fevers were the most common severe toxicity with dabrafenib, and were occasionally associated with hypotension requiring temporary drug cessation and intravenous hydration. Hypoglycemia was also observed.

4.2.6 Summary

Although clinical activity cannot be directly compared across trials, vemurafenib and dabrafenib provide fairly equivalent benefit for patients with $BRAF^{V600E}$ mutant melanoma [12, 19]. Median PFS and response rates were comparable. Side effect profiles were also similar with phototoxicity and elevated liver function tests occurring more frequently with vemurafenib and pyrexia more commonly observed with dabrafenib. A suggestion of fewer cutaneous SCCs was also considered with dabrafenib in the phase III trial but this was called into question in a subsequent trial [20]. See Sect 5.5 for the discussion of BRAF inhibitor therapy in brain metastases and in alternative BRAF mutations (non-V600E).

4.3 MEK Inhibitors

4.3.1 Selumetinib

Selumetinib (AZD-6244, AstraZeneca) is a selective MEK1/2 inhibitor which demonstrated pre-clinical efficacy against BRAF mutant melanoma cell lines. In an unselected melanoma population, selumetinib was compared with temozolomide and did not demonstrate any improvement in PFS [21]. In a randomized phase II trial, selumetinib combined with dacarbazine was compared to dacarbazine alone in BRAF mutant mel-

anoma. The combination arm demonstrated improved PFS (5.6 vs. 3 months) but no change in OS [22]. Although this agent is undergoing further development in other malignancies (lung adenocarcinoma, thyroid carcinoma, leukemias), it is not likely selumetinib will be used in BRAF mutant melanoma in the future.

4.3.2 Trametinib

4.3.2.1 Early Phase Trials

Trametinib (Mekinist, GSK1120212, GlaxoSmithKline, London) is a newer generation selective MEK1/2 inhibitor which has been widely tested in melanoma. A phase I trial was conducted which included 30 patient with BRAF mutant melanoma not previously treated with a BRAF inhibitor and 39 BRAF wild type patients [23]. The response rate was 40% in the untreated BRAF mutant group with a median PFS of 5.7 months. Notably, 10% of patients in the BRAF wild type group also demonstrated an objective response. Within this BRAF wild type cohort, a patient later found to have $BRAF^{L597V}$ mutant melanoma also experienced a response. Side effects were relatively minor and commonly included acneiform rash (38%), diarrhea (35%), and peripheral edema (31%). No cSCCs were identified, and no episodes of retinal vein occlusion (RVO) occurred (complications of early generation MEK inhibitors) in patients receiving the RP2D of 2 mg daily.

4.3.2.2 Phase III Trial

A phase III trial (METRIC) was then conducted 322 patients with advanced $BRAF^{V600E/K}$ mutant melanoma, randomized in a 2:1 fashion to trametinib or investigator's choice of cytotoxic chemotherapy (dacarbazine or carboplatin/paclitaxel). Improved overall survival was demonstrated (hazard ratio for death 0.54, $p=0.01$), despite 47% of patients on the chemotherapy arm crossing over and receiving trametinib. Other key clinical outcomes favored trametinib including median PFS (4.8 months vs. 1.5 months, $p<0.001$), and objective response rate (22 vs. 8%, $p=0.01$). Although only 22% of patients met criteria for RECIST partial responses, >70% experienced at least some disease regression. Toxicity profile was similar to the phase I trial although one case of reversible chorioretinopathy occurred. Cardiotoxicity was seen in 7% who developed decreased ejection fraction and two patients who experienced grade 3 cardiac events requiring drug cessation. Based on the results of this trial, trametinib received FDA approval in May 2013.

4.3.2.3 Trametinib in BRAF Inhibitor-Resistance

Since many of the mechanisms of acquired resistance to BRAF inhibitors could be hypothesized to confer sensitivity to MEK inhibition, a phase II trial was conducted to assess the efficacy of trametinib in this setting. A total of 40 patients received

trametinib following progression with a BRAF inhibitor (either vemurafenib or dabrafenib). Of the patients truly refractory to BRAF inhibitors, no patients had objective responses with 11 patients (28 %) experiencing temporary stable disease. Two patients who had developed BRAF inhibitor toxicity but had not progressed on BRAF inhibitor therapy before receiving trametinib did experience a partial response. Median PFS was 1.8 months in this cohort. A sequential strategy of BRAF inhibitors followed by MEK inhibitors is thus not of clinical benefit.

4.3.3 Binimetinib (MEK162)

Binimetinib (MEK162; Novartis) is an experimental small molecule inhibitor of MEK1/2 with a recently completed phase II study. The response rate in the BRAF V600 mutant group was 23 % with a median PFS of 3.6 months. In contrast to other MEK inhibitors, binimetinib induced responses in NRAS mutant melanoma (response rate 20 %). Clinical development for this agent as monotherapy has largely focused on the 15–20 % of melanomas harboring NRAS mutations. However, trials in combination with encorafenib are also ongoing for patients with BRAF mutant melanoma.

4.3.4 Conclusions

Trametinib, the only currently approved MEK inhibitor, is an active therapy and is superior to cytotoxic chemotherapy. The single agent activity appears to be somewhat inferior to vemurafenib or dabrafenib with a lower response rate and lower median PFS (although no direct comparison has been performed). Trametinib has minimal benefit following progression on BRAF inhibitors and is not used widely as monotherapy currently except in patients with contraindications to vemurafenib and dabrafenib. Its role in combination therapy, however, may be much more significant. Binimetinib and other experimental MEK inhibitors may also have clinical utility in the future.

4.4 Combination Therapy

4.4.1 Rationale and Efficacy

The inevitable onset of acquired resistance and disease progression in patients treated with BRAF or MEK inhibitor monotherapy led to significant interest in combining these agents. Pre-clinical rationale for combination therapy was strong, as many mechanisms of acquired resistance involve reactivation of the MAPK pathway, including acquired NRAS mutations, [24] MEK1 mutations [25], COT overexpression [26], BRAF amplification [27], alternate splicing of BRAF [28] and

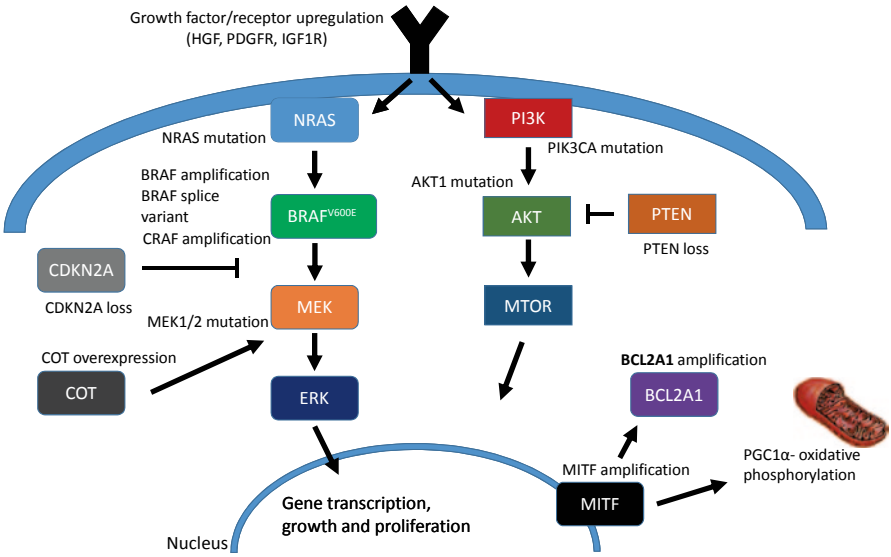

Fig. 4.3 Mechanisms of acquired resistance to BRAF inhibitors. Resistance arises reactivation of the MAPK pathway, growth factor upregulation, dysregulation of the PI3K-AKT pathway, and decreased apoptosis

loss of CDKN2A (through indirect dysregulation of MAPK signaling) [29]. Growth factor upregulation, alterations in the PI3K-AKT-MTOR pathway and decreased apoptosis, also appear to play a role in acquired resistance which may not respond to combined BRAF/MEK inhibition [29–34] (Fig. 4.3).

A phase I/II trial evaluating dabrafenib and trametinib was conducted with rapid dose escalation to a recommended phase II dosing [20]. A randomized comparison of combination therapy (dabrafenib 150 mg twice daily and trametinib 1 mg or 2 mg daily) to dabrafenib monotherapy was then performed in 162 patients. Patients on the 150/2 mg dosing arm had improved median PFS of 9.4 months compared to 5.6 months with dabrafenib alone, with 41% of patients remaining progression-free at 12 months (hazard ratio for death or progression of 0.39; $p<0.001$). Improvements were demonstrated regardless of BRAF mutation (V600E or K) and across metastatic stages (M1a/b and M1c). Objective responses occurred more frequently in the combination therapy arm (76 vs. 54%, 9% vs. 4% CR rate). For responding patients, the median duration of response was also superior (10.5 months vs. 5.6 months). Despite the clear improvement in PFS and response rate, an improvement in OS has not yet been demonstrated. An OS benefit may be observed with continued follow-up.

4.4.2 Toxicity

The toxicity profile was significantly altered by combining BRAF and MEK inhibition compared with monotherapy. The incidence of cutaneous squamous cell

carcinoma was decreased (19 vs. 7%) as was the classic BRAF inhibitor-associated dermatitis (36 vs. 27%). The addition of a MEK inhibitor appears to attenuate the risk of secondary malignancies by preventing paradoxical MAPK activation. The acneiform dermatitis induced by MEK inhibitors also appeared to occur less frequently than in the METRIC trial [35]. Other class toxicities characteristic of trametinib were observed in the combination group including decreased ejection fraction (9%) and ocular events (one patient with retinopathy). Also significantly, 25% of patients on the combination 150/2 mg arm developed severe pyrexia (defined as associated with severe chills, hypotension, or requiring hospitalization). Anti-pyretics and temporary interruption of therapy are generally sufficient in mild cases although severe cases may necessitate intravenous fluid repletion and oral steroids. The onset of pyrexia is not predictable and may occur even after prolonged therapy. Neutropenia (11%), fatigue, nausea, and diarrhea also occurred more commonly in the combination arms.

4.4.3 Crossover

Patients initially assigned to dabrafenib monotherapy were eligible for crossover to combination therapy. In this BRAF inhibitor resistant population, the combination was much less effective (median PFS 3.6 months, objective response rate 9%) compared to BRAF inhibitor naïve patients [36]. A long duration of PFS on dabrafenib monotherapy appeared to predict a longer benefit from crossover although this was not universal. Patients who rapidly progressed on dabrafenib generally received minimal or no benefit from the combination. In our opinion, BRAF inhibitor resistant patients could be considered for crossover if they derive a long term benefit from monotherapy (>12 months).

4.4.4 Current Status of Combination Therapies

The combination of dabrafenib and trametinib has advanced through the developmental pipeline and received regulatory approval in January 2014. We strongly consider this combination for patients as first-line treatment or following progression with an immune-based regimen. Clinical trials are also ongoing for vemurafenib plus the MEK inhibitor cobimetinib (GDC-0973, Roche/Genentech) and encorafenib plus binimetinib.

A large variety of trials assessing other combinations in the BRAF inhibitor naïve and refractory populations are also ongoing. These include BRAF inhibitors plus agents inhibiting one of the following: the PI3K-AKT pathway, colony-stimulating factor-1 receptor (CSF-1R), cyclin dependant kinase signaling (CDK4/6), heat-shock protein-90 (HSP90), hepatocyte growth factor, fibroblast growth factor receptor (FGFR) and angiogenesis. Table 4.1 is a non-comprehensive list of currently accruing trials combining BRAF inhibitors with other agents [37]. Although each combination has pre-clinical rationale, it is not clear whether one combination

Table 4.1 Currently accruing combination therapy trials including BRAF inhibitors as of January 27, 2014

Investigational agents	Mechanism of action	National clinical trials identification number	Phase of development
Trials only including BRAFi naïve patients			
Vemurafenib and Cobimetinib vs. Vemurafenib alone	BRAFi	NCT01689519	III
	MEKi		
Dabrafenib and Trametinib vs. Vemurafenib alone	BRAFi	NCT01597908	III
	MEKi		
LGX818 and MEK162 or LGX818 alone vs. Vemurafenib alone	BRAFi	NCT01909453	III
	MEKi		
Vemurafenib Interleukin-2	BRAFi	NCT01683188	IV
	Immune therapy		
Dabrafenib Trametinib	BRAFi	NCT01726738	II
	MEKi		
Vemurafenib Bevacizumab	BRAFi	NCT01495988	II
	Anti-angiogenic		
Vemurafenib	BRAFi	NCT01603212	I/II
Interleukin-2	Immune therapy		
Interferon-alpha	Immune therapy		
Dabrafenib	BRAFi	NCT02027961	I/II
Trametinib	MEKi		
MEDI4736	Anti-PD-L1		
Vemurafenib Metformin	BRAFi	NCT01638676	I/II
	Anti-diabetic		
Vemurafenib BKM120	BRAFi	NCT01512251	I/II
	PI3K inhibitor		
Vemurafenib PLX3397	BRAFi	NCT01826448	Ib
	CSF1R inhibitor		
Vemurafenib MPDL3280A	BRAFi	NCT01656642	Ib
	Anti-PD-L1		
Vemurafenib Hydroxychrolorquine	BRAFi	NCT01897116	I
	Unknown		
Dabrafenib	BRAFi	NCT01767454	I
Trametinib	MEKi		
Ipilimumab	Anti-CTLA4		
Vemurafenib XL888	BRAFi	NCT01657591	I
	HSP inhibitor		
Dabrafenib	BRAFi	NCT01940809	I
Trametinib	MEKi		
Ipilimumab	Anti-CTLA4		

Table 4.1 (continued)

Investigational agents	Mechanism of action	National clinical trials identification number	Phase of development
Vemurafenib Cabozantinib	BRAFi	NCT01835184	I
	MET inhibitor		
Trials allowing for BRAFi resistant patients			
Dabrafenib Trametinib	BRAFi	NCT01619774	II
	MEKi		
LGX818 and[a] MEK162 or	BRAFi	NCT01820364	II
	MEKi		
LEE011 or	CDK4/6 inhibitor		
BGJ398 or	FGFR inhibitor		
BKM120 or	PI3K inhibitor		
INC280	MET inhibitor		
Vemurafenib P1446A-05	BRAFi	NCT01841463	I/II
	CDK4/6 inhibitor		
Vemurafenib Decitabine	BRAFi	NCT01876641	I/II
	Hypomethylating agent		
LGX818	BRAFi	NCT01777776	I/II
LEE011	CDK4/6 inhibitor		

All trials are evaluating combination therapy with agents listed in "Investigational agents" column
BRAFi BRAF inhibitor, *MEKi* MEK inhibitor, *NCT* National Clinical Trials
[a] Choice of combination therapy is determined by molecular testing at the time of progression

will emerge as clearly superior. Likely, a personalized approach will be needed and will be assessed in a planned trial (LOGIC 2, Novartis).

4.4.5 Summary

The combination of BRAF and MEK inhibitors appears to represent a step forward in therapy for $BRAF^{V600}$ mutant melanoma, leading to improved outcomes via enhanced blockade of the MAPK pathway. However, acquired resistance and disease progression still occurs in less than one year for most patients, suggesting that blockade of additional signaling pathways and alternate treatment strategies may be necessary to achieve more durable clinical benefit. Clinicians should note that the toxicity profile is distinct from BRAF inhibitor monotherapy, with decreased incidence of cSCCs and less theoretical concern of promotion of other RAS mutated malignancies [15]. However, systemic side effects including pyrexia, hypotension, and neutropenia occur more frequently with this regimen and patients should be monitored closely.

4.5 Special Clinical Situations

4.5.1 Targeted Therapy in Brain Metastases

Targeted therapies may play a key role in the multidisciplinary management of patients with brain metastases. Although BRAF inhibitors do not appear to cross an intact blood brain barrier in pre-clinical studies, multiple trials have demonstrated their efficacy in brain metastases [38]. Evidence of activity is limited to vemurafenib and dabrafenib; no clinical trials evaluating MEK inhibitors in brain metastases have been performed.

Dabrafenib has been studied most extensively in this setting. The phase I trial of dabrafenib led by Falchook and colleagues initially suggested activity. Ten patients with untreated brain metastases were included, and eight experienced a decrease in size of their intracranial disease [11]. A phase II trial (BREAK-MB) was then conducted exclusively for patients with BRAF V600E ($n=139$) or V600K ($n=33$) mutant melanoma with brain metastases [39]. Two cohorts were evaluated; cohort A with untreated brain metastases ($n=89$) and cohort B with previously treated but progressing brain metastases ($n=83$). Clinical activity was similar in both cohorts for patients with $BRAF^{V600E}$ mutant melanoma; the objective intracranial response rate was 39% and 31% with a durable intracranial disease control rate of 81 and 89% respectively. Response rates appeared to be lower in the $BRAF^{V600K}$ mutant group in both cohort A (intracranial responses in 1 of 15 patients) and cohort B (4 of 18). Median PFS for both groups was similar at approximately 4 months and median OS was nearly 8 months.

In a single center subset of patients from the BREAK-MB trial, intracranial tumor regression correlated well with extracranial responses although exceptions did occur [40]. At the time of disease progression, several patterns of tumor growth were noted. These included systemic progression with intracranial disease control, isolated intracranial progression, or commonly, multiple foci of intracranial progression. The median time to intracranial progression in this subset was 16–20 weeks. Dabrafenib has also been reported to have intracranial activity for patients with $BRAF^{V600R}$ melanoma [41].

Vemurafenib also appears to have activity in patients with brain metastases. A pilot study was performed in heavily pre-treated patients [42]. Of 19 evaluable patients, seven had intracranial tumor shrinkage with three meeting criteria for partial response; median PFS was 3.9 months. Functional outcomes were also improved, with 25% of patients reporting a reduction in pain, 83% of patients with improvement in performance status, and 67% of patients with decreased corticosteroid requirements.

No clinical trials have been performed to evaluate the role of BRAF inhibitors in conjunction with local therapies. For patients with significant neurologic deficits on presentation, radiation therapy or surgery should be considered prior to initiating a BRAF inhibitor. However, for patients with asymptomatic brain metastases or when symptoms are controlled with steroids, BRAF inhibitors can be considered

prior to or instead of local therapies, particularly when rapidly progressing extracranial disease is present [43]. Mixed responses may be observed in some patients, necessitating local treatment to enlarging lesions. Additionally, a recent case report demonstrated the feasibility and potentially durable benefit of neoadjuvant vemurafenib followed by resection [44]. This approach can be considered particularly for patients with borderline resectable melanoma or a metastasis that is too large for stereotactic radiosurgery. Also, the combination of vemurafenib and radiation has been described to cause skin toxicity; we therefore hold BRAF inhibitors for 2–3 days around radiation [45]. The complexity of management in some cases highlights the need for multidisciplinary input into treatment decisions.

4.5.2 Treatment Beyond Progression

Selected patients develop progression at isolated disease sites while being treated with BRAF inhibitors which can be managed with local therapies (surgery, stereotactic radiosurgery). A retrospective analysis suggests that continuation of BRAF inhibitor therapy following local treatment for a solitary site of progression may be beneficial in this group of patients [46]. Patients in the initial phase I trial who continued vemurafenib following local therapy had a further progression-free interval of 3.6 months with a median OS which had not been reached at 6 month follow up. By contrast, patients who discontinued vemurafenib had a median overall survival of only 1.4 months. This finding may be a surrogate for the pace of disease progression (e.g. BRAF inhibitors are discontinued when there is obvious, rapid progression) or may be a genuine effect of continuing therapy.

Additionally, there have been case reports of objective responses occurring with re-treatment following a treatment-free interval. Two patients who developed disease progression (on vemurafenib and dabrafenib, respectively) had a treatment-free interval of 8 and 4 months [47]. Upon BRAF inhibitor rechallenge, both patients experienced dramatic regression in their melanoma (qualifying as mixed response and partial response by RECIST criteria). This strategy can be considered in selected patients.

4.5.3 Non-V600E Melanoma

The most common oncogenic point mutation in BRAF mutant melanoma results in substitution of a valine for a glutamic acid at codon 600 (V600E) which comprises 80–90% of BRAF V600 mutations [48]. Pre-clinical experiments and clinical experience suggest that alternate V600 mutations also confer sensitivity to BRAF inhibitors [49]. These genetic alterations do confer sensitivity to approved therapies and may be missed on standard $BRAF^{V600E}$ mutational testing. The second most common BRAF mutation is $BRAF^{V600K}$ which also appears to be quite sensitive to BRAF and MEK inhibition. $BRAF^{V600R}$ mutations also occur infrequently, although

in one small series five of six patients with $BRAF^{V600R}$ mutant melanoma experienced an objective response to dabrafenib [41]. Additionally, a patient with melanoma harboring both BRAF V600E and V600M mutations experienced a dramatic response to dabrafenib [50].

Mutations in BRAF at locations other than codon 600 may also occur, most commonly at codon 597. These genetic alterations may occur with a frequency of up to 5 % in presumed BRAF wild-type melanoma. Based on pre-clinical and limited clinical experience, these mutations appear to confer sensitivity to MEK inhibitors, including one patient with $BRAF^{L597S}$ mutant melanoma who experienced a partial response to TAK-733, an experimental MEK inhibitor [51]. Pre-clinical data does not clearly define whether these melanomas should be sensitive to BRAF inhibitors although one patient with a $BRAF^{L597R}$ mutation experienced a major response to vemurafenib [52]. Additionally, BRAF fusions have been recently described in melanoma and seem to confer sensitivity to MEK inhibitors in pre-clinical studies. A clinical trial of trametinib for patients with these uncommon BRAF alterations is planned.

4.6 Conclusion and Future Directions

In conclusion, targeted therapy with BRAF and MEK inhibitors as monotherapy or in combination represents a major step forward in the management of patients with BRAF mutant melanoma. Although dramatic and rapid responses occur in the majority of patients, acquired resistance limits the duration of benefit for these patients. Improved combinations of targeted therapies to forestall acquired resistance are urgently needed. Currently, ongoing clinical trials are evaluating BRAF inhibitors in conjunction with MEK inhibitors as well as a large variety of other targeted agents. Agents targeting ERK, the final common signaling partner in the MAPK pathway are also ongoing. Additionally, the combination of immune therapies with these agents is an intriguing avenue to pursue (see Chap. 9).

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