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Management of V600E and V600K *BRAF*-Mutant Melanoma

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Opinion statement

The optimal management of advanced stage *BRAF*-mutated melanoma is widely debated and complicated by the availability of several different regimens that significantly improve outcomes but have not been directly compared. While there are many unanswered questions relevant to this patient population, the major uncertainty in current practice is the choice between BRAF/MEK inhibitors or immunotherapy for those with previously untreated metastatic or high-risk disease. Decisions regarding first line therapy should include consideration of patient preference as well as the presence of symptomatic metastatic disease and degree of comorbidity, particularly secondary to any history of severe auto-immune disorder.

BRAF/MEK inhibitors have a high response rate and rapid onset and thus can be quickly introduced when patients are symptomatic. They have also produced long-term responses in a subset of patients with more favorable prognostic indicators. In addition, impressive survival benefits have also been observed in patients with resected stage 3 disease at high risk of recurrence. On the other hand, anti-PD-1 monotherapy is associated with high rates of clinical benefit (~45% response rate in the metastatic setting) and low rates of severe toxicity. In many patients with adverse prognostic features, we use combined anti-PD-1 and anti-CTLA-4 for metastatic disease. While associated with high rates of toxicity, adverse events are largely manageable with corticosteroids and treatment cessation, in which case patients may continue to benefit even after a limited duration of treatment.

Multiple treatment options exist for patients with BRAF V600 mutant melanoma. Herein, we review the clinical data for safety and efficacy of these options.

Keywords

Melanoma; BRAF; MEK; PD-1; PDL-1; CTLA-4; Dabrafenib; Encorafenib; Binimetinib; Cobimetinib; Trametinib; Ipilimumab; Nivolumab; Pembrolizumab

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Compliance with Ethical Standards

Conflict of Interest

Alexandra M. Haugh declares that she has no conflict of interest.

Introduction

Therapeutic advances within the last decade have radically transformed the treatment landscape for advanced stage melanoma. Prior to 2011, no treatment had been shown to improve survival in a randomized phase III trial and metastatic melanoma was considered an almost universally fatal diagnosis. Targeted therapies and immune checkpoint inhibitors have since continued to improve outcomes and alter treatment paradigms for melanoma, which are now particularly complex in the setting of a *BRAF* V600 mutation. In this review, we briefly describe the advances that have shaped treatment guidelines for *BRAF*-mutated melanoma as well as highlight emerging therapies and areas of debate with a particular focus on choice of front-line agent and the combination of checkpoint inhibitors and targeted therapies.

Targeted therapies: inhibition of the MAP kinase pathway

The mitogen-activated protein kinase (MAPK) pathway is a complex signaling pathway involved in a wide variety of cell functions, including proliferation, differentiation, cell survival, and stress response. In the physiologic state, the MAPK cascade is first initiated by the binding of extracellular signaling molecules to receptor tyrosine kinases, which subsequently stimulate successive phosphorylation and activation of several downstream proteins [1]. The first of these is the RAS family of GTPases (NRAS, KRAS, HRAS), which subsequently activate the RAF kinase family (ARAF, BRAF, CRAF). RAF kinases bind to and phosphorylate MEK, which then activates the effector kinase ERK, which ultimately promotes survival and proliferation within the cell nucleus. Activating mutations that lead to constitutive MAPK pathway activation are highly prevalent among many different malignancies. Melanoma is associated with a high rate of mutations in *BRAF* (nearly 50%), primarily at the V600 codon [2].

BRAF inhibitors

As *BRAF* V600E and V600K mutations were found to be prevalent in melanoma, several pre-clinical studies confirmed that the associated mutant kinase was likely an oncogenic driver [2, 3]. Small molecule inhibitors of BRAF were thus among the first targeted therapies to be tested in melanoma patients. While initial studies of relatively non-specific kinase inhibitors such as sorafenib did not produce substantial antitumor activity, the subsequent development of BRAF-specific inhibitors represented a major breakthrough in the treatment of metastatic melanoma.

The first kinase inhibitor to more specifically bind and target the mutated BRAF kinase was vemurafenib. Early clinical studies demonstrated that response appeared to be dependent on the presence of a *BRAF* V600 mutation and subsequent trials were thus limited to patients with BRAF-mutated melanoma [4]. After success in early phase trials, a phase III trial comparing vemurafenib with dacarbazine in 675 previously untreated patients with *BRAF* V600E mutations showed a marked difference in response rate (48% vs 5%) as well as an overall survival benefit (84% vs 64% at 6 months), which persisted at 5-year follow-up (Table 1) [5, 6]. Vemurafenib was thus FDA approved in 2011 as the first targeted therapy for metastatic melanoma.

Subsequent BRAF inhibitors showed a similar benefit in patients with V600 mutations. A phase III trial of 250 patients treated with either dabrafenib, a mutant specific BRAF inhibitor, or dacarbazine demonstrated a significant improvement in PFS with dabrafenib (median 5.1 vs. 2.7 months), which was subsequently approved in 2013 [8]. The most recent BRAF inhibitor to obtain FDA approval for use in melanoma is encorafenib, a small molecule inhibitor that binds mutant BRAF with a markedly longer dissociation half-life than dabrafenib or vemurafenib [28]. In a large phase III study, largely designed to test the combination of encorafenib and the MEK inhibitor binimetinib with encorafenib or vemurafenib alone, encorafenib was also compared with vemurafenib. Encorafenib was associated with improved PFS (median 9.6 vs 7.3 months) and OS (median 23.5 vs. 16.9 months) at a median of 36.8 months of follow-up compared with vemurafenib [17••, 18••]. Additional head-to-head data comparing the efficacy of specific BRAF inhibitors is unlikely, particularly as they are now rarely used as monotherapy.

MEK inhibitors

Growing evidence regarding the integral role of MAPK signaling in melanoma and other malignancies also resulted in the development of small molecule inhibitors of MEK, a kinase located downstream from BRAF in the MAPK cascade. Early clinical trials comparing the MEK inhibitor selumetinib with traditional chemotherapy did not initially limit enrollment to patients with *BRAF* mutations [29, 30]. However, retrospective genomic analysis performed where available found *BRAF* mutations in almost all patients who responded to therapy, with no responses seen in *BRAF* wild-type tumors. A similar trend was observed in early phase trials of the MEK inhibitor cobimetinib [31]. Enrollment in larger trials was thus generally limited to patients with *BRAF* V600 mutations.

The first phase III trial to demonstrate the benefit of MEK inhibition in melanoma was the METRIC trial, in which 322 patients with *BRAF* V600 mutant melanoma were randomized to either trametinib or chemotherapy (dacarbazine or paclitaxel) [10]. Trametinib was associated with improved PFS (median 4.8 vs 1.5 months) and 6-month OS (81% vs 68%) with a response rate of 22% and was FDA approved for use in melanoma in 2013. Although still a significant improvement when compared with chemotherapy, extrapolation from trial data unsurprisingly suggested a less robust response to MEK inhibition than that seen with BRAF inhibitors in terms of response and PFS (Table 1).

Combined BRAF and MEK inhibition

As discussed in more detail below, persistent activation of the MAPK pathway was ultimately found to represent a major mechanism of tumor resistance to BRAF inhibition. Inhibition at multiple sites along the pathway was thus introduced as both an attempt to mitigate eventual tumor resistance as well to promote more sustained and dramatic responses to therapy. A phase I/II study comparing dabrafenib + trametinib with dabrafenib monotherapy showed such a marked improvement in overall response rate (76% vs. 54%) and PFS (median 9.4 vs 5.8 months) that combination therapy was FDA approved in 2014 prior to the reporting of phase III data [32]. A subset of patients in this trial who progressed on dabrafenib monotherapy were permitted to cross over and receive combination therapy.

Median PFS and response rates after crossover were markedly inferior to those of front-line combination therapy, which thereafter became the standard of care [33].

The benefit of combination therapy was further validated in the COMBI-d and COMBI-v studies, two phase III trials that compared dabrafenib + trametinib with BRAFi monotherapy. In the COMBI-d trial, combination therapy was associated with superior PFS (median 11 vs 9.9 months), OS (median 25.1 vs 18.7 months), and response rate (69% vs 53%) when compared with dabrafenib monotherapy [12]. The COMBI-v trial also demonstrated superior PFS (median 11.4 vs 7.3 months) and OS (72% vs 65% at 12 months) with this combination when compared with vemurafenib [13]. At 5-year follow-up, OS and PFS rates were 34% and 19% among the 563 patients enrolled in either study [14].

Following success with dabrafenib and trametinib, alternative BRAF/MEK inhibitor combinations were also evaluated and subsequently FDA approved for use in metastatic or unresectable melanoma. The CoBRIM trial demonstrated superior PFS (median 12.3 vs 7.2 months), response rate (68% vs 45%), and OS (median 22.3 vs 17.4 months) with the combination of vemurafenib + cobimetinib compared with vemurafenib monotherapy [15, 16]. The COLUMBUS trial randomized 577 patients with metastatic melanoma to treatment with encorafenib + binimetinib, single-agent encorafenib, or single-agent vemurafenib in a 1:1:1 fashion [17••]. Combination therapy showed significant improvement in PFS when compared with vemurafenib (median 14.9 vs 7.3 months). Although suggestive of an improvement, the difference in PFS between combination therapy and encorafenib monotherapy did not reach statistical significance (median 14.9 vs 9.6 months, HR 0.75, $p = 0.051$). This was likely due to a somewhat surprisingly robust response to encorafenib, as described earlier.

At a median of 36.8 months of follow-up, overall survival was also markedly improved with encorafenib + binimetinib compared with that with vemurafenib monotherapy (median 33.6 vs 16.9 months) but not statistically different from encorafenib monotherapy (median 23.5 months) [18]. As with BRAF inhibitor monotherapies, comparison of different combination regimens is limited by a lack of head-to-head data. While encorafenib was superior to vemurafenib in the COLUMBUS trial, it is unclear whether this combination is superior to dabrafenib + trametinib or vemurafenib + cobimetinib.

Combination therapy also importantly does not seem to increase the incidence of severe toxicity significantly above that seen with BRAF or MEK inhibitor monotherapy (Table 1). While BRAF inhibitors are associated with an increased risk of secondary cutaneous malignancy or other hyperproliferative skin lesions due to paradoxical MAPK activation in *BRAF* wild-type cells, this phenomenon seems to be mitigated by the addition of MEK inhibitors [34]. MEK inhibitors are associated with rare yet potentially severe cardiac and ocular toxicities, which may limit use in patients with these comorbidities [10]. The three available combination regimens exhibit largely similar toxicity profiles with relatively high rates of gastrointestinal symptoms, fatigue, and myalgia or arthralgia with some notable differences. Dabrafenib + trametinib is associated with high rates of pyrexia whereas vemurafenib + cobimetinib is associated with photosensitivity [12, 13, 15]. The most common adverse events with encorafenib + binimetinib include certain laboratory

abnormalities and hypertension, as well as lower rates of pyrexia and gastrointestinal symptoms [17].

Resistance to BRAF/MEK inhibitors

While targeted inhibition of the MAPK pathway represents a major therapeutic breakthrough in the treatment of melanoma and can promote a dramatic initial antitumor response, these regimens are limited by a high incidence of eventual resistance. Unlike many other RTK-driven malignancies treated with targeted therapy, melanoma cells have not been shown to bring about resistance via mutations acquired in the kinase itself. Resistance is instead thought to be driven by persistent activation of the downstream MAPK pathway through a variety of mechanisms, including transcriptional modifications that ultimately result in a lack of negative feedback on the pathway [35, 36]. Surviving cells will then eventually acquire new genetic modifications that confer further resistance to therapy. These include mutations in genes involved in the MAPK and PI3K/AKT/mTOR pathways as well as amplification and/or downregulation of proteins involved in cell cycle progression. Some studies have also suggested that melanoma cells may become “addicted” to MAPK inhibition and develop resistance more quickly with more frequent dosing with potential response after a treatment break [37–39]. In clinical practice, resistance to BRAF/MEK should not preclude re-introduction of BRAF/MEK inhibitors at a later date if other options are exhausted, as such an approach has been shown to result in responses nearly as favorable as in the first treatment course [40].

Despite a previously pervasive sense that resistance to MAPK inhibition is inevitable, recently published 5-year follow-up data from the COMBI-v and COMBI-d trials demonstrated potential for long-term benefit in a subset of patients [14••]. Of the 563 patients enrolled in either study, 109 demonstrated a complete response to therapy. Of the 72 of these patients followed through data cutoff, 51 (71%) were alive at 5 years compared with 34% of patients in the overall cohort. Baseline factors associated with increased overall and progression-free survival included older age, female sex, normal lactate dehydrogenase level, and less than three organ sites with distant metastasis. Thus, a small proportion of patients treated with BRAF + MEK inhibitors (15–20%) do seem to experience extremely durable responses, and perhaps even long-term remissions or cures. Further molecular and clinical characterizations of this subgroup may help inform difficult treatment decisions and/or uncover new therapeutic targets.

ERK inhibitors

As ERK represents the final converging step in the MAPK pathway with effects directly on the cell nucleus, direct inhibition of ERK has also been proposed as a mechanism to circumvent upstream pathway re-activation. Inhibition of this final effector kinase would have potential benefit in both previously untreated and BRAF/MEKi-resistant melanoma. Several ERK inhibitors have been developed but translation into clinical trials has been limited by the difficulty in establishing appropriate therapeutic windows. The trial with the most clinical data to date is a phase 1 trial involving 135 patients treated with Ulixertinib (BVD-523) with 108 patients in the dose expansion phase [41•]. Partial responses were

seen in 11 of 81 (14%) evaluable patients in dose expansion and included those with *NRAS*-mutated melanoma ($n = 3$), BRAF/MEK inhibitor–resistant *BRAF*-mutated melanoma ($n = 1$), and with other *BRAF*-mutated cancers ($n = 7$). A substantial proportion of patients, however, required dose reductions during treatment due to side effects (65%). It also remains unclear if and how certain driver mutations involving the MAPK pathway ultimately influence response to these agents, and thus it is difficult to determine which patients should be targeted in upcoming trials.

Immune checkpoint inhibitors

Melanoma is considered one of the more immunogenic types of cancer. The presence of tumor-infiltrating lymphocytes on biopsy is generally considered a favorable prognostic factor and spontaneous tumor regression, likely due to host-mediated immune destruction, is not uncommon. Despite a relatively high mutational burden that should trigger an immune response, melanoma cells can often alter the tumor microenvironment to avoid detection by the host immune system [42]. Immune escape is modulated in part by “immune checkpoints” such as PD1 and CTLA4, which serve to decrease inflammation and promote self-tolerance primarily through effects on T cell activation and response. Inhibition of these molecules therefore leads to increased T cell activation in peripheral tissues and ideally to improved detection and destruction of malignant cells.

Prior to the advent of immune checkpoint inhibitors, several trials demonstrated benefit in melanoma patients treated with high-dose IL-2 or cancer vaccines that make use of similar principles [43, 44]. The first immune checkpoint inhibitor to be developed was ipilimumab, a human monoclonal antibody to CTLA-4, which was approved in 2011 after demonstrating significant improvement in overall survival in a phase 3 randomized trial (Table 1) [19]. Subsequent anti-PD1 antibodies, including nivolumab and pembrolizumab, were found to be superior to ipilimumab with regards to response rate (33.7% vs 11.9% for pembrolizumab; 40.0% vs 13.9% for nivolumab), progression-free survival (31.2% vs 13.5% at 2 years for pembrolizumab; median 5.1 vs 2.2 months for nivolumab), and overall survival (55.1% vs 43% at 2 years for pembrolizumab; 72.9% vs 42.1% at 1 year for nivolumab) [20, 22, 45].

The impact of checkpoint inhibition was ultimately found to be most dramatic when PD1 and CTLA-4 agents were used in combination. The CheckMate-067 phase III trial enrolled 945 patients with untreated melanoma to receive ipilimumab, nivolumab, or ipilimumab and nivolumab in a 1:1:1 fashion [24]. Combination therapy resulted in improved PFS (median 11.5 vs 6.9 vs 2.9 months) and overall response rate (59% vs 44% vs 19%) compared with either agent as monotherapy. While differences in PFS or OS between combination therapy and nivolumab did not reach statistical significance, both were superior to ipilimumab. At 4-year follow-up, overall survival was 53% in the combination group, 46% in the nivolumab group, and 30% in the ipilimumab group [25]. Patients with *BRAF*-mutated tumors seemed to benefit most obviously from combination therapy with a 4-year survival of 62% compared with 50% with nivolumab and 33% with ipilimumab. While *BRAF* V600 mutation status in general has not been shown to significantly influence response to anti-PD1, response may be affected by *BRAF* genotype. Patients with *BRAF* V600K melanoma seem to have better

outcomes with anti-PD1 as well as inferior outcomes with BRAF/MEKi when compared with patients with V600E mutations [46•].

Grade 3–4 adverse events occurred in 59% of patients on the combination regimen in the CheckMate-067 trial, 40% of whom discontinued treatment early due to side effects [25]. Post hoc analysis, however, found similar PFS and OS between these patients and those who remained on therapy. Collectively, the patients in the combination arm received a median of 4 doses of each agent. Despite a relatively high rate of discontinuation due to adverse events, patients who receive only a few months of therapy with these agents may still experience significant long-term benefit.

First-line therapy

There are as of yet no prospective head-to-head data comparing the use of front-line immunotherapy with BRAF/MEK inhibitors in patients with *BRAF*-mutated melanoma. The optimal sequence of therapy is debated, although several phase III trials are currently underway that may help guide consensus opinion (including the DREAMSEQ trial, NCT02224781). BRAF/MEK inhibitors have generally been associated with a more robust and rapid initial response but eventual progression while checkpoint inhibitors may show lower initial response rates but have the potential for more durable long-term benefit. Patients with symptoms from metastatic disease are often offered BRAF/MEK inhibitors to promote more rapid symptom relief. The use of checkpoint inhibitors may also be limited in some patients by the potential for severe and occasional long-lasting toxicity, yet ongoing trials comparing different dosing regimens continue to improve safety profiles [47•, 48]. Shared decision making regarding optimal first-line therapy is thus often guided by consideration of the specific clinical context as well as discussion of potential toxicities and patient/physician preferences.

Initial retrospective studies found that patients who progressed on BRAFi monotherapy almost never responded to ipilimumab [49, 50]. Responses are somewhat better with more modern regimens (e.g., anti-PD-1–based regimen following BRAFi/MEKi), although still inferior to those seen in BRAF/MEKi-naive patients [26, 51]. Patients who progress on anti-PD1 also seem to have poor outcomes when treated with subsequent BRAF/MEKi with an OS of 10.6 months from the time of BRAF/MEKi initiation compared with 40.3 months in patients who received first-line BRAF/MEKi [51]. Treatment with anti-PD1 also seems to increase both the frequency and severity of adverse events associated with BRAF/MEK inhibitors, which may impact outcomes in this setting [52••]. Retrospective analysis found no significant difference in overall survival among patients treated with initial MAPK inhibition followed by anti-PD1 and those who received initial anti-PD1 followed by BRAF/MEK inhibitors (median 40.3 vs 27.5 months, $p = 0.71$) [51]. Patients who responded to BRAF/MEK inhibitors for > 6 months were significantly more likely to respond to subsequent anti-PD1 than those who responded to BRAF-directed therapy for less than 6 months (ORR 34% vs 15%, $p = 0.04$). Resistance to either regimen thus seemed indicative of a lower likelihood of response when switched to the alternative. The presence of a population of patients that seemed to benefit from both agents as well as the poor responses

seen in both second-line settings corroborates growing molecular evidence suggestive of overlapping mechanisms of resistance to these two classes of therapy.

Tumors with innate resistance to anti-PD1 demonstrated a unique transcriptional signature (IPRES or innate anti-PD1 resistance) in one study that involves upregulation of genes involved with cell regulation of mesenchymal transition, cell adhesion, extracellular matrix remodeling, angiogenesis, and wound healing [53•]. The BRAFi-resistant state shares many of these same features. Treatment with MAPK inhibitors has been shown to lead to upregulation of several genes associated with IPRES, which may represent a mechanism for subsequent resistance to immunotherapy [54]. A recent study that evaluated genomic features associated with response to BRAF/MEK inhibition did not find a correlation between the IPRES signature and response to these agents [55]. Melanomas from patients who experienced complete response did, however, demonstrate an enriched expression of genes involved in immune response, including genes related to cytotoxic T cells, antigen-presenting cells, and natural killer cells. Immune activation seems to be involved in response to both classes of therapy, which may be at least partially explained by increasing evidence that MAPK activation may play a role in immune escape [56–58]. The interplay between these two seemingly separate pathways could also plausibly result in a synergistic anti-tumor effect when given simultaneously.

Combination checkpoint and MAPK pathway inhibitors

Several pre-clinical animal models confirmed an enhanced anti-tumor effect when MAPK inhibitors and anti-PD1 agents were used in combination. BRAF/MEK inhibitors have been shown to enhance T cell infiltration into the tumor microenvironment and tumor antigen expression and promote cytotoxic T cell function, augmenting the effects of checkpoint inhibition [59, 60]. Early clinical studies of combination therapy, however, were limited by high rates of adverse events [61, 62]. In phase I of the KEYNOTE-022 trial, 15 patients with *BRAF*-mutated melanoma were treated with a combination of dabrafenib, trametinib, and pembrolizumab [63•]. Although reversible in most cases, toxicity leading to dose interruptions or modifications was seen in 93% of patients. Most participants responded (n = 11, 73%) and several (n = 6, 40%) demonstrated continued response at a median follow-up of 27 months. Median PFS was 15 months for all patients.

Another phase I trial assessed the use of atezolizumab, an anti-PDL1 agent, with either vemurafenib or vemurafenib and cobimetinib [64•]. A regimen involving a 28-day run-in period with vemurafenib + cobimetinib followed by initiation of atezolizumab was ultimately expanded to 39 checkpoint inhibitor–naive patients. As in the previously mentioned trial, a majority of patients demonstrated objective response (72%), which lasted for a median of 17 months. Grade 3–4 related toxicities occurred in 67% of patients.

In the phase II portion of the KEYNOTE-002 trial, 120 previously untreated patients with *BRAF*-mutated melanoma were randomized to receive dabrafenib/trametinib in combination with pembrolizumab (n = 60) or placebo (n = 60) [65•]. Response rates were similar between the two groups (63% with the combination and 72% with BRAF/MEK alone) with a longer duration of response seen in the combination arm (median 18.7 vs 12.5

months). Patients in the combination group also demonstrated longer PFS (median 16.0 vs 10.3 months) although the difference did not reach statistical significance. Grade 3–4 treatment-related toxicities were observed in 58% and 27% of patients in each group.

While these studies demonstrate a promising response rate and duration of benefit associated with the simultaneous use of checkpoint inhibitors and targeted therapy, treatment-related toxicities remain a significant barrier. It is also unclear whether similar benefit may be observed with the use of sequential therapy. Ongoing phase III trials comparing combination therapy with BRAF/MEK inhibitors and different sequential regimens will likely provide more insight.

Adjuvant or neo-adjuvant therapy for stage III melanoma

While earlier trials focused primarily on metastatic or unresectable melanoma, more recent studies have shown a potential benefit of systemic therapies in the setting of high-risk resectable tumors. The COMBI-AD trial randomized 870 patients with *BRAF*-mutated resected stage III melanoma to receive 12 months of either dabrafenib/trametinib or placebo [66••]. At a median follow-up of 44 months (treatment) and 42 months (placebo), relapse-free survival rates were found to be significantly higher in the treatment group (4-year RFS 54% vs 38%) [67].

Immunotherapies are also effective in this setting. An initial trial comparing ipilimumab with placebo in the adjuvant setting was limited by high rates of toxicity, possibly due to the high dose chosen for the study (10 mg/kg) [68, 69]. The CheckMate-238 trial found improved 1-year RFS (70.5% vs 60.8%) and decreased toxicity (grade 3 or 4 AEs in 14.4% vs 45.9%) with use of nivolumab (3 mg/kg) compared with high-dose ipilimumab (10 mg/kg) [70]. While benefit was seen regardless of *BRAF* mutation status with nivolumab compared with ipilimumab, patients with *BRAF* mutations may have benefited less significantly than those who were *BRAF* wild-type (HR for recurrence or death 0.72 vs 0.58). Pembrolizumab also demonstrated improvement in RFS (75.4% vs 61.0%) when compared with placebo in this setting with a similar frequency of grade 3 or 4 adverse events (14.7%) [71].

In another recent phase II trial, a total of 35 patients were enrolled to receive 12 weeks of neoadjuvant dabrafenib + trametinib followed by 40 weeks of adjuvant therapy [72••]. All 35 patients demonstrated a pathologic response at week 12 with 49% demonstrating a complete pathologic response. Overall and complete radiologic responses were comparable (86%, 46%). At a median follow-up of 27 months, however, 20 patients had recurred (57%), almost half within the first year ($n = 8$, 23%). Promising activity has been seen with neoadjuvant immunotherapy with preliminary data suggestive of lower rates of recurrence yet optimal regimens remain unclear [73].

Conclusion

The management of *BRAF* mutant melanoma has been transformed by recent advances in targeted and immune therapies. Optimal first-line management remains unclear but will be informed by ongoing phase III trials. Overcoming acquired resistance in targeted

therapy and intrinsic resistance in immune therapy remain the key challenges in this patient population.

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Table 1.

Outcomes and toxicities of treatment regimens for BRAF-mutant melanoma

Agent	Trial	*N*	Overall response rate	Median PFS (months)	Median OS (months)	OS notes	Common grade 3+ toxicities	Serious AEs (%)
Vemurafenib	BRIM-3 [5–7]	337	57% *	6.9 [6.1–7.0]	13.6 [12.0–15.2]	Median f/u of 13.4 months 4-year OS of 17.0%	Rash Arthralgia Photosensitivity Keratoacanthoma Cutaneous SCC	49
Dabrafenib	BREAK-3 [8, 9]	187	50% * [42.4–57.1]	6.9	18.2 [16.6–NR]	Median f/u of 15.2 months	Pyrexia Arthralgia Hyperkeratosis Cutaneous SCC	--
Trametinib	METRIC [10, 11]	214	29% * [22.6–35.1]	4.9	15.6	Median f/u of 14.7 months 5-year OS of 13.3%	Hypertension Rash	12
Dabrafenib + trametinib	COMBI-d + COMBI-v [12–14]	563	68% **	11.1 [9.5 – 12.8]	25.9 [22.6–31.5]	Median f/u of 22 months 5-year OS of 34%	Pyrexia Hypertension Decreased ejection fraction	48
Vemurafenib + cobimetinib	CoBRIM [15, 16]	247	70% ** [63.5–75.3]	12.3 [9.5 – 13.4]	22.3 [20.3–NR]	Median f/u of 18.5 months 2-year OS 48.3%	Increased liver function tests Increased creatine kinase Rash Diarrhea	37
Encorafenib + binimetinib	COLUMBUS [17••, 18••]	192	64% *	14.9 [11.0 – 20.2]	33.6 [24.4–39.2]	Median f/u of 36.8 months 2-year OS 57.6%	Increased liver function tests Increased creatine kinase Hypertension	34
Ipilimumab	MDX010-20 [×] [19]	137	10.9% **	2.86 [2.76 – 3.02]	10.1 [8.0–13.8]	Median f/u 27.8 months 2-year OS of 23.5%	Diarrhea/colitis Fatigue Dyspnea	–
Nivolumab	CHECKMATE-066 [×] [20, 21]	210	42.9% **	5.1 [3.5 – 10.8]	37.5 [25.5–NR]	Minimum f/u 38.4 months 3-year OS of 51.2%	Diarrhea Pruritis Vomiting Rash	15
Pembrolizumab	KEYNOTE-006 [×] [22, 23]	556	42% * [38.1–46.5]	8.4 [6.6–11.3]	32.7 [24.5–41.6]	Median f/u 57.7 months for surviving patients 5-year OS 38.7%	Diarrhea/colitis Fatigue Auto-immune Hepatitis Pneumonitis	14
Ipililumab + nivolumab	CHECKMATE-067 [×] [24, 25]	314	57.6% ** [52.0–63.2]	11.5 [8.7–19.3]	NR [38.2–NR]	Median f/u 46.9 months 4-year OS 53%	Diarrhea/colitis Increased lipase Increased liver function tests Fatigue	–

* Independent Review Committee reported

** Investigator reported

x BRAF mutation status was unknown in the ipilimumab trial and the CHECKMATE-066 trial was limited to BRAF wild-type melanoma. Subsequent retrospective studies have not found a correlation between BRAF mutant status and response to nivolumab or ipilimumab monotherapy [26, 27]. The KEYNOTE-006 and CHECKMATE-067 trials enrolled patients with both BRAF-mutant and BRAF wild-type melanomas. Response to pembrolizumab was similar in both groups in the KEYNOTE-006 trial while patients with BRAF mutations seemed to benefit more from anti-PD1/anti-CTLA4 combination therapy (in terms of OS) than those who were BRAF wt when compared with anti-PD1 monotherapy in the CHECKMATE-067 trial