Ipilimumab, Vemurafenib, Dabrafenib, and Trametinib: Synergistic Competitors in the Clinical Management of BRAF Mutant Malignant Melanoma

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ABSTRACT

There have been significant advances in the treatment of malignant melanoma with the U.S. Food and Drug Administration approval of two drugs in 2011, the first drugs approved in 13 years. The developments of immune checkpoint modulation via cytotoxic T-lymphocyte antigen-4 blockade, with ipilimumab, and targeting of BRAFV600, with vemurafenib or dabrafenib, as well as MEK, with trametinib, have been paradigm changing both for melanoma clinical practice and for oncology therapeutic development. These advancements, however, reveal new clinical questions regarding combinations and optimal sequencing of these agents in patients with BRAF mutant disease. We review the development of these agents, putative biomarkers, and resistance mechanisms relevant to their use, and possibilities for sequencing and combining these agents. The Oncologist 2013;18:717–725

Implications for Practice: Ipilimumab, vemurafenib, dabrafenib, and trametinib have recently significantly advanced the management of patients with BRAF mutant melanoma. Clinical trials that would guide the use of combinations and/or sequencing of these drugs are currently in progress or being developed. Until those data are available, we suggest that patients with good performance status be treated with immunotherapy prior to consideration of kinase inhibitors such as vemurafenib, dabrafenib, and trametinib. This recommendation is based on the potential time required for induction of an antitumor immune response by ipilimumab, the modest durability of clinical benefit by kinase inhibitors and the observation that a not-insignificant proportion of patients treated initially with kinase inhibitors are unable to later complete ipilimumab induction due to clinical decline.

INTRODUCTION

The treatment of malignant melanoma was revolutionized with the approval by the U.S. Food and Drug Administration (FDA) of ipilimumab for medically appropriate patients regardless of BRAF mutational status and vemurafenib for those who harbor BRAFV600 mutations. Both drugs have demonstrated improved overall survival (OS) and are indicated for unresectable and metastatic melanoma (any line of therapy). Additionally, the BRAFV600 inhibitor dabrafenib and the MEK inhibitor trametinib have also demonstrated improved progression-free survival (PFS) and OS, though they have yet to be considered for regulatory approval.

Each drug has advantages but multiple questions remain, such as sequencing of agents in BRAFV600 mutant disease, the potential for clinical synergy or antagonism, and the best methods for comparing efficacy beyond OS. Herein, we discuss the risks and benefits of these agents and anticipate how they will influence the treatment of melanoma in the future.

THE DEVELOPMENT OF IPOILIMUMAB

Immunotherapy has long been utilized for malignant melanoma treatment, but historically these approaches have demonstrated significant toxicity with modest clinical benefit [1]. More recent immunotherapeutic approaches have involved augmenting cell-mediated immunity by blocking key immune checkpoints [2], such as cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab is a fully human, monoclonal antibody that inhibits binding of CTLA-4 to its ligands CD80 and CD86 (Fig. 1A-B) [3]. When expressed on activated T cells, CTLA-4 counteracts costimulatory signaling through CD28, thus limiting antitumor immunity [3]. Blockade of CTLA-4 enhances antitumor immunity by potentiating T-cell responses and abrogating physiologic T-cell suppression [4].

Preclinical observations that CTLA-4-blocking antibodies could induce tumor regression [5–8] led to clinical evaluation of an anti-CTLA-4 antibody as monotherapy, in multiple combinations with other agents, and at doses up to 20 mg/kg [9, 10]. These studies revealed clinical activity, alone or with various other therapies, including interleukin-2, and a side-effect profile that differed from that of chemotherapy or targeted therapies. Described by the FDA as adverse events of special interest, these toxicities are likely the result of immune activation.

Figure 1. The role of CTLA-4 in T cell activation versus anergy. (A): Upon antigen presentation, T cells become activated or suppressed depending on secondary stimuli through CD28 or CTLA-4. (B): Ipilimumab binds CTLA-4, permitting increased signaling through CD28 and leading to T-cell activation. (C): Putative biomarkers for ipilimumab efficacy and toxicity.
tion (i.e., dermatitis, colitis). In phase I/II analyses, these adverse events were common, affecting approximately 60% of patients, with grade 3 or 4 events occurring in less than 15% of patients.

Because some early preclinical and clinical correlates suggested that continued dosing of anti-CTLA-4 may help to maintain T-cell potentiation, two trials investigated ipilimumab induction followed by maintenance (10 mg/kg every 3 weeks for four cycles followed by every 3-month dosing) [11, 12]. These studies suggested a dose dependency for both response rate (RR; <11% at 10 mg/kg and 30% disease control) and toxicity (adverse events occurred in 27%, 65%, and 70% of patients at 0.3, 3, and 10 mg/kg of ipilimumab, respectively, with grade ≥ 3 toxicities in approximately 25%). Because of an observed potential for ipilimumab-related bowel inflammation, the corticosteroid budesonide was evaluated as a prophylactic measure, but no differences in either ipilimumab efficacy or rates of immune-related colitis were observed [13].

Some clinical responses to ipilimumab are distinct from those of cytotoxic drugs, as time to tumor regression varies because of inherent variability among individual patients’ immune systems. Sometimes progression or development of new lesions may be observed prior to disease control. A set of novel response criteria, termed immune-related response criteria, have been developed to capture these responses and validate them with the gold-standard of OS. These evaluation criteria compare "total tumor burden" to baseline measurements over time (before and after standard progression of disease). To demonstrate this phenomenon of late response, a combined analysis of the CA184-008 and CA184-022 ipilimumab trials was performed. Among 227 patients treated with ipilimumab at 10 mg/kg, 123 exhibited modified (immune response) World Health Organization criteria evidence of progressive disease at 12 weeks. Prospective follow-up of 57 of these patients identified 14 (thus at least 11% of those with PD at 12 weeks or 6% of all patients) who experienced delayed clinical benefit from ipilimumab [14].

Randomized phase III studies confirmed the OS benefit of ipilimumab and led to its FDA approval in 2011. Ipilimumab (3 mg/kg every 3 weeks for 4 doses), alone and in combination with a glycoprotein 100 (gp100) vaccine, improved OS in previously treated patients (including those with treated central nervous system disease) compared with gp100 peptide vaccine alone [15]. This study randomized HLA-A*0201-positive patients in a 3:1:1 fashion to the combination, ipilimumab alone, and gp100 vaccine alone. The study documented an improvement in median OS of approximately 3.6 months, including a subset of patients who exhibited a long-term durable benefit of up to 4.5 years. Grade 3 or 4 immune-related toxicity in the ipilimumab-treated groups was 15% compared to 3% for the gp100 group. The second randomized phase III study compared ipilimumab (10 mg/kg, induction followed by maintenance) plus dacarbazine chemotherapy to dacarbazine alone (1:1) [16]. Median OS in the combination arm (11.1 months) was significantly greater than that in the dacarbazine arm (9.1 months), with subsequent improvements in 1-, 2-, and 3-year survival rates. The combination was significantly more toxic than dacarbazine monotherapy (56.3% vs. 27.5% grade 3/4 toxicity). Also of note, the immune-related toxicity of ipilimumab was apparently altered when combined with dacarbazine, with a higher incidence of hepatitis than colitis. The immunologic rationale for this is not clear, but it is possible that inclusion of dacarbazine modifies ipilimumab-mediated immune activation somehow. This will have to be closely monitored as part of future development of ipilimumab combination regimens.

Ipilimumab’s improvement of OS has changed the therapeutic landscape for melanoma, but most patients still do not receive a significant clinical benefit. As such, predictive biomarkers of clinical benefit and toxicity need to be developed to better select patients for this therapy. Several factors have been preliminarily indicated as biomarkers for ipilimumab activity, though none have been prospectively validated (Fig. 1C) [3]. To date, neither immune-mediated toxicity [17–19] nor HLA haplotype [9] was significantly associated with clinical benefit in prospective or retrospective analyses [20].

Several other potential pretreatment or early-on treatment predictive biomarkers are being evaluated for ipilimumab. An association between the development and resolution of immune-related colitis and IL-17 levels, but not other cytokines, was described in a retrospective analysis, but this association did not significantly influence long-term outcomes [21]. The predictive value of immune status against the cancer testis antigen NY-ESO-1 was investigated in 144 patients who received ipilimumab at various doses. A significant association with clinical benefit at 24 weeks was observed among the 16% and 22% of patients who exhibited pre- or post-treatment presence of NY-ESO-1 serum antibody, respectively [22]. Further analysis revealed greater clinical benefit and survival advantage if the NY-ESO-1-seropositive patient also exhibited a CD8+ T-cell response. Beyond, NY-ESO-1 status, conflicting data suggests that absolute lymphocyte count (ALC) may predict for benefit with ipilimumab. A single institution analysis reported a correlation between ALC after two treatments with response and survival [23], and a subsequent larger analysis correlated ALC after one dose with response [24]. The association with ALC after two doses and outcome was not reported in this study. The longstanding observation of a negative association between proangiogenic molecules, such vascular endothelial growth factor (VEGF), and response to immunotherapies [25, 26] suggests that inhibition of angiogenesis may act synergistically with ipilimumab. Preliminary assessment of this combination appears to be promising, especially for those patients with high pre-treatment VEGF levels [27]. Finally, analysis of the tumor microenvironment may eventually become helpful in patient selection for ipilimumab. Specifically, baseline and treatment-related changes in T-cell subsets, the expression of immune-related genes (such as FoxP3, indoleamine 2,3-dioxygenase, and Th1-associated markers including ICOS [28]) and post-treatment increases in tumor-infiltrating lymphocytes may be useful [29, 30]. Some of these markers have previously been evaluated in the context the anti-CTLA4 antibody tremelimumab; however, they have not correlated closely with response or long-term outcome [31, 32].

**The Development of BRAF and MEK Inhibitors for Melanoma**

Activating mutations in the BRAF V600 codon appear in approximately 50% of melanomas [33]. Initial unsuccessful attempts to target BRAF with the tyrosine kinase inhibitor
sorafenib [34, 35] led to structure-guided design of an inhibitor with specificity for the ATP-binding pocket of mutant BRAF. The result was a panel of molecules with specificity for BRAF<sup>V600E</sup> that abrogated downstream MAPK pathway phosphorylation and exerted antiproliferative effects in cell lines and in vivo tumor models [36, 37].

PLX4032 (now known as vemurafenib), the most pharmacologically viable of these compounds, was subsequently reformulated to improve its pharmacokinetic profile and underwent phase I investigation in patients with BRAF mutation-activated tumors [38]. Among 16 patients with melanoma who received doses of 240 mg twice daily and higher (960 mg twice daily becoming the recommended phase II dose), 10 partial responses and 1 complete response were noted. In a subsequent dose expansion of 32 patients with BRAF<sup>V600E</sup> mutant melanoma, an 81% RR (56% when adjusted for RECIST 1.1) [39] was observed. The toxicities of vemurafenib were manageable and included photosensitivity, rash, fatigue, and arthralgia. As well, the unexpected complication of squamous cell carcinoma (SCC) of the skin was noted in 33% of patients. Given these initial results, vemurafenib was moved into phase II and III investigations. The phase II (BRIM-2) trial included 132 total patients and confirmed the RR of vemurafenib at 53%. To date, patients enrolled in BRIM-2 have been described in follow-up to a median of 12.9 months with a median OS of 15.9 months. Treatment benefit was consistent across levels of disease burden (M1a–c) and confirmed the toxicity profile seen in the phase I study. One quarter of patients developed SCC the majority were keratoacanthoma (KA) type. Notably, upon progression of disease, 32 patients (24%) went on to receive ipilimumab. The investigators reported that removing these 32 patients from the analysis did not significantly alter the median OS rate [39].

BRIM-3 [40] was a randomized phase III trial comparing vemurafenib (960 mg twice daily) with dacarbazine (1000 mg/m<sup>2</sup> every 3 weeks), in 675 patients with BRAF<sup>V600E/K</sup>-mutant metastatic melanoma. Primary endpoints were OS and PFS. Updated results have described that, at 6 months, OS and PFS were 84% and 6.9 months versus 66% and 1.6 months for the vemurafenib and dacarbazine arms, respectively [41]. Vemurafenib demonstrated a higher RR than dacarbazine (57% vs. 9%) and nearly all vemurafenib-treated patients obtained at least some reduction in tumor burden. Toxicity was similar to that observed in other vemurafenib studies, with common adverse events including rash, photosensitivity, arthralgia, and fatigue; 38% of patients required dose reductions. Nineteen percent of patients treated with vemurafenib developed SCC, 11% KA, and 28% skin papilloma. Median OS values for vemurafenib and dacarbazine were 13.6 and 9.7 months, respectively, after median follow-up times of 12.5 and 9.5 months. Relevant to discussion regarding sequencing of vemurafenib and ipilimumab, 18% and 22% of vemurafenib- and dacarbazine-treated patients, respectively, received ipilimumab post-progression with no differences in disease stage (IIIC/M1a/ M1b). It should also be noted that in BRIM-2 and BRIM-3, a 40% RR was observed in non-BRAF<sup>V600E</sup> melanoma. Multiple vemurafenib studies are ongoing including an adjuvant trial (NCT01667419).

A second inhibitor of BRAF<sup>V600E</sup>, dabrafenib, is also of relevance to the future treatment of patients with BRAF<sup>V600E</sup> melanoma. Dabrafenib is an ATP-competitive inhibitor of BRAF with anti-tumor activity documented both within the brain and systemically. In a phase 1 study of 184 patients with solid tumors harboring either BRAF<sup>V600E/K</sup> mutations, a phase II dose of 150 mg twice daily was established, though maximum tolerated dose was never reached [42]. The toxicity profile was manageable and generally similar to that of vemurafenib with the exception of an increased incidence of pyrexia in 6% of patients and lower incidence of SCC (11%). Tumor shrinkage was observed in nine of 10 patients with melanoma and previously untreated brain metastases. In this context, a phase II study (BREAK-MB) examining dabrafenib specifically in patients with BRAF<sup>V600E/K</sup> mutant melanoma and either untreated or locally treated brain metastases was performed [43]. This study enrolled 172 patients and confirmed the activity of dabrafenib in both of these settings with RR of 39.2% and 30.8%, respectively. Toxicity was again manageable and similar to vemurafenib with the exception of pyrexia (6%) and cutaneous SCC (cSCC) (6%). Finally, a phase III study (BREAK-3) of dabrafenib versus dacarbazine showed an improvement in PFS, and OS as a secondary endpoint [44]. This study of 250 patients involved a 3:1 randomization to dabrafenib, with crossover at progression. The median PFS for dabrafenib was 5.1 months compared with 2.7 months for dacarbazine. Data on OS were preliminary at the time of reporting; however, an HR for survival benefit was observed at 0.61 (confidence interval (CI), 0.25–1.48). Toxicities were consistent with those observed with previous dabrafenib trials.

One issue that remains with selective BRAF inhibition is the durability of responses. Vemurafenib and dabrafenib clinical trials have described PFS of approximately 7 and 5 months, respectively. Thus, the development of resistance within these tumors is common. It is therefore essential to continue exploring the biology of RAF signaling and the mechanisms underlying drug resistance to improve treatment and inform development of future targeted therapies.

The molecular biology of mutant RAF signaling is complex, and significant efforts have been made to elucidate it. Upon upstream mitogenic stimuli, wild-type BRAF dimers (either homodimerization or heterodimerization with the other RAF isoforms ARAF and CRAF) leading to downstream MAPK pathway signaling. In contrast, mutated BRAF is constitutively activated in a monomeric state and activates MAPK signaling independent of upstream signals. Although vemurafenib blocks this activation, it can also cause downstream MEK activation through ARAF or CRAF homo- and heterodimerization in non-BRAF mutated cells [45]. This is caused by transactiva-
tion of the nondrug-bound partner in BRAF to CRAF heterodimers, or CRAF to CRAF homodimers, by vemurafenib [46]. This paradoxical downstream activation of MEK explains the development of SCC during vemurafenib treatment. In non-BRAF mutant cells, dimers formed from drug-bound BRAF and CRAF transactivate MEK and perpetuate downstream signaling [47, 48], a phenomenon that may be dose-dependent [47]. Further, upstream activation, predominately by RAS mutation, is required to facilitate this effect in non-melanoma tissues [49]. This RAS activation is not unexpected, given the prevalence of such mutations in sun-damaged skin.

This complex biology also relates to the development of resistance to BRAF inhibitors. Generally speaking, mechanisms of resistance to kinase inhibitors can be divided into three general categories: a secondary reactivating mutation in the kinase, development of a mutation in an associated gene that bypasses the blocked kinase, or activation of another growth pathway (Fig. 2A). Interestingly, whereas in most tumor models, the first of these is most common [50, 51], in BRAF mutant melanoma, the second appears to dominate. Confirmed mechanisms of resistance to vemurafenib described to date include upstream mutation of NRAS, activation of membrane-bound kinases (platelet-derived growth factor receptor-β or insulin-like growth factor-1 receptor) with subsequent signaling through other growth pathways such as phosphatidylinositol 3-kinases (PI3K/AKT) [52], overexpression of COT [53], downstream mutation of MEK [54], the development of RAS-independent BRAF heterogeneous isoform splice variants [55], and amplification of mutant BRAF [56]. Additionally, microenvironment-mediated resistance through stromal secretion of hepatocyte growth factor has been demonstrated in both preclinical systems and in patient-derived samples [57, 58]. Notably, most of these mechanisms reactivate the MAPK pathway, eventually resulting in ERK phosphorlylation; and preliminary data suggest that addition of a MEK inhibitor would improve the efficacy, delay resistance, and reduce toxicity of a BRAF inhibitor [59].

In this regard, it is important to note that an inhibitor of MEK, trametinib, has been evaluated in clinical trials and will soon become an important agent in the armamentarium of melanoma therapy. Trametinib is a selective, allosteric inhibitor of MEK1/2. In a phase I study of 206 patients with advanced solid tumors, a recommended phase II dose was determined to be 2 mg per day and showed an RR of 10% [60]. The most common toxicities were cutaneous (rash) and diarrhea with dose-limiting toxicities including these as well as central serous retinopathy. A substudy of this trial included melanoma patients only [61]. Within this cohort, 97 patients were treated, including 36 BRAFV600E/K mutant patients, 38 BRAF wild-type, 6 BRAF status unknown, and 16 uveal melanoma. Within the untreated BRAF mutant population, an RR of 33% and PFS of 5.7 months were described. BRAF wild-type patients had an RR of 10%. Toxicities were similar to the overall phase I population, and no cSCC were observed. These data led to a phase II study (METRIC) comparing trametinib with chemotherapy (dacarbazine or paclitaxel) in BRAFV600E/K mutant melanoma [62]. This study enrolled 322 patients in a 2:1 randomization to trametinib and allowed cross-over at progression. In the intention-to-treat population, a PFS of 4.8 months for trametinib was observed compared with 1.5 months for chemotherapy. Though follow-up was ongoing at the time of report, an HR for death of 0.54 (CI, 0.32–0.92) was observed in favor of trametinib, despite approximately half of patients crossing over from chemotherapy. Common toxicities were similar to those reported in the phase I trial, predominately including cutaneous, diarrhea, and fatigue. Toxicities particularly of note included cardiac toxicity (decreased ejection fraction or ventricular dysfunction), which was observed in 7% of patients, and ocular toxicity (blurred vision or reversible chorioretinopathy) in 9%. Notably, no cases of retinal-vein occlusion or cSCC were observed.

Given that the majority of resistance mechanisms to BRAF inhibitors have been described to reactivate the MAPK pathway, there has been interest in sequencing or combining BRAF and MEK inhibitors. Two important studies have now been reported regarding this. A phase II study of trametinib in patients with BRAF mutant melanoma who have been previously treated with either a BRAF inhibitor or are BRAF inhibitor naïve, revealed a PFS of 4 months in BRAF inhibitor–naïve patients and only 1.8 months in those who had received a BRAF inhibitor [63]. Similarly, the RR was 25% and 0% for naïve and pretreated patients, respectively. MEK inhibition as a single agent thus appears to have limited value after progression on a BRAF inhibitor. The combination of BRAF and MEK inhibitors appears to be much more promising however. In a phase I/II study of dabrafenib (150 mg twice daily) combined with trametinib (2 mg daily) in patients with BRAFV600E/K mutant melanoma, an increased RR, 76% versus 54% (p = .03) and PFS, 9.4 versus 5.8 months (HR = 0.39; 95% CI, 0.25–0.62; p < .001) were observed [59]. Additionally, the combination was more tolerable than dabrafenib alone with decreased pyrexia, 71% versus 26%, and incidence of cSCC (including KA), 7% versus 19%. Phase III studies of dabrafenib combined with trametinib in patients with BRAF-mutant melanoma are currently recruiting, including an adjuvant trial (NCT01682083, NCT01584648, and NCT01597908).

### Pros, Cons, and Potential Synergy of the Combination

For patients with BRAF mutant melanoma, ipilimumab and MAPK inhibitors have contrasting advantages and disadvantages. Where ipilimumab has a modest RR, it delivers an OS benefit and the possibility of long-term durable disease control. In contrast, MAPK inhibitors deliver an impressive RR and OS benefit. Given that the majority of resistance mechanisms to BRAF inhibitors have been described, decisions regarding sequencing of these agents must be dictated by patient circumstances. Given that ipilimumab may take time to generate an antitumor immune response, many melanoma oncologists, including the National Comprehensive Cancer Network guideline panel [1], have suggested ipilimumab in the upfront setting regardless of BRAF status. This is especially applicable to patients with low disease burden, minimal disease-related symptoms, or a slower tempo of disease progression. Unfortunately, patients with rapidly progressive disease and/or symptoms may require im-
mediate intervention for disease control. For patients with BRAF mutant melanoma in this situation, vemurafenib would likely be preferred. Specific clinical circumstances should also be taken into consideration, such as the presence of brain metastases, although efficacy in this setting has been described for both ipilimumab and vemurafenib [64, 65]. Additionally, there may be synergy between ipilimumab and radiation, which could be relevant to a single metastatic site [66].

Although upfront MAPK inhibitors are often attractive when tumor shrinkage, disease control, and improvement in cancer-related symptoms are warranted, this scenario complicates the decision of when to administer ipilimumab. The

Figure 2. Resistance to vemurafenib. (A): Resistance to targeted oncogene inhibition can occur through oncogene reactivation or activation of a bypass pathway. (B): Clinical resistance to vemurafenib. Seven mechanisms, most of which reactivate MAPK signaling, have been described.
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standard paradigm in oncology would be to continue MAPK inhibitors until disease progression. Some argue that continuous dosing of BRAF inhibitors is not the most efficacious strategy, however, and that intermittent dosing may delay the development of resistance [67]. In addition, continuous dosing leaves little space for transition to immunotherapy as patients may be too ill to wait for the immune response to take effect. Further, the phenomenon of “tumor flare” has been documented in other models of oncogene inhibition [68] and may be relevant to BRAF. It is possible that removal of MAPK inhibitors following drug resistance may result in a more rapid clinical decline for a subset of patients. Recently, the outcomes of 28 patients with BRAFV600-mutated metastatic melanoma treated at a single-institution with vemurafenib or dabrafenib followed by ipilimumab 3 mg/kg were analyzed [69]. Twelve (43%) patients had rapid disease progression resulting in death and were unable to complete all four inductions of ipilimumab; median OS was 5.7 months (95% CI, 5.0 – 6.3). Sixteen (57%) patients had slower disease progression and were able to complete induction therapy with ipilimumab; median OS was significantly longer at 18.6 months (95% CI, 3.2 – 41.3; p < .0001). These data suggest that concomitant treatment with ipilimumab and a BRAF inhibitor is more suitable for patients with poor prognostic factors than sequential therapy. Furthermore, in a retrospective analysis of 43 patients with malignant melanoma treated with immunotherapy (ipilimumab or IL-2) before or after vemurafenib, all 10 patients who received ipilimumab after progression achieved no further tumor response and all showed disease progression by 6 months (five patients within weeks) [70]. Conversely, of the 16 patients that received vemurafenib after immunotherapy, 12 (75%) responded.

Thus, there are multiple approaches to this sequencing, all of which require validation. The most obvious is to use immunotherapy in the upfront setting when possible, transitioning to BRAF-directed therapy after disease progression or clinical decline. A second possibility would be to first achieve disease control with BRAF inhibitor and then transition to ipilimumab before resistance develops. Another strategy would be indefinite treatment with a BRAF inhibitor, adding in local intervention to sites of disease progression or, potentially, immunotherapy such as ipilimumab. The latter combination strategy could perhaps take advantage of any potential synergy between BRAF inhibition and immunotherapy from the start of therapy [71, 72].

CONCLUSIONS

The development of ipilimumab, vemurafenib, dabrafenib, and trametinib has been paradigm shifting in melanoma. Ongoing research will inform decisions to sequence or combine these agents, but until these results are available, combination therapy outside of a clinical trial is discouraged. Given the lack of high-quality evidence to guide clinical decisions, our experience suggests that pursuing ipilimumab as first-line therapy followed by MAPK inhibitors offers patients the maximum opportunity for benefit. This decision is based on the documented potential for long-term disease control as well as the treatment kinetics of the immune response associated with ipilimumab. This choice is predicated on the setting of a patient whose disease is minimally symptomatic, is not rapidly progressing, and who values maximizing number of treatment options (as opposed to considerations such as toxicity profile of treatment). At the same time, it also seems reasonable that MAPK inhibitors should be employed initially when there is a large disease burden, or symptoms, with a bridge to immunotherapy considered afterward. In making these recommendations, we fully admit that BRAF inhibitors may also have optimal efficacy and durability in those patients who have less advanced disease and that issues of disease burden and velocity of tumor progression were not considered in the FDA approval of these agents. Recommendations such as these will have to be considered in an ongoing fashion as longer-term outcome data becomes available for vemurafenib as well as dabrafenib and trametinib.

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