

Immunotherapy or Molecularly Targeted Therapy: What Is the Best Initial Treatment for Stage IV *BRAF*-Mutant Melanoma?

Geoffrey T. Gibney, MD, and Michael B. Atkins, MD

Geoffrey T. Gibney, MD, is an attending physician at the Georgetown-Lombardi Comprehensive Cancer Center and the Department of Medicine at Medstar-Georgetown University Hospital in Washington, DC. Michael B. Atkins, MD, is the deputy director of the Georgetown-Lombardi Comprehensive Cancer Center, a professor of oncology at Georgetown University Medical Center, and a professor of medicine at Medstar-Georgetown University Hospital in Washington, DC.

Corresponding author:
Geoffrey T. Gibney, MD
Lombardi Comprehensive Cancer Center
Medstar Georgetown University Hospital
3800 Reservoir Rd, NW, Podium A
Washington, DC 20007
Phone: 202-444-1145
Fax: 202-444-1229
E-mail:
geoffrey.t.gibney@gunet.georgetown.edu

Abstract: The recent developments in *BRAF*-targeted therapy and checkpoint inhibitor immunotherapies for metastatic melanoma patients have led to better tolerability and markedly improved clinical outcomes, including higher objective response rates and longer survival. Treatment planning has become complex in patients with metastatic *BRAF*-mutant melanoma, with several options for *BRAF*- and/or MEK-targeted therapy (vemurafenib, dabrafenib, and trametinib) and immunotherapy (interleukin 2, ipilimumab, pembrolizumab, and nivolumab). Clinicians must weigh various patient factors, including the extent of disease (eg, symptomatic visceral metastases vs limited disease) and central nervous system involvement, as well as factors related to the therapeutic agent, such as rate of clinical response, durability of response, and impact on median and long-term survival. The combination regimen of dabrafenib plus trametinib has become a standard treatment strategy, and ipilimumab plus nivolumab is emerging as a promising treatment strategy. In this review, we discuss the benchmark trials leading to the approval of these new agents and provide emerging data on their use in sequence and impact on overall survival, with the goal of helping oncologists navigate treatment decisions for patients with metastatic *BRAF*-mutant melanoma.

Introduction

The discovery of activating *BRAF* mutations in half of all melanomas has led to the development of molecularly targeted therapy for patients with advanced melanoma.¹ *BRAF* mutations are most commonly seen at the V600 codon (V600E and V600K), leading to activation of the mitogen-activated protein kinase (MAPK) pathway and oncogenic development. The first phase 1 trial with a selective *BRAF* V600 mutant inhibitor (PLX4032, vemurafenib [Zelboraf,

Keywords

BRAF mutations, checkpoint inhibitors, immunotherapy, melanoma, targeted therapy

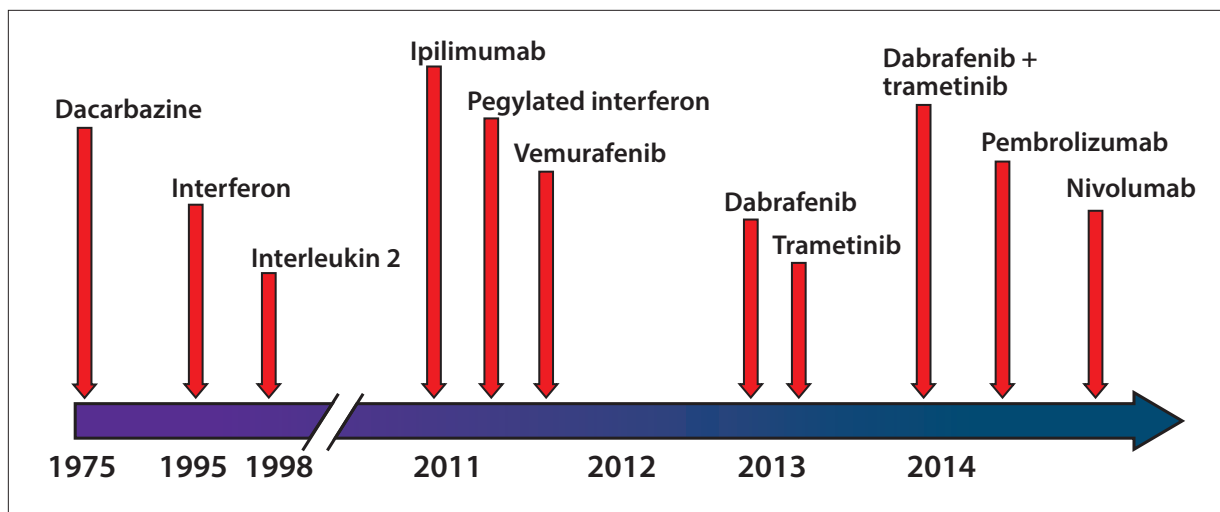


Figure 1. Timeline for US Food and Drug Administration approval of agents in metastatic melanoma.

Genentech/Daiichi Sankyo]) demonstrated objective responses in 81% of patients treated in the extension phase.² Most patients had multiple prior lines of therapy. We have now seen the rapid clinical development and US Food and Drug Administration (FDA) approval of 3 BRAF pathway inhibitors (see Figure 1): vemurafenib and dabrafenib (Tafinlar, GlaxoSmithKline), which inhibit BRAF; and trametinib (Mekinist, GlaxoSmithKline), which inhibits MEK. Dual blockade with concurrent BRAF and MEK inhibition has emerged as a superior therapeutic strategy based on recent phase 3 trials. The combination of dabrafenib and trametinib was FDA approved in 2014 and has largely replaced single-agent BRAF inhibitor therapy in patients with *BRAF*-mutant melanoma.

Concurrent with the development of BRAF-targeted therapies, marked gains also have been made in immunotherapy strategies for patients with metastatic melanoma. Prior to 2011, interleukin 2 (IL-2) was the treatment of choice in appropriately selected patients with metastatic melanoma because of the potential to produce long-term treatment-free survival.³ However, objective responses occur in fewer than 20% of patients treated with IL-2 and toxicities are common, including hypotension, renal insufficiency, and fluid overload, which necessitate its administration in an inpatient setting. The past decade has witnessed the development of therapies that target various immune checkpoints, specifically cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway, thereby unleashing a tumor-specific immune response in a subset of patients. The selective immune checkpoint inhibitors—ipilimumab (Yervoy, Bristol-Myers Squibb), pembrolizumab (Keytruda, Merck), and nivolumab (Opdivo, Bristol-Myers Squibb)—have

demonstrated clinical benefit in patients with advanced melanoma regardless of BRAF status and with considerably less toxicity than is seen with IL-2, leading to their FDA approvals.

Now that multiple distinct treatment options are available, particularly for patients with metastatic *BRAF*-mutant melanoma, physicians need to determine which approach makes the most sense for a particular patient. Factors such as the rapidity of clinical benefit, response rate, activity against brain metastasis, potential for long-term survival, and toxicity profile, as well as patient goals and preferences, need to be considered for each treatment. In this review, we look at the clinical data from recent trials of BRAF-targeted therapies and immunotherapies in patients with *BRAF*-mutant melanoma, with the goal of helping guide clinicians in treatment decisions in particular patients.

Updated Clinical Outcomes With BRAF-Targeted Therapies

BRAF Inhibitors

During early development of the selective BRAF inhibitors vemurafenib and dabrafenib, clear clinical benefit was seen in patients with melanoma harboring *BRAF* V600 mutations.^{2,4} Tumor responses can occur very quickly, and positron emission tomography scans show dramatic reduction in hypermetabolic activity within 2 weeks of therapy initiation.^{5,6} Two phase 3 trials have been completed comparing vemurafenib (960 mg orally twice daily) or dabrafenib (150 mg orally twice daily) with dacarbazine.^{7,8} In long-term follow-up of the vemurafenib phase 3 study BRIM-3, 57% of patients receiving vemurafenib had an objective response, whereas only 9% of patients responded to dacarbazine. Median progression-free survival (PFS)

and overall survival (OS) were also superior with vemurafenib compared with dacarbazine (median PFS, 6.9 vs 1.6 months; median OS, 13.6 vs 9.6 months).⁹ The OS hazard ratio (HR) was 0.70 ($P=.0008$) for vemurafenib compared with dacarbazine. Of note, the 18-month OS rate for vemurafenib was 39%. On subgroup analyses, although response rates and median OS were longer for patients with M1a and M1b disease, response rate and survival enhancement relative to dacarbazine were more evident in patients with poor prognostic factors such as elevated lactate dehydrogenase (LDH) and/or M1c (visceral metastatic) disease. Clinical activity seemed to be independent of prior immunotherapy status. Updated data on the dabrafenib phase 3 study BREAK-3 have shown similar findings for dabrafenib, with an objective response rate (ORR) of 50%, median PFS of 6.9 months, and median OS of 18.2 months.¹⁰ Both the BRIM-3 and BREAK-3 studies met their primary endpoints of improved OS (of note, BRIM-3 also had improved PFS as a co-primary endpoint, which was met).

Both vemurafenib and dabrafenib have demonstrated activity against melanoma brain metastases (MBM), which occur in more than one-third of patients with advanced melanoma.¹¹ The phase 2 study of dabrafenib (BREAK-MB) showed objective intracranial responses in 39% of patients without prior MBM therapy and 31% of patients with prior MBM treatment, such as surgery or radiation (among the *BRAF* V600E-mutant melanoma population).¹² The median duration of intracranial response was 4.7 and 6.6 months, respectively, and median OS was 7.7 and 7.3 months, respectively. Objective responses were also seen in the *BRAF* V600K-mutant melanoma patient cohorts. These findings were clearly superior to historical data with other systemic therapies used to treat patients with active MBMs.¹¹ Similar clinical benefit in patients with *BRAF* V600E-mutant melanoma has been reported for the phase 2 MBM study of vemurafenib.¹³

Although vemurafenib and dabrafenib—which are administered on a continuous basis—are generally well tolerated, toxicities lead to dose reduction or discontinuation in 28% to 38% of patients.^{7,8} The most common adverse events are arthralgias (more often seen with vemurafenib), pyrexia (more often seen with dabrafenib), rash, fatigue, headache, nausea, and vomiting. Also, secondary neoplasms can be seen with these agents, such as keratoacanthomas, squamous cell carcinoma, new primary melanomas, and in rare cases other malignancies, all of which are believed to be related to paradoxical activation of the MAPK pathway.¹⁴

MEK Inhibitors

MEK 1 and 2 are protein kinases within the MAPK pathway that are activated by mutant BRAF, leading to

signal transduction that regulates cell proliferation and survival. The selective MEK1/2 inhibitor trametinib also was investigated as a therapeutic strategy in patients with *BRAF*-mutant melanoma during the same period as the BRAF inhibitors. The phase 3 METRIC trial compared trametinib (2 mg oral daily) with dacarbazine or paclitaxel in patients with *BRAF* V600E- and V600K-mutant melanoma.¹⁵ Objective responses were seen in 22% of patients receiving trametinib, compared with 8% of patients receiving chemotherapy. Enhanced clinical benefit for trametinib was also seen in median PFS (4.8 months; HR, 0.45; $P<.0001$; primary endpoint) and OS (HR, 0.54; $P=.01$). Improvement in survival was observed in all subgroups of patients. Common adverse events seen with trametinib include rash, diarrhea, peripheral edema, and fatigue, with dose interruptions needed in 35% of patients. Based on the significantly improved PFS, trametinib was approved by the FDA. However, in clinical practice, its use as a single agent is limited owing to the superior results seen with BRAF inhibitors in this patient population.

Combination Treatment:

BRAF Inhibitors Plus MEK Inhibitors

Because the majority of patients with *BRAF*-mutant melanoma treated with BRAF inhibitors develop resistance (either intrinsic or acquired) at a median of 6 to 8 months, new therapeutic strategies have been investigated to enhance the clinical activity of these agents. At the time of progression, reactivation of the MAPK pathway is a common finding, regardless of the mechanism of resistance. In a retrospective study by Rizos and colleagues, 79% of BRAF inhibitor-resistant melanomas showed reactivation of the MAPK pathway through *BRAF* amplification, *BRAF* splice variants, activating MEK or *NRAS* mutations, receptor tyrosine kinase activation, and other events.¹⁶ Preclinical and early clinical data showed clear efficacy gains with the combination of BRAF and MEK inhibitors relative to single-agent BRAF inhibitors. A randomized phase 1/2 trial of dabrafenib plus trametinib, at either 1 or 2 mg daily, demonstrated enhanced clinical responses and PFS relative to dabrafenib alone.¹⁷ The clinical benefit of this combination was recently confirmed in two phase 3 studies comparing dabrafenib plus trametinib with either single-agent dabrafenib plus placebo, or vemurafenib plus placebo.^{18,19} These studies showed ORRs of 67% and 64%, respectively, and superior PFS and OS, with the combination. Subgroup analyses also showed that this benefit was particularly robust in patients with poor prognostic features. Another phase 3 study of vemurafenib plus the MEK inhibitor cobimetinib vs vemurafenib alone demonstrated similar findings.²⁰ Unfortunately, patients still progressed on BRAF plus MEK inhibition, with a median PFS of 9.3

to 11.4 months. Median OS was not yet reached in the phase 3 studies, but updated data from the phase 1/2 study showed it to be 25 months with the dabrafenib/trametinib combination.²¹ In particular, patients with good prognostic factors (M1a or M1b or normal LDH) exhibited exceptionally long survival, with a 2-year OS rate of 75%. Despite the fact that a substantial subset of patients are exhibiting prolonged survival on BRAF/MEK inhibitor therapy, including approximately 10% of patients with ongoing complete responses, little is known about the ability to discontinue treatment in such patients with long-term tumor responses.

Similar to the experiences with single-agent vemurafenib and dabrafenib, the combination of dabrafenib and trametinib generally is well tolerated.^{18,19} However, dose reductions were required in 25% to 33% of patients and permanent discontinuation occurred in 9% to 13% of patients owing to adverse events. Pyrexia, elevated transaminase, and hypertension rates were slightly more prevalent with the combination compared with dabrafenib alone. This was offset by the lower frequency of hand-foot syndrome, hyperkeratosis, keratoacanthomas, and squamous cell carcinoma, likely due to blocking of the paradoxical activation of the MAPK pathway associated with the BRAF inhibitor by concomitant use of the MEK inhibitor.

Clinical Outcomes With Checkpoint Inhibitor Immunotherapies

Anti-CTLA-4 Therapy

Ipilimumab, a monoclonal antibody that targets the CTLA-4 checkpoint, was the first agent to demonstrate improved OS in patients with metastatic melanoma in a randomized phase 3 trial.²² Objective responses were seen in 11% of patients, and another 17.5% of patients had stable disease with the approved ipilimumab dosing regimen (3 mg/kg intravenously every 3 weeks for 4 doses). Although the median PFS and OS were short—at 3 and 10 months, respectively—the survival curves suggested the potential for long-term clinical benefit in a subset of patients, similar to high-dose IL-2.³ A pooled analysis involving long-term data from 10 prospective and 2 retrospective studies of ipilimumab has shown a median OS of 11.4 months and a plateau in the survival curve at 3 years, with 22% of patients alive.²³ Subset analyses suggest less benefit in patients with elevated LDH or visceral disease. Similar disease control rates were seen in patients with *BRAF*-mutant and wild-type melanoma treated with ipilimumab in the expanded access program.²⁴ Median OS was 11.6 months for patients with *BRAF*-mutant disease and 8.5 months for patients with wild-type disease, but this difference was not statistically significant.

Furthermore, MBM responses have been demonstrated with ipilimumab at similar rates as extracranial disease in patients not requiring corticosteroids at the time of therapy initiation.²⁵

Significant toxicities (grade 3/4 adverse events) were seen in 23% to 25% of patients treated with ipilimumab.^{22,26} These were largely immune-related adverse events such as rash/pruritus, diarrhea/colitis, hepatitis, and endocrinopathies. Grade 3 immune-related adverse events are generally well managed with high-dose corticosteroids followed by a slow taper over 4 weeks. Patients with endocrinopathies (eg, hypophysitis, thyroiditis, and adrenalitis) require symptom management and, frequently, permanent hormone replacement therapy.

Anti-PD-1 Therapies

The monoclonal anti-PD-1 antibodies, pembrolizumab and nivolumab, block the PD-1/PD-L1 interaction between T cells and primarily tumor cells in the tumor microenvironment, thereby unleashing tumor antigen-specific cytotoxic T-cell activity. This strategy has demonstrated significant clinical activity in patients with metastatic melanoma and other malignancies. The phase 1 trial of pembrolizumab, at either 2 mg/kg or 10 mg/kg, included 173 patients with metastatic melanoma refractory to ipilimumab. The ORR was 26%.²⁷ In the approved dose cohort level (2 mg/kg every 3 weeks), the median PFS was 31 weeks and 58% of patients were alive at 1 year. Also of interest, 18% of the patients enrolled in the phase 1 study of pembrolizumab had *BRAF* mutations and previously received BRAF-targeted therapy. The ORR in the *BRAF*-mutant subgroup was 19%, compared with 28% in the *BRAF* wild-type subgroup (not a statistically significant difference). These results led to FDA approval of pembrolizumab in September 2014 at a dose of 2 mg/kg intravenously every 3 weeks in patients with prior ipilimumab and, if indicated, BRAF inhibitor therapy. The benefit of pembrolizumab (10 mg/kg or 2 mg/kg) relative to chemotherapy was evaluated in patients with ipilimumab-refractory metastatic melanoma (also previously treated with a BRAF inhibitor if *BRAF* mutant) in a randomized phase 2 trial (KEYNOTE-002).²⁸ Both pembrolizumab dose levels (10 mg/kg and 2 mg/kg) demonstrated superior response rates compared with chemotherapy (25% and 21% vs 4%, $P < .0001$) and improved PFS (HRs of 0.50 and 0.57 for both pembrolizumab doses compared with chemotherapy, $P < .0001$).

Nivolumab was first evaluated in a phase 1/2 dose-escalation cohort expansion study in patients with multiple malignancies, including patients with advanced melanoma.²⁹ In this study, 107 patients were treated at doses from 0.1 to 10 mg/kg every 2 weeks for up to 96 weeks. Objective complete or partial responses were

observed in 34 of 107 patients (32%). Treatment was discontinued for reasons other than progressive disease in 21 cases; 14 of these 21 continued to be progression-free. In a recent update presented at the 2014 Society of Melanoma Research annual meeting, median OS was 17 months and the 1-, 2-, and 3-year OS rates were 63%, 48%, and 42%, respectively.³⁰ In a subsequent phase 3 study of nivolumab (3 mg/kg intravenously every 2 weeks in patients with metastatic melanoma who were previously treated with ipilimumab and a BRAF inhibitor–based regimen, if *BRAF* mutant), the ORR was 32%.³¹ Although follow-up times have been short, many of the responses appear to be durable. These results led to FDA approval of nivolumab in December 2014 at a dose of 3 mg/kg every 2 weeks. Nivolumab has also been evaluated as frontline therapy compared with dacarbazine in patients with *BRAF* wild-type melanoma, which again confirmed superiority over chemotherapy, with a response rate of 40% (vs 14% for dacarbazine) and an OS HR of 0.42 ($P < .0001$).³²

Although drug-related adverse events have been reported in a majority of patients receiving either pembrolizumab or nivolumab, only 8% to 15% experienced significant side effects (grade 3-5).²⁷⁻³² Serious immune-related events such as dermatitis, diarrhea/colitis, hepatitis, and pancreatitis have been reported in relatively few patients (up to 2%). A phase 3 trial comparing pembrolizumab (2 groups with pembrolizumab 10 mg/kg every 2 or 3 weeks) with ipilimumab in patients with advanced melanoma was recently published (KEYNOTE-006).³³ Lower rates of treatment-related grade 3 to 5 adverse events were observed in the pembrolizumab groups (13% and 10%) compared with the ipilimumab group (20%). Furthermore, the ORR was superior in the pembrolizumab groups (33% and 34% compared with 12%, respectively; $P < .001$), as well as improved PFS and OS rates. Subgroup analyses showed that enhanced survival with pembrolizumab was maintained in the *BRAF*-mutant and *BRAF*-wild-type populations.

Concurrent Anti-CTLA-4/Anti-PD-1 Therapy

The combination of CTLA-4 and PD-1 checkpoint blockade using concurrent ipilimumab and nivolumab has yielded exciting results in a phase 1 study, with apparent enhanced clinical activity compared with either agent alone or the 2 agents used in sequence.^{34,35} The cumulative ORR from various dose level cohorts was 43% (13% complete response rate), with an aggregate clinical activity rate of 65%. Interestingly, 36% of patients had an 80% or more reduction in tumor burden by 12 weeks. *BRAF* mutational status was known in 90 of 94 patients. Twenty-four patients had *BRAF*-mutant melanoma, and 11 of these patients had previously received a BRAF inhibitor. The ORRs were 38% and 42% in

BRAF-mutant and *BRAF* wild-type melanoma patients, respectively. Although median OS has not been reached, data on the first 3 cohorts of patients receiving concurrent therapy showed a 2-year OS rate of 79%. Similar results were seen in the recently published randomized double blind phase 2 trial of ipilimumab/nivolumab combination therapy compared with ipilimumab monotherapy in patients with metastatic melanoma.³⁶ Combined ipilimumab/nivolumab yielded a superior ORR (61% vs 11%) and PFS compared with ipilimumab alone (HR, 0.40; $P < .001$) in the *BRAF*-wild type population. Within the *BRAF*-mutant population, the response rate was 52% in the combination group vs 10% in the monotherapy group, along with an improved PFS.

In contrast to single-agent checkpoint inhibitors, significant treatment-related toxicities occurred in a majority of patients receiving the ipilimumab/nivolumab combination.^{35,36} The types of adverse events were similar to those seen with ipilimumab as a single agent, such as dermatitis, colitis, hepatitis, and endocrinopathies. A large percentage of events were primarily laboratory only (increased hepatic transaminases and pancreatic enzymes). Most were manageable with drug interruption/discontinuation, high-dose corticosteroids, and supportive care.

Based on the enhanced clinical activity seen with combination checkpoint blockade, a frontline phase 3 study comparing concurrent ipilimumab/nivolumab with ipilimumab/placebo and nivolumab/placebo has now been conducted (Checkmate 067).³⁷ Co-primary endpoints were PFS and OS. Improved PFS was observed in the concurrent ipilimumab/nivolumab arm compared with the monotherapy arms (median PFS, 11.5 months for concurrent ipilimumab/nivolumab, 6.9 months for nivolumab, 2.9 months for ipilimumab). Benefit was seen irrespective of *BRAF* mutational status. Because of the short follow-up time (approximately 12 months), data on OS were not included. Higher objective response and toxicity rates were observed for the concurrent ipilimumab/nivolumab arm, comparable to data from the phase 1 and 2 studies. Of note, concurrent ipilimumab/nivolumab is also being tested in patients with asymptomatic central nervous system metastases (NCT02320058).

Discussion

With the FDA approval of multiple therapeutic options for the management of patients with metastatic *BRAF*-mutant melanoma, treatment decisions have become increasingly complex. In the absence of prospective data on the optimal sequence of therapy, clinicians must rely on their interpretation of the results from various trials of BRAF-targeted therapy and immunotherapy, especially results in subgroups distinguished by tumor stage and patient performance

Table. Comparisons of BRAF-Targeted Therapy and Checkpoint Inhibitor Immunotherapies

Attribute	BRAF-Targeted Therapy	Immunotherapy
Schedule	- Administered as continuous oral medications	- Ipilimumab administered IV every 3 weeks × 4 doses only - Anti-PD-1 therapies administered IV every 2-3 weeks
Safety (related adverse events)	- Grade 3/4 events in 35%-52% of patients receiving dabrafenib/trametinib ^{18,19} - Dose reductions in 25%-33% and discontinuations in 9%-13% of patients receiving dabrafenib/trametinib ^{18,19}	- Grade 3/4 events in 23%-27% of patients receiving ipilimumab ^{22,26,37} - Grade 3/4 events in 8%-16% and drug discontinuations in 2%-9% of patients receiving anti-PD-1 therapies ^{27-33,37} - Grade 3/4 events in 54%-68% and drug discontinuations in 36% of patients receiving ipilimumab/nivolumab ³⁵⁻³⁷
Objective response rate	- ORR of 64%-67% for dabrafenib/trametinib ^{18,19}	- ORR of 11%-19% for ipilimumab ^{22,36,37} ; 17% in <i>BRAF</i> -mutant subset analysis ²⁴ - ORR of 21%-43% for anti-PD-1 therapies ^{27-33,37} ; 19% in <i>BRAF</i> -mutant subset analysis ²⁷ - ORR of 43%-62% for ipilimumab/nivolumab ³⁵⁻³⁷ ; 38%-52% in <i>BRAF</i> -mutant subset analysis ^{35,36}
Survival	- Median OS of 25 months and 2-year OS rate of 51% for dabrafenib/trametinib. ²¹ - Unclear durability of response after drug discontinuation	- Median OS of 10-11 months and 3-year OS rate of 22% with ipilimumab ^{22,23} ; 11.6 months for <i>BRAF</i> -mutant subset analysis ²⁴ - Median OS of 17 months and 2-year OS rate of 43% with nivolumab ³⁹ - 2-year OS rate of 79% for ipilimumab/nivolumab ³⁵ - Durable responses seen off therapy

IV, intravenously; PD-1, programmed death 1; ORR, objective response rate; OS, overall survival.

status, as well as retrospective studies (see the table).

In patients with *BRAF*-mutant melanoma who have extensive, symptomatic disease, most clinicians would favor the use of BRAF-targeted therapy (dabrafenib/trametinib). Subgroup analyses from multiple BRAF trials have demonstrated strong clinical benefit in patients with the most advanced and aggressive disease (elevated LDH, M1c), whereas similar analyses for immunotherapies have tended to favor patients with less aggressive or advanced disease. The arguments favoring BRAF-targeted therapy also include the relative ease of oral drug administration and the rapid clinical and radiographic responses that can be seen with BRAF-targeted agents. Although responses to ipilimumab are typically more delayed, including an approximately 10% incidence of “pseudo-progression” that later responds,³⁸ the median time to response for nivolumab regimens appears to be shorter. For example, in the phase 3 nivolumab trial, the median time to response was 2.1 months (range, 1.6 to 7.4 months)³¹ and initial data for combined ipilimumab/nivolumab therapy showed responses that were rapid and deep, with a majority of responding patients exhibiting 80% or greater tumor shrinkage at 12 weeks into treatment.³⁴

Another patient population in which up-front BRAF-targeted therapy would be preferred is patients with active *BRAF*-mutant MBM not amenable to surgery or stereotactic radiosurgery. Data have shown that BRAF inhibitors (dabrafenib and vemurafenib) produce higher ORRs (as well as intracranial disease control) than those seen with chemotherapy or ipilimumab.^{11,25} No prospective data are yet available for BRAF/MEK inhibitor combinations or anti-PD-1–based therapies. However, these are areas

of clinical interest with ongoing trials (NCT02039947; NCT02085070).

In patients with *BRAF*-mutant melanoma without extensive central nervous system disease or symptomatic systemic metastases, the decision for up-front therapy has become debated. The focus has largely shifted to the durability of response with each therapy. For BRAF-targeted therapy, one of the main concerns has been the tumor resistance that ultimately develops in most patients, typically before 12 months. This has led many to believe that long-term off-treatment survival with BRAF therapy alone is seldom achieved. However, long-term follow-up data on vemurafenib and dabrafenib studies to support this assumption are lacking (largely owing to the relatively recent application of these agents). With dabrafenib/trametinib, complete responses were reported in 10% to 13% of patients from the recent phase 3 trials,^{18,19} and updated data from the phase 1/2 study showed a 2-year survival of 51% with this combination,²¹ which suggests that durable responses may occur more frequently than originally anticipated.

On the other hand, existing long-term data support the durability of responses seen with immunotherapies. Thirty to fifty percent of patients who respond to high-dose IL-2 exhibit long-term disease control or remission.³ Similarly, durable responses with ipilimumab have been reported and long-term survival is achieved in more than 20% of patients.²³ Although follow-up remains immature for anti-PD-1 therapies and concurrent ipilimumab/nivolumab, the 2-year survival rates of 43% and 79%, respectively, are highly encouraging.^{35,39}

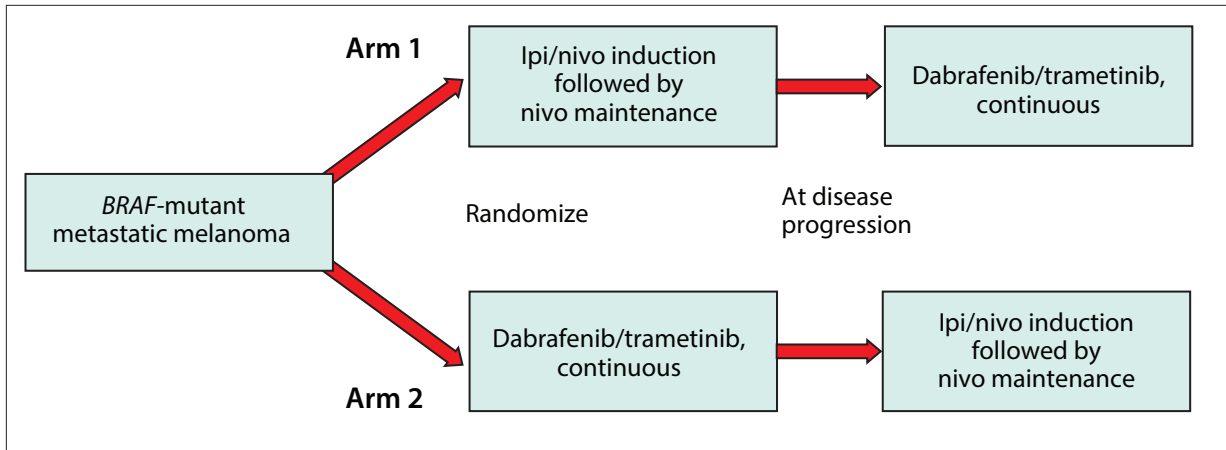


Figure 2. The EA6134 cooperative group protocol will determine which sequence of therapies in *BRAF*-mutant metastatic melanoma patients will lead to improved overall survival.

Ipi, ipilimumab; nivo, nivolumab.

Two retrospective data series have also suggested that clinical benefit may be superior when immunotherapy is administered prior to BRAF-targeted therapy rather than in the reverse order. In a study of 275 patients treated sequentially with BRAF inhibitors and immunotherapy (IL-2 or ipilimumab), differences in median OS were statistically nonsignificant, but tended to be longer in the patients receiving immunotherapy first (19.6 vs 13.4 months).⁴⁰ Furthermore, no responses to ipilimumab were seen in post-BRAF inhibitor patients and only half were able to receive all 4 standard doses. Another study looking at sequential BRAF inhibitor and ipilimumab therapies in an Italian cohort of 93 patients showed significantly longer OS in patients receiving ipilimumab prior to BRAF inhibitor therapy (14.5 vs 9.9 months, $P=.04$), although this may have been confounded by a lower percentage of patients with elevated LDH and brain metastases in the ipilimumab-first group.⁴¹ In contrast to the prior analysis, similar objective response and disease control rates were seen with ipilimumab in both groups. In either case, because response rates to BRAF inhibitor therapy were similar in patients with or without prior immunotherapy, starting with immunotherapy would enable patients to have a chance at long-term benefit without compromising the chance to benefit from BRAF inhibitor therapy.

Based on these data, the use of immunotherapies as front-line treatment in patients with limited metastatic *BRAF*-mutant melanoma is favored by many melanoma experts. Published guidelines by the Society for Immunotherapy of Cancer and the National Comprehensive Cancer Network provide similar advice to clinicians.^{42,43} However, the above data are confounded by the lack of prospective randomization of the 2 treatment sequences. Further, as noted above, PD-1 pathway blockers appear to have activity in patients with disease progression

following BRAF inhibitor therapy roughly comparable to that in patients who are BRAF inhibitor-naïve, and anecdotal data have reported significant responses to the ipilimumab/nivolumab combination in this patient population. The planned cooperative group EA6134 protocol (NCT02224781) should help resolve ongoing questions that remain about the optimal sequence of BRAF-targeted therapy and immunotherapy in *BRAF*-mutant melanoma patients (Figure 2). This is designed as a randomized trial (stratified for ECOG [Eastern Cooperative Oncology Group] performance status and LDH) with 2 sequential therapy arms: ipilimumab/nivolumab followed by dabrafenib/trametinib at progression (arm 1) vs dabrafenib/trametinib followed by ipilimumab/nivolumab at progression (arm 2). The primary objective is to assess differences in the 2-year overall survival rates between the 2 groups.

In conclusion, clinical outcomes have been greatly improved for patients with metastatic *BRAF*-mutant melanoma. However, this has created a complicated landscape of therapeutic options. In patients with limited disease burden, the focus has shifted toward immunotherapy strategies, whereas BRAF-targeted agents are utilized in patients with extensive, symptomatic disease and active brain metastases. Questions remain around the optimal sequence of these therapeutic strategies in order to improve long-term patient outcomes. Extended follow-up from ongoing trials and future protocols should provide objective guidance.

Disclosures

Dr Gibney has served as a consultant/steering committee member for Genentech/Roche and a consultant for Bristol-Myers Squibb and Novartis. Dr Atkins has served as a consultant to Bristol-Myers Squibb, Genentech/Roche, Merck, GlaxoSmithKline, Novartis, Amgen, and NeoStem.

References

- Salama AK, Flaherty KT. BRAF in melanoma: current strategies and future directions. *Clin Cancer Res*. 2013;19(16):4326-4334.
- Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363(9):809-819.
- Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17(7):2105-2116.
- Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet*. 2012;379(9829):1893-1901.
- Carlino MS, Saunders CA, Haydu LE, et al. (18F)-labelled fluorodeoxyglucose-positron emission tomography (FDG-PET) heterogeneity of response is prognostic in dabrafenib treated BRAF mutant metastatic melanoma. *Eur J Cancer*. 2013;49(2):395-402.
- McArthur GA, Puzanov I, Amaravadi R, et al. Marked, homogeneous, and early [18F]fluorodeoxyglucose-positron emission tomography responses to vemurafenib in BRAF-mutant advanced melanoma. *J Clin Oncol*. 2012;30(14):1628-1634.
- Chapman PB, Hauschild A, Robert C, et al; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516.
- Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.
- McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014;15:323-332.
- Hauschild A, Grob JJ, Demidov LV, et al. An update on BREAK-3, a phase III, randomized trial: dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM) [ASCO abstract 9013]. *J Clin Oncol*. 2013;31(15)(suppl).
- Gibney GT, Forsyth PA, Sondak VK. Melanoma in the brain: biology and therapeutic options. *Melanoma Res*. 2012;22(3):177-183.
- Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087-1095.
- Kefford RF, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicenter study [Society for Melanoma Research]. *Pigment Cell Melanoma Res*. 2013;26(6):965.
- Gibney GT, Messina JL, Fedorenko IV, Sondak VK, Smalley KS. Paradoxical oncogenesis—the long-term effects of BRAF inhibition in melanoma. *Nat Rev Clin Oncol*. 2013;10(7):390-399.
- Flaherty KT, Robert C, Hersey P, et al; METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114.
- Rizos H, Menzies AM, Pupo GM, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. *Clin Cancer Res*. 2014;20(7):1965-1977.
- Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367(18):1694-1703.
- Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371(20):1877-1888.
- Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372(1):30-39.
- Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867-1876.
- Flaherty K, Daud A, Weber JS, et al. Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM) [ASCO abstract 9010]. *J Clin Oncol*. 2014;32(5)(suppl).
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
- Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J Clin Oncol*. 2015;JCO.2014.56.2736.
- Ascierto PA, Simeone E, Sileni VC, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. *J Transl Med*. 2014;12:116.
- Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012;13(5):459-465.
- Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30(21):2691-2697.
- Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.
- Ribas A, Puzanov I, Dummer R, et al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory (IPI-R) melanoma (MEL) [Society for Melanoma Research LBA]. *Pigment Cell Melanoma Res*. 2014;27(6).
- Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
- Hodi FS, Kluger HM, Sznol M, et al. Long-term survival of ipilimumab-naïve patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1; BMS-936558, ONO-4538) in a phase 1 trial [Society for Melanoma Research]. *Pigment Cell Melanoma Res*. 2014;27(6):1199.
- Weber JS, Minor DR, D'Angelo S, et al. A phase 3 randomized, open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice chemotherapy (ICC) in patients with advanced melanoma after anti-CTLA-4 therapy [ESMO abstract LBA3]. *Ann Oncol*. 2014;25(5):1-41.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.
- Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma [published online April 19, 2015]. *N Engl J Med*.
- Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133.
- Kluger HM, Sznol M, Callahan MK, et al. Survival, response duration, and activity by BRAF mutation status in a phase 1 trial of nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab concurrent therapy in advanced melanoma (MEL) [Society for Melanoma Research]. *Pigment Cell Melanoma Res*. 2014;27(6):1203.
- Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017.
- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma [published online May 31, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1504030.
- Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.
- Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020-1030.
- Ackerman A, Klein O, McDermott DF, et al. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. *Cancer*. 2014;120(11):1695-1701.
- Ascierto PA, Simeone E, Sileni VC, et al. Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: data from the Italian cohort of the ipilimumab expanded access program. *Cancer Invest*. 2014;32(4):144-149.
- Kaufman HL, Kirkwood JM, Hodi FS, et al. The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. *Nat Rev Clin Oncol*. 2013;10(10):588-598.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®). Melanoma. v.3.2015. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Updated March 11, 2015. Accessed May 26, 2015.