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

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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. 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,
Genentech/Daiichi Sankyo) demonstrated objective responses in 81% of patients treated in the extension phase. 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 \(\text{BRAF}\)-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. 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 \(\text{BRAF}\)-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 \(\text{BRAF}\)-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 \(\text{BRAF}\) V600 mutations. Tumor responses can occur very quickly, and positron emission tomography scans show dramatic reduction in hypermetabolic activity within 2 weeks of therapy initiation. Two phase 3 trials have been completed comparing vemurafenib (960 mg orally twice daily) or dabrafenib (150 mg orally twice daily) with dacarbazine. 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). 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. 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. 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). 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. Similar clinical benefit in patients with BRAF V600E–mutant melanoma has been reported for the phase 2 MBM study of vemurafenib.

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. 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.

**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. 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. 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. 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. 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. 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.\textsuperscript{23} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23}

Significant toxicities (grade 3/4 adverse events) were seen in 23% to 25% of patients treated with ipilimumab.\textsuperscript{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%.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 dis-
continued 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 mut)ant), 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 pem-
brolizumab or nivolumab, only 8% to 15% experienced
significant side effects (grade 3-5).27-32 Serious immune-
related events such as dermatitis, diarrhea/colitis, hepatic-
tis, and pancreatitis have been reported in relatively few
patients (up to 2%). A phase 3 trial comparing pembro-
lizumab (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 pembro-
lizumab 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 appar-
ent enhanced clinical activity compared with either agent
alone or the 2 agents used in sequence.34,35 The cumu-
lative 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 mel-
noma, 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 combina-
tion 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 combina-
tion.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 percent-
age 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 tox-
icity 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
complicated. In the absence of prospective data on the optimal
sequence of therapy, clinicians must rely on their interpre-
tation of the results from various trials of BRAF-targeted
therapy and immunotherapy, especially results in subgroups
distinguished by tumor stage and patient performance.
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 responses seen 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

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<tr>
<th>Attribute</th>
<th>BRAF-Targeted Therapy</th>
<th>Immunotherapy</th>
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<tbody>
<tr>
<td>Schedule</td>
<td>- Administered as continuous oral medications</td>
<td>- Ipilimumab administered IV every 3 weeks x 4 doses only</td>
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<tr>
<td></td>
<td>- Anti–PD-1 therapies administered IV every 2-3 weeks</td>
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<tr>
<td>Safety (related adverse events)</td>
<td>- Grade 3/4 events in 35%-52% of patients receiving dabrafenib/trametinib18,19</td>
<td>- Grade 3/4 events in 23%-27% of patients receiving ipilimumab22,26,37</td>
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<td></td>
<td>- Dose reductions in 25%-33% and discontinuations in 9%-13% of patients receiving dabrafenib/trametinib18,19</td>
<td>- Grade 3/4 events in 8%-16% and drug discontinuations in 2%-9% of patients receiving anti–PD-1 therapies27-33,37</td>
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<td>- Grade 3/4 events in 54%-68% and drug discontinuations in 36% of patients receiving ipilimumab/nivolumab15-37</td>
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<td>Objective response rate</td>
<td>- ORR of 64%-67% for dabrafenib/trametinib35,39</td>
<td>- ORR of 11%-19% for ipilimumab22,36,37; 17% in BRAF-mutant subset analysis39</td>
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<td>- ORR of 21%-43% for anti–PD-1 therapies27-33,37; 19% in BRAF-mutant subset analysis37</td>
<td>- ORR of 43%-62% for ipilimumab/nivolumab35-37; 38%-52% in BRAF-mutant subset analysis35,36</td>
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<td>Survival</td>
<td>- Median OS of 25 months and 2-year OS rate of 51% for dabrafenib/trametinib.21</td>
<td>- Median OS of 10-11 months and 3-year OS rate of 22% with ipilimumab22,23; 11.6 months for BRAF-mutant subset analysis24</td>
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<td></td>
<td>- Unclear durability of response after drug discontinuation</td>
<td>- Median OS of 17 months and 2-year OS rate of 43% with nivolumab29</td>
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<td>- 2-year OS rate of 79% for ipilimumab/nivolumab39</td>
<td>- Durable responses seen off therapy</td>
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IV, intravenously; PD-1, programmed death 1; ORR, objective response rate; OS, overall survival.
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–naive, 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


