The role of targeted therapy for melanoma in the immunotherapy era

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Abstract

Over the past 10 years of remarkable development of both molecularly targeted and immune-targeted therapy for the treatment of melanoma, a clear preference of immunotherapy over molecularly targeted therapy has emerged among melanoma treatment providers. Still, the clinical data remain remarkable for patients with BRAF-mutant stage III and IV melanoma, and there seems to be a clear benefit of BRAF-targeted therapy for these patients. The key, then, is to identify the best way to use BRAF-targeted therapy. In this review, the clinical data of molecular-targeted therapy are summarized, mechanisms of resistance to single-agent BRAF and combined BRAF with mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitor are discussed, and strategies to overcome this resistance are presented; then, we review a number of clinical dilemmas that influence the decision-making of using targeted therapy over immunotherapy, and vice-versa, and help define the specific role of targeted therapy in the immunotherapy era.

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In 2018, the field of oncology has definitively entered the immunotherapy era. While the initial description of Coley’s, describing the spontaneous regression of tumors in the context of life-threatening erysipelas, was made over 100 years ago, the era of widely available cancer immunotherapy for many malignant disorders has truly just begun.1 There are now US Food and Drug Administration (FDA)-approved agents against cytotoxic T lymphocyte-associated antigen 4 (CTLA4), the programmed death 1 receptor (PD-1), and its ligand (PD-L1), as well as an oncolytic herpes simplex virus (talimogene laherparevic) have all been FDA approved for the treatment of advanced melanoma, with nivolumab also receiving approval for stage III melanoma.6,9 During this same period, 2 BRAF inhibitors, a mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) inhibitor, and 3 combinations of BRAF/MEK inhibitor have demonstrated improvement in overall survival (OS) in patients with BRAFV600-mutated melanoma, offering an alternative to immunotherapy in this patient population.10-13 Still, the general bias of medical oncologists treating melanoma, BRAF mutated or not, is to offer upfront immunotherapy. With the marked investment by grant-funding agencies (such as the National Cancer Institute), researchers, patients, and pharmaceutical companies in the promise and power of immunotherapy, it is the right time to wonder whether there remains a role for targeted therapy in the treatment of melanoma.

What follows is a detailed summary of the clinical data of molecular-targeted therapy, which for the purposes of this chapter will mean small-molecule inhibitors of mutated oncogenes (such as BRAF) or mediators of the mitogen-activated protein kinase (MAPK) pathway, which is constitutively activated in the setting of oncogenic mutations like BRAF and NRAS. Furthermore, mechanisms of resistance to single-agent BRAF and combined BRAF/MEK inhibitor will be discussed as will strategies to overcome this resistance. Finally, a series of clinical dilemmas that influence the decision-making of using targeted therapy over immunotherapy, and vice-versa, and help define the specific role of targeted therapy in the immunotherapy era will be presented.

Targeting BRAF

Clinical data with BRAF-targeted therapy in patients with advanced melanoma

The identification of oncogenic BRAF was made in a landmark report in 2002, which identified that mutations at the V600 position (in error initially thought to be the V599 position)—most commonly a point mutation leading to substitution of valine for glutamic acid (V600E)—were present in a variety of cancers.15 In initial series of melanoma samples, this mutation was noted to be present in up to 70% of cases and, speaking to its importance as an early driver of disease,
over 80% of benign nevi. In later series, in particular The Cancer Genome Atlas, this mutation is seen in approximately 50% of cutaneous melanomas and a lesser percentage of acral and mucosal melanomas. Importantly, the ramifications of oncogenic BRAF were also sorted out on a molecular level and shown to be associated with hyperactivation of the MAPK pathway. Specifically, mutant BRAF, which signals as a constitutively activated monomer, as compared with nonmutated but activated BRAF that dimerizes to signal, phosphorylates and activates MEK, which in turn activates extracellular signal-regulated kinase (ERK). ERK is a more promiscuous kinase, and its activation leads to a number of downstream events that favor proliferation, survival, invasion/metastasis, and immune evasion.

Given the frequency of BRAF mutations in melanoma, the development of BRAF inhibitors was a major priority for the melanoma treatment community. In preclinical studies, it became clear that inhibitors of BRAF and MEK had activity in BRAF-mutant cell lines, but the translation of these findings took a bit of time. Specifically, a series of trials with suboptimal BRAF inhibitors (including sorafenib and RAF265) were performed, yet the first major breakthrough occurred with the potent and specific BRAF inhibitor vemurafenib. The phase I data with vemurafenib were a revelation, with responses seen in the clear majority of patients whose tumors harbored a BRAFV600E mutation, a first for a study treating patients with metastatic melanoma. Quickly, a phase III trial (BRIM3) was launched that demonstrated the superiority of vemurafenib compared with dacarbazine with respect to objective response rate, progression-free survival (PFS), and OS in patients with BRAF-mutant advanced melanoma. These data led to the regulatory approval by the FDA of vemurafenib in 2011. A second BRAF inhibitor, dabrafenib, was developed soon after, which showed similar improvements to vemurafenib, compared to chemotherapy in a phase III trial, trametinib was shown to be superior to chemotherapy in patients with BRAF-mutant advanced melanoma, data that led to its approval in this patient population.

Amazingly, in a span of 4 years from the original report of the phase I trial of vemurafenib, 3 randomized trials were launched, accrued, and reported to demonstrate the superiority of MAPK inhibition compared with chemotherapy, with all culminating in the approval of the investigational agent. In a disease that had seen only 2 agents approved prior to 2011, the availability of 3 new agents was remarkable. However, despite these advances, the reality was that the great majority of patients treated with BRAF or MEK inhibitors would experience disease progression within a year. One interesting idea to overcome this limitation of single-agent therapy was to test the combination of BRAF and MEK inhibition. While the combination of small-molecule kinase inhibitors has generally been challenging due to toxicity, a unique aspect of BRAF inhibitors made this combination possible. Importantly, BRAF inhibitors such as vemurafenib and dabrafenib inhibit the monomeric signaling of mutated BRAF but augment signaling of BRAF, through paradoxal activation of the MAPK pathway through the promotion of hetero- and homodimerization of nonmutant RAF. Alternatively, MEK inhibitors similarly inhibit MEK in BRAF-mutant and -nonmutant cells, thus setting up a situation in which there is mitigation of some toxicity, most specifically cutaneous and gastrointestinal toxicity. Of more importance, 3 BRAF and MEK inhibitor combinations have demonstrated superior efficacy (response rate, PFS, OS) compared to single-agent BRAF inhibitor therapy in 4 randomized trials, establishing this approach as the standard BRAF-targeted therapy approach.

Mechanisms of resistance and strategies to overcome it
Despite the remarkable data with single-agent BRAF and MEK inhibitor therapy and the combination of the two, the great majority of patients treated with BRAF-targeted therapy will develop resistance and disease progression. With single-agent BRAF inhibition, this occurs typically within 6 to 8 months, and 10 to 14 months with combination therapy. Multiple mechanisms of resistance have been described and can be summarized into those that reactivates the MAPK pathway and those that do not. As opposed to many other oncogene-targeted therapies—such as inhibitors of BCR-ABL, EGFR, and ALK—so-called gatekeeper mutations do not occur with any significant frequency. However, activation genetic mutations may be acquired during the course of therapy, such as upstream mutations in NRAS and downstream mutations in MEK, as may post-translational modifications of BRAF in the form of a splice variant of mutant BRAF. Alternatively, receptor tyrosine kinase activation is another known mechanism of resistance and can involve hyperactivation of MAPK, presumably through the above-mentioned paradoxical activation of MAPK or through activation of alternative pathways such as the phosphoinositide 3-kinase (PI3K) pathway.

There are other common genetic events associated with acquired resistance, including the development of loss-of-function mutations in tumor suppressor genes such as CDKN2A, PTEN, STAG2/3, and PIK3R1. With a myriad of mechanisms of resistance, the development of strategies to overcome these seems daunting. However, because the majority either activate MAPK or PI3K pathways, targeting these pathways makes logical sense. Inhibition of the PI3K pathway has also been investigated, although one major challenge to these approaches is the tolerability of...
dual MAPK and PI3K pathway inhibition. The most—albeit limited—success to date has been to target ERK with molecule inhibitors in patients with progression following BRAF or combined BRAF/MEK inhibition. There are now 2 ERK inhibitors that have shown activity in this setting, ulixertinib (BVD-523) and MK-8353. The most robust data have been with ulixertinib. In the phase I dose-escalation and expansion study, 3 of 20 patients with previous BRAF-targeted therapy had a partial response. With MK-8353, only 4 such patients (previous BRAF-targeted therapy) were treated, with 1 patient responding. While these data are only in a limited number of patients, it is promising that downstream targeting of ERK might be a potential option for a subset of patients in this situation. Additionally, this level of activity suggests that ERK inhibition should be evaluated in a variety of combinations in order to build more effective regimens after initial BRAF-targeted therapy.

Another way to target the MAPK pathway in patients with BRAF-mutant melanoma who develop resistance with BRAF-targeted therapy is to stop therapy and retreat at a later time point. This strategy has been shown to be associated with significant activity in both retrospective and prospective studies. Specifically, in a multicenter retrospective analysis of 116 patients with BRAF-mutant melanoma previously treated with BRAF-targeted therapy, the response rate to rechallenge was 43% and the median PFS and OS were 5 and 9.6 months, respectively. In a prospective study of 25 patients previously treated with BRAF-targeted therapy, treatment with dabrafenib and trametinib was associated with a partial response in 8 patients (32%). Importantly, these studies are confounded by selection bias because those patients with rapidly progressing disease on BRAF-targeted therapy or subsequent therapy (eg, immunotherapy, chemotherapy, etc) may not be candidates for rechallenge. However, patients who remain candidates for therapy after interim therapy or perhaps a break in therapy may benefit from this approach.

Clinical dilemmas in BRAF-mutant melanoma

Optimal sequencing of BRAF-targeted therapy with PD-1 inhibitor-based therapy

An obvious dilemma when multiple treatment options are available for a given patient population is the selection of upfront therapy. In the ideal setting, tissue- and/or blood-based biomarkers would be available to determine which patients are helped most by which therapies, algorithms would be easy to generate to help guide clinical decision-making, and randomized clinical trial data validating the biomarker(s) would be available as a validation to the approach. Unfortunately, no randomized trial data are available about optimal sequencing, and the current biomarkers available do not clearly define which patients with BRAF-mutant melanoma should receive BRAF-targeted therapy and which patients should receive immunotherapy with a PD-1 inhibitor as a single agent or in combination with ipilimumab. For example, expression of PD-L1—the ligand for PD-1—is associated with improved response in patients with metastatic melanoma, independent of BRAF mutation status, but this is not so strong an association that BRAF-targeted therapy should not be used in patients with PD-L1 expression. Furthermore, PD-L1 expression does not appear to be associated with responsiveness to or OS from BRAF-targeted therapy in patients with BRAF-mutant melanoma.

In the absence of a clinically validated biomarker approach and/or prospective trial data supporting a specific frontline approach, we are left with retrospective data and physician discretion to help select front-line therapy. In this context, there are a few scenarios in which the decision is obvious. These are situations in which patients with BRAF-mutant melanoma have immediately life-threatening, disease-related complications that require a treatment that has the best chance of leading to tumor regression as quickly as possible. While combined immune checkpoint inhibitor therapy is associated with high response rates, combined BRAF-targeted therapy is associated with improvement in disease-related symptoms almost immediately. Another scenario in which upfront BRAF-targeted therapy is an obvious decision is for BRAF-mutant melanoma patients with conditions that require active immunosuppression to treat autoimmune disease or reduce cerebral edema, as is often the case in patients with multiple central nervous system (CNS) metastases or leptomeningeal disease.

In patients in whom either BRAF-targeted therapy or immune checkpoint inhibitor therapy is possible, there are retrospective data to help decision-making. For example, when ipilimumab was the only regularly available immune checkpoint inhibitor, 2 retrospective series were published supporting the use of ipilimumab prior to BRAF-targeted therapy. In a multicenter analysis of 274 patients who either were treated with immunotherapy (ipilimumab or high-dose IL-2) or targeted therapy (vemurafenib, dabrafenib, or combined dabrafenib and trametinib), the response rate of BRAF-targeted therapy was not lower following prior immunotherapy, yet the clinical activity of ipilimumab was very low after BRAF-targeted therapy. In a second study, data from 93 patients treated with ipilimumab as part of the Italian expanded access protocol (EAP) showed an improvement in OS in patients treated with ipilimumab and then targeted therapy than those treated with ipilimumab after targeted therapy. These 2 studies help to justify the practice of starting with upfront immune checkpoint inhibitor therapy (ipilimumab, anti-PD, or the combination of both) while relegating BRAF-targeted therapy as a salvage treatment. More recently, a multi-institutional retrospective study of 114 patients with BRAF-mutant melanoma treated with an anti-PD-1 or anti-PD-L1 inhibitor therapy was reported. In this dataset, there were 3 possible
clinical scenarios: (1) patients treated with anti-PD-1/PD-L1 inhibitor only, (2) patients treated with anti-PD-1/PD-L1 inhibitor before BRAF-targeted therapy, and (3) patients treated with BRAF-targeted therapy before anti-PD-1/PD-L1 therapy. When patients from the first 2 groups were compared to patients in the third group, there was no significant difference in OS. However, when the 3 distinct groups were compared, the first—not surprisingly—did the best, followed by the third and then the second. In direct contrast to the data from the Italian ipilimumab EAP, in patients who received both types of treatment, those treated with BRAF-targeted therapy first did better than those who received anti-PD-1/PD-L1 inhibitor therapy first. While thought-provoking, it is not clear how to include these data into clinical decision-making, and more likely, providers will wait until the results of 2 ongoing randomized trials (EA6134 – NCT02224781, SECOMBIT – NCT0231447) evaluating sequencing are reported.

A final piece of information to help determine the optimal sequencing and/or timing of BRAF-targeted therapy comes from a pooled analysis of all patients treated with combined dabrafenib/trametinib as part of 2 randomized phase III trials, COMBI-v and COMBI-d, investigating the role of combined BRAF/MEK inhibition versus single-agent BRAF inhibitor therapy.30,51 In 563 patients with advanced melanoma treated with dabrafenib and trametinib in one of these 2 trials, univariate and multivariate analyses were performed to evaluate the prognostic significance of baseline factors, and then regression tree analysis was performed to identify the most significant prognostic factors.52 The 2 most significant factors were baseline actate dehydrogenase (LDH) level (elevated/nonel- evated and elevated ≥2 times upper limit of normal/1-2 times upper limit of normal/not elevated) and number of metastatic sites (≥3 sites/≤3 sites). Remarkably, using these 2 factors, a group of patients was identified, namely those with a normal LDH, fewer than 3 sites of disease, and low-volume disease (sum of longitudinal diameter <66 mm), such that 42% were progression free at 3 years. In comparison, none of the 65 patients in the analysis with a baseline LDH of 2 times the upper limit of normal or higher were progression free at 3 years, and only 2% were at 2 years. In light of these data, a strong case can be made that BRAF-targeted therapy should be considered for patients with the least aggressive disease, and immune checkpoint inhibition—particularly combined ipilimumab and nivolumab—should be considered for those with the most aggressive disease.

**Optimization of treating brain metastasis**

Brain metastases are common in patients with melanoma and are associated with significant morbidity and worse survival.53 In melanoma patients with **BRAF** mutations and CNS metastasis, BRAF-targeted therapy is associated with tumor reduction in the majority of patients and protocol-defined responses in approximately 30% to 35% of patients.54 More recently, the data from the COMBI-MB study that enrolled patients in 4 distinct cohorts: asymptomatic patients with **BRAF** mutation without (cohort A, 76 patients) or with (cohort B, 16 patients) prior local therapy with a good performance status [Eastern Cooperative Oncology Group, [ECOG], performance status 0 or 1], asymptomatic patients with **BRAF** mutation with or without prior local therapy and an ECOG performance status of 0 or 1 (cohort C, 16 patients), and symptomatic patients with or without prior local therapy with an ECOG performance status of 0 to 2.55 Across all cohorts, intracranial (IC) response rates ranged from 44% to 59%, which was consistent with overall response rates, which ranged from 44% to 65%. The median PFS of the largest group (cohort A) was 5.6 months, and median PFS ranged from 4.2 to 7.2 months, all lower than the expected PFS of over 11 months for the combination in patients without brain metastases. Furthermore, less than 20% of all patients were progression free at 1 year. The major conclusion here is that this combination is clearly active and leads to marked responses in the majority of patients who are symptomatic or asymptomatic; however, this therapeutic approach is not likely to lead to long-term disease control.

The data with immune checkpoint inhibitors are also encouraging in patients with metastatic melanoma. There have now been 3 clinical trials published or presented describing the efficacy of either single-agent anti-PD-1 therapy or the combination of ipilimumab and nivolumab, although these studies enrolled patients independent of BRAF mutation status. In a trial of single-agent pembrolizumab in patients with either melanoma or non-small cell lung cancer and asymptomatic brain metastasis, 18 patients were treated, and 4 (22%) had an IC response and remained progression free at 6 months.56 In the Australian Anti-PD-1 Brain Collaboration study, 60 patients with melanoma and asymptomatic CNS metastases were randomized to receive either single-agent nivolumab or the combination of ipilimumab and nivolumab.57 IC and extracranial (EC) responses were seen in 20% and 29%, respectively, of patients treated with nivolumab, and 46% and 56% of patients treated with the combination. Perhaps more importantly, median and 6-month PFS were much better for patients treated with the combination (median not reached, 6-month 53%) versus single-agent therapy (median 2.5 months, 6-month 20%). In Checkmate 204, 75 patients with asymptomatic melanoma brain metastases were enrolled to receive the combination of ipilimumab and nivolumab. IC and EC response rates were 49% and 55%, respectively, the median PFS was not reached, and the 6-month PFS was 67%.58

In reflecting on all these data, the clear conclusion seems to be that BRAF-targeted therapy is the best option to control disease in the shortest amount of time and the greatest number of patients, but the long-term data with this approach are underwhelming. Therefore, BRAF-targeted therapy in patients...
with **BRAF**-mutant melanoma and brain metastasis is used if there is no other option, such as the scenario described above in which patients are unable to discontinue corticosteroids due to symptomatic disease associated with significant cerebral edema. In all other patients who are willing and able to receive combination ipilimumab and nivolumab, they should do so.

**Adjuvant treatment selection**

For years, adjuvant therapy options for patients with stage III and resected stage IV melanoma have been limited. While adjuvant interferon—either in high-dose or pegylated versions—consistently demonstrated an improvement in relapse-free survival (RFS), the impact on OS was minimal at best, which led many experts to recommend against interferon due to its significant toxicity. Additional strategies such as biologic therapy—which, in a randomized trial (S0008), was associated with clear improvement in RFS compared to high-dose interferon—have also been tested; the toxicity of this approach was substantial and treatment considered impractical in the absence of an OS benefit. More recently, the US FDA approved ipilimumab in the resected stage III setting, following the results of the EORTC 18071 study demonstrating that ipilimumab improved both RFS and OS compared to placebo. However, the toxicity of ipilimumab was extreme (54% grade 3 or 4 toxicity; 1.1% grade 5), which greatly reduced the widespread use of this therapy for this patient population. So in 2017, remarkably, despite all the advances that had been made to treat advanced melanoma, the use of adjuvant therapy in patients with high-risk melanoma remained controversial.

At the 2017 European Society for Medical Oncology annual meeting, data from 3 adjuvant trials in high-risk melanoma were presented that changed the narrative forever about adjuvant therapy. In the Checkmate 238 study, patients with resected stage III, IIIC, and IV melanoma were presented that changed the narrative for adjuvant therapy. In the Checkmate 238 study, adjuvant nivolumab was compared to adjuvant ipilimumab ever about adjuvant therapy. In the Checkmate 238 study, adjuvant nivolumab was compared to adjuvant ipilimumab.

For the first time since adjuvant therapy was approved by the US FDA for patients with resected stage III melanoma, ipilimumab improved both RFS and OS compared to placebo. However, the toxicity of ipilimumab was extreme (54% grade 3 or 4 toxicity; 1.1% grade 5), which greatly reduced the widespread use of this therapy for this patient population. So in 2017, remarkably, despite all the advances that had been made to treat advanced melanoma, the use of adjuvant therapy in patients with high-risk melanoma remained controversial.

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At the 2017 European Society for Medical Oncology annual meeting, data from 3 adjuvant trials in high-risk melanoma were presented that changed the narrative forever about adjuvant therapy. In the Checkmate 238 study, adjuvant nivolumab was compared to adjuvant ipilimumab in a placebo-controlled, randomized trial of 908 patients with resected stage IIIB, IIIC, and IV melanoma. Patients treated with nivolumab had improved RFS rates and lower treatment-related adverse events compared to those patients treated with ipilimumab; these data led to the US FDA approval of adjuvant nivolumab in patients with resected stage III and IV melanoma. In the BRIM8 study, 2 cohorts of patients were enrolled and randomized, with 314 and 184 patients with stage IIIC/IIIA/IIIB and stage IIIC BRAFV600E/K melanoma, respectively, to receive 1 year of vemurafenib or placebo. In a curious trial design, cohort 2 needed to determine the superiority of vemurafenib on RFS; otherwise, the entire study would be considered negative. When looking at patients enrolled in cohort 2, the 1-year RFS rate was significantly better for patients treated with vemurafenib than placebo (79% versus 58%); however, the 2-year RFS was virtually identical, and the RFS curves were not significantly different (P = .26). Interestingly, patients treated in cohort 2 had improved RFS rates at 1 year and 2 years, suggesting that, in this lower-risk cohort, adjuvant single-agent BRAF inhibitor therapy was superior to placebo. But given the study’s design, the trial was considered to be negative, and it is unlikely that vemurafenib will receive regulatory approval in the adjuvant setting. Finally, the COMBI-AD study randomized 870 patients with resected stage III BRAFV600E/K–mutant melanoma to receive either the combination of dabrafenib and trametinib or double placebo. Combination therapy was associated with an improved RFS compared to placebo, a finding that held up in every predefined subgroup (stage, micro- versus macronodal metastasis, ulceration status, V600 E versus K, gender, and age). Additionally, dabrafenib with trametinib was associated with improved OS compared to placebo; FDA approval of this combination in patients with stage III BRAFV600E/K melanoma is expected in 2018.

As with the advanced/metastatic setting, there are data supporting the use of adjuvant immune checkpoint inhibitors and BRAF-targeted therapy in patients with high-risk, resected BRAF-mutant melanoma and no level 1 evidence to help decide which therapy to offer. Remarkably, the performance of BRAF-targeted therapy, either with single-agent vemurafenib or combination dabrafenib/trametinib, appears as good or better in the lower-risk setting (stage IIIC-IIIB), which goes along with the general theme for patients with unresectable or metastatic melanoma that patients with the lowest risk have the most benefit from BRAF-targeted therapy. Furthermore, while it is not believed that BRAF-targeted therapy is ever—or perhaps only rarely—curative in the unresectable or metastatic setting, it may be in the adjuvant setting. However, anti-PD-1 antibody therapy is associated with long-term survival in up to 30% of advanced melanoma patients who complete 1 to 2 years of therapy and may or may not perform any better in the adjuvant setting. To put it another way, BRAF-targeted therapy seems to be more effective in the adjuvant than metastatic setting, whereas there is no evidence that there is a similar scenario for immune checkpoint inhibitors. In the absence of better data, this supports the use of BRAF-targeted therapy over anti-PD-1 therapy in the adjuvant setting.

**Targeted therapy for non-BRAF-mutant melanoma**

While targeting BRAF with small-molecule inhibitors has been a successful strategy for the largest molecularly defined subset of patients with melanoma, namely those with a BRAFV600E mutation, success with targeted therapy in other subgroups has been limited and has not led to regulatory approval. Specifically, inhibitors of KIT have shown responses in 15% to 25% of patients with KIT aberrations (either mutations or high-level amplifications), with all responding patients having an abnormality seen in either exon 11 or 13. While these data are encouraging, KIT mutations are uncom-
mon in cutaneous melanoma, and though enriched in acral and mucosal melanoma, large confirmatory trials are lacking. Furthermore, while responses are seen, these tend to be relatively short-lived. Therefore, it is recommended that patients with acral and mucosal melanoma have molecular testing that includes \textit{KIT}, but \textit{KIT} inhibitors should only be considered in those patients who have an exon 11 or 13 abnormality and have a contraindication for or have already received immune checkpoint inhibitor therapy.

Activating mutations of \textit{NRAS} are seen in up to 25\% of patients with melanoma and are associated with constitutive activation of the MAPK pathway.\textsuperscript{17} Preclinical data support the use of MAPK pathway inhibition, and activity has been seen with MEK and ERK inhibitors in patients with metastatic, \textit{NRAS}-mutant melanoma.\textsuperscript{20,69,70} However, the response rate with these approaches does not exceed 20\%, and in a recently reported randomized trial of the MEK inhibitor binimetinib compared with dacarbazine, the median PFS of binimetinib was only 2.8 months.\textsuperscript{27,41,42,71} Additionally, there was no improvement in OS. Building upon single-agent MEK inhibition in \textit{NRAS}-mutant melanoma, preclinical studies have identified that dual inhibition of MEK and cyclin-dependent kinases 4 and 6 (CDK4/6) is associated with superior outcomes.\textsuperscript{69} In patients, however, it has been challenging to deliver dual MEK-CDK4/6 inhibition because of toxicity, and it remains to be seen whether an efficacious regimen can be developed that will be tolerable.\textsuperscript{72,73}

**Conclusions**

In 2018, the predominant driving force of clinical, translation-al, and basic research in melanoma revolves around immunotherapy. However, molecularly targeted therapy, particularly BRAF-targeted therapy, continues to have a role in this new era of oncology. The challenge as we move forward in this “immunotherapy era” is to continue to work towards understanding the optimal timing and sequencing of the ever-expanding armamentarium of therapy for patients with melanoma.

**References**


The role of targeted therapy for melanoma in the immunotherapy era


