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Therapeutic Advances and Treatment Options in Metastatic Melanoma

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Abstract

Over the past several years, management of advanced melanoma has been transformed by the development and approval of novel therapeutic approaches. Genetically targeted therapies are now effective treatment options for the approximately 50% of patients whose melanomas harbor activating point mutations in BRAF. Combination regimens of small-molecule inhibitors have been developed to delay the onset of acquired resistance. Specifically, combined BRAF and MEK inhibition improves response rates and survival compared with single-agent BRAF inhibitors and has now received regulatory approval. During the same time frame, excitement has surrounded the development of immunotherapy with checkpoint inhibitors. New immune checkpoint inhibitors blocking cytotoxic T lymphocyte antigen-4 (CTLA4) or programmed death-1 receptor/ligand (PD-1/PD-L1) improve patient outcomes by promoting an antitumor immune response. These agents have been associated with an increasing number of durable responses and are being developed in various combinations. In this review, we discuss the development of these targeted and immune therapies, review current patient management, and highlight future directions.

Introduction

Advanced melanoma has traditionally been associated with a dismal prognosis, recalcitrance to cytotoxic chemotherapy, and limited treatment options. Responses to chemotherapy were uncommon (10%-15%), and durable remissions rarely occurred. Over the past several years, however, unprecedented advances in 2 distinct therapeutic classes have completely altered treatment strategies for this disease. Accordingly, marked improvements in outcomes from historic norms have been observed. Genetically targeted small-molecule inhibitors of the

oncogenic BRAF V600 mutation or a downstream signaling partner (MEK) are effective treatment options for the 40% to 50% of melanomas that harbor mutations in BRAF. Selective BRAF and MEK inhibitors induce frequent and dramatic objective responses and markedly improve survival compared with cytotoxic chemotherapy. Effective and tolerable immune therapies have also been recently developed. These immune checkpoint inhibitors remove key negative regulators of T-cell activation and thereby induce antitumor immune responses. These novel agents prolong survival and produce durable responses in increasing numbers of patients. In this review, we discuss the development and current status of the expanding landscape of melanoma therapeutics.

Targeted Therapy

Activation of the mitogen-activated protein kinase (MAPK) pathway is a hallmark of melanoma. Mutations in pathway members or promoters (including NRAS, BRAF, and NF1, and less commonly KRAS, MEK1/2) occur in most melanomas. The identification of BRAF V600 mutations in 40% to 50% of melanomas in 2002 uncovered a potential therapeutic strategy for this genetically defined subset.1 Attempts to target this mutation with early putative BRAF inhibitors (eg, sorafenib tosylate) were largely disappointing in initial trials.2 Subsequently, however, more selective BRAF inhibitors have been developed. Effective targeted therapy strategies have also been identified for a small subset of patients harboring KIT mutations and are being intensively investigated for other genetically defined cohorts.3,4 We largely focus on the BRAF-mutant population and briefly review KIT inhibitors and strategies for other genetic subsets. See Table 1 for a summary of activity of genetically targeted therapies in melanoma.

BRAF Inhibitors

Vemurafenib (PLX4032, RG7204) was the first selective BRAF inhibitor evaluated in clinical trials. In phase I/II trials, vemurafenib induced objective responses in approximately 50% of patients, with a median progression-free survival (PFS) of approximately 7 months.13,14 Responses were often dramatic and rapid, with tumor regression and improved symptoms reported even within days of treatment initiation. The median overall survival (OS) from the phase II study was 15.9 months.14 These studies led to a phase III trial comparing vemurafenib with dacarbazine. Patients in the vemurafenib group had a decreased risk of progression (hazard ratio [HR], 0.26; $P < .001$) and death (HR, 0.37; $P < .001$), leading to the regulatory approval of vemurafenib.15 Extended follow-up confirmed the benefit of vemurafenib with improved median survival (13.6 vs 9.7 months; $P < .001$) and median PFS (6.9 vs 1.6 months; $P < .001$).5 Outcomes appeared equivalent for the 9% who harbored BRAF V600K mutations, with a median OS of 14.5 months (vs 13.3 months for those with the more common BRAF V600E mutation).

Dabrafenib (GSK2118436), another BRAF inhibitor, was subsequently developed and showed similar activity to vemurafenib. In the phase I clinical trial, a confirmed objective response rate (ORR) of 50% and a median PFS of 5.5 months were observed.16 A phase III clinical trial then compared dabrafenib with chemotherapy; this study demonstrated a 53% ORR for the dabrafenib group and improved PFS (HR, 0.3; $P < .001$).6 Notably, crossover was permitted at progression and the study was not powered to detect a difference in OS (HR, 0.61 [95% CI, 0.25-1.48]).

BRAF inhibitor monotherapy is generally well tolerated, although arthralgias, skin rash, and cutaneous squamous cell carcinomas (SCCs) occur frequently. Intriguingly, cutaneous SCCs arise from indolent premalignant lesions harboring oncogenic mutations, largely in RAS. BRAF inhibitors then paradoxically activate the RAS-RAF-MEK-ERK pathway further, and thereby promote and unmask these previously undetected precancers.17 Development of more serious RAS-mutant malignant neoplasms, including pancreatic cancer and chronic leukemia, has been a concern and has occurred occasionally.18,19 Although both agents are similar, vemurafenib causes more phototoxic effects and likely more cutaneous SCCs, whereas fevers occur more often with dabrafenib.20 Unfortunately, nearly all patients treated with BRAF inhibitors experience disease progression during the first 1 to

2 years of therapy. Therefore, elucidating mechanisms of acquired resistance has been a major clinical and research focus. Unlike many other cancers, resistance in BRAF-mutant melanoma is not the result of second site mutations in the target gene, BRAF. Instead, a diverse array of resistance mechanisms have been uncovered, largely involving acquired alterations in the MAPK pathway or parallel signaling networks.21-23 Marked genetic tumor heterogeneity at the onset of resistance may limit the effectiveness of postprogression targeted strategies and suggests that focusing on preventing resistance may be advisable. As such, attention has shifted to BRAF inhibitor–MEK inhibitor combinations targeting distinct MAPK pathway components (see Combined BRAF/MEK Inhibition subsection).

MEK Inhibitors

Single-agent MEK inhibitors also have activity in BRAF V600–mutant melanoma. Trametinib is an allosteric inhibitor of MEK1/2 and initially showed a 33% ORR in a phase I study.24 A phase III clinical trial then compared trametinib with chemotherapy (dacarbazine or paclitaxel) in BRAF-mutant melanoma. Improved median PFS (4.8 vs 1.5 months; $P < .001$) and OS (HR, 0.54; $P = .01$) were observed despite permitting crossover at progression.7 Frequent low-grade rash, diarrhea, and peripheral edema occurred along with occasional reversible decreases in cardiac ejection fraction and ocular events (central serous retinopathy). Although trametinib was approved by the Food and Drug Administration in 2013, it is rarely used as monotherapy because of presumably inferior efficacy compared with single-agent BRAF inhibitors. Newer MEK inhibitors are also being evaluated currently (cobimetinib, binimetinib).

Combined BRAF/MEK Inhibition

The finding that acquired resistance to BRAF inhibitors largely reactivates the MAPK pathway led to interest in BRAF and MEK cotargeting. A randomized phase II clinical trial compared dabrafenib and trametinib with dabrafenib alone. The ORR (76% vs 54%) and median PFS (9.4 vs 5.8 months) were superior in the combination arm.25 Of interest, cutaneous SCCs were less frequent with the combination therapy (7% vs 19%), supporting the hypothesis that concurrent MEK inhibition attenuates paradoxical MAPK activation. Pyrexia occurred more often with combination therapy. On the basis of this study, dabrafenib and trametinib received FDA approval in early 2014.

A phase III clinical trial then compared dabrafenib and trametinib with vemurafenib. Combination therapy produced a superior ORR (64% vs 51%), median PFS (11.4 vs 7.3 months; $P < .001$), and OS (HR, 0.59; $P = .005$). Cutaneous SCCs occurred in only 1% of patients treated with the combination compared with 19% of those receiving vemurafenib.8 Another phase III study comparing dabrafenib and trametinib with dabrafenib alone also demonstrated the superiority of the combination. Differences in this study were more modest (median PFS, 9.3 vs 8.8 months, $P = .03$; ORR, 67% vs 51%, $P = .002$).26 Vemurafenib and cobimetinib have also been compared with vemurafenib alone in a phase III study. The ORR (68% vs 45%; $P < .001$), median PFS (9.9 vs 6.2 months; HR, 0.51; $P < .001$), and OS (HR, 0.65; $P = .046$) were all improved with combination therapy in this study as well.9 Of note, the latter 2 studies demonstrated OS advantages for combination therapy although the prespecified stopping boundaries were not reached. These studies have established combined BRAF and MEK inhibition as the standard first-line targeted therapy for patients with BRAF V600–mutant melanoma.

These combinations have also been evaluated in sequence, given at the time of progression with single-agent BRAF inhibitor therapy. The activity in this situation is markedly inferior. In patients who experienced progression while receiving vemurafenib and then switched to vemurafenib and cobimetinib, the combination was associated with a 15% ORR and median PFS of 2.8 months.27 Similarly, in patients who experienced progression while receiving dabrafenib and then switched to dabrafenib and trametinib, the combination demonstrated a 13% ORR and median PFS of 3.6 months.28 The latter study suggested that patients with prior prolonged benefit from BRAF inhibitor

monotherapy (≥6 months) benefited more than those with previous rapid progression (ORR, 26% vs 0%; median PFS, 3.9 vs 1.8 months). Combination therapy can be considered, therefore, following extended benefit from BRAF inhibitor monotherapy.

Other Genetic SubsetsNRAS mutations are present in 15% to 20% of melanomas and have historically been refractory to targeted therapy. A phase II study of a MEK inhibitor, binimetinib (MEK162), has challenged this paradigm, reporting a 20% ORR in the NRAS cohort.10 A phase III study comparing binimetinib to chemotherapy is now ongoing. Combination MEK inhibitor strategies are also in development. Binimetinib and LEE011 (CDK4/6 inhibitor) demonstrated a 33% ORR and some degree of tumor regression in nearly all of the 21 patients treated in a phase I study.29 Although activity has been promising, serious toxic effects have occurred in some patients and dose determination is ongoing.

Activating mutations in KIT occur in melanomas arising from mucosal and acral surfaces (15%-20%, respectively) and chronically sun-damaged skin (1%-2%). Several phase II clinical trials have been conducted testing KIT inhibition with imatinib. Approximately 20% of patients experienced an objective response, and greater activity (approximately 50% ORR) is observed in patients with activating exon 11 mutations.3,4,11 Individual case reports of responses to dasatinib, nilotinib, and sunitinib therapy have also been reported.30,31

Nearly 90% of uveal melanomas harbor activating mutations in the g-proteins GNAQ and GNA11 that promote downstream MAPK signaling.32 In a phase II study, the MEK inhibitor selumetinib (AZD6244) was compared with chemotherapy (temozolomide) in patients with uveal melanomas. Selumetinib demonstrated improved PFS (15.9 vs 7.0 weeks; HR, 0.46; $P < .001$), response rates (14% vs 0%), and a statistically nonsignificant improvement in OS (11.8 vs 9.1 months; $P = .09$).12 Clinical activity did not correlate with GNAQ/GNA11 mutation status, however. Phase II clinical trials for trametinib in this cohort are also ongoing.

Atypical BRAF mutations (non-V600) are present in nearly 5% of melanomas.33,34 On the basis of preclinical and limited clinical experience, these alterations seem to confer sensitivity to MEK inhibitors but not BRAF inhibitors.24,34,35 Furthermore, fusions in BRAF that remove the inhibitory RAS-binding domain and constitutively activate BRAF have been recently described in 2% to 3% of melanomas.36 These fusion proteins also seem sensitive to MEK inhibition in vitro. A phase II clinical trial of trametinib in the atypical BRAF population is now ongoing.

Immune Therapy

Immune therapy agents, starting with high-dose interleukin 2 (IL-2) and now with newer immune checkpoint inhibitors, are a cornerstone of melanoma therapeutics. In contrast to targeted therapies, objective responses occurred less frequently (until recently) but were more durable. Identifying biomarkers to predict response to therapy has also been an unmet need. Newer immune checkpoint inhibitors are challenging these traditional concepts of immune therapies with improved response rates and promising candidate biomarkers. See Table 2 for a summary of activity and toxicity of immune checkpoint inhibitors.

Interleukin 2

High-dose IL-2 has been a pillar of melanoma therapeutics for many years. Although therapy is limited to young and otherwise healthy patients in experienced centers, 5% to 8% of patients experience durable complete responses.44,45 The intensive nature and severe acute toxic effects of therapy have precluded randomized comparisons with other treatments, and thus, the effect of IL-2 on OS has not been established. Although the advent of less toxic immune checkpoint inhibitors has decreased IL-2 use, it remains an appropriate therapeutic strategy in

carefully selected, robust patients with normal organ function because of the long–term disease-free survival with follow-up beyond 10 years.

Anti-CTLA4

Ipilimumab is a monoclonal antibody to cytotoxic T lymphocyte antigen 4 (CTLA4) and was the first agent to demonstrate an OS advantage in melanoma. Ipilimumab blocks this negative regulator of T-cell activation and thus promotes previously inhibited immune responses. Early studies demonstrated that whereas objective responses were not common, patients often had prolonged stable disease or mixed responses.46,47 On the basis of these unusual response patterns, new radiographic assessment criteria were developed (immune-related response criteria).48 Two phase III clinical trials evaluating ipilimumab were conducted. In previously treated patients, ipilimumab improved median OS compared with an experimental peptide vaccine (10.1 vs 6.4 months; HR, 0.66; P = .003).37 In the first line, the combination of ipilimumab and dacarbazine improved survival compared with dacarbazine monotherapy.49 Increased incidence of adverse events and lack of clear advantage to combination therapy halted subsequent development of ipilimumab and dacarbazine, however. Notably, another anti-CTLA4 agent, tremelimumab, has been developed and may induce similar long-lasting responses. No survival advantage over chemotherapy was observed in a phase III clinical trial, however.50 Development of tremelimumab is now ongoing in combination with other immune therapies. Ipilimumab received FDA approval in 2011 and is an appropriate first-line treatment option for patients with or without BRAF mutations.

The acute toxic effects of ipilimumab therapy are well characterized and quite distinct from those of both IL-2 and cytotoxic chemotherapy. The most common immune-related manifestations are colitis, endocrinopathies, hepatitis, dermatitis, and neuropathy. Although these events generally resolve with high-dose corticosteroid use, life-threatening events occasionally occur and require more intensive immune modulation. Myasthenia gravis, hemophilia, and Guillain-Barré syndrome are among the rare complications reported.51-53 In the large phase III trial, 19.1% of patients experienced immune-related and non–immune-related grade 3 to 4 toxic effects.37

With extended follow-up now nearly 10 years after early ipilimumab trials, long-term survival data are maturing. Among patients treated in early-phase studies, approximately 20% have 5-year survival; in previously untreated patients, 5-year survival may exceed 25%.54 With the possibility of long-term survival, evaluating the chronic effects and long-term functional status of patients will be critical.55 Although direct comparisons are still ongoing, most experts believe that therapies directed toward antibodies to programmed cell death-1 receptor (PD-1) will supplant ipilimumab in the future. Long-term survival data from anti–PD-1 therapies have not yet matured, however. Furthermore, ipilimumab may play a major role in sequence or in combination with these newer agents.

Anti-PD-1/PD-L1

Antibodies to PD-1 (nivolumab, pembrolizumab) or its ligand (PD-L1; MPDL3280A, MEDI4736) have also been recently tested in melanoma. PD-L1 is frequently expressed by numerous malignant neoplasms as a mediator of immune escape.56 The interaction between PD-1 and PD-L1 induces T-cell anergy and ineffective antitumor responses in the so-called exhausted T cell. Inhibiting this interaction, therefore, restores T-cell function in the tumor microenvironment. At this time, the most effective target in this axis (PD-1 or PD-L1) is not clear. These agents, however, each have substantial clinical activity. Their toxicity profiles compare favorably to ipilimumab, with a less than 10% rate of grade 3 to 4 immune-related adverse events. At the time of this writing, both pembrolizumab and nivolumab have received FDA approval for melanoma therapy following progression after ipilimumab and BRAF-targeted therapy (for patients with BRAF V600 mutations).

Nivolumab

Nivolumab (BMS-936558) was the first fully human IgG4 monoclonal antibody to PD-1 evaluated therapeutically. The initial phase I clinical trial was conducted in patients with melanoma, non–small-cell lung cancer (NSCLC), renal cell carcinoma, and a limited number of other cancers. Among patients with melanoma, 29% of patients experienced an objective response and 6% of all patients experienced grade 3 to 5 immune-related adverse events.57 Pneumonitis occurred in 1%, emerging as the most clinically concerning toxic effect of this class of therapies. Follow-up data from this trial demonstrated a 43% 2-year survival rate, with the majority of responses continuing even after treatment discontinuation.58 An additional phase II clinical trial demonstrated an ORR of 25% among patients treated with nivolumab following progression during ipilimumab therapy.39

Two phase III studies have confirmed and clarified the activity of nivolumab both prior to and after ipilimumab therapy. In recently presented results, 370 patients who previously received ipilimumab were randomized to receive nivolumab or chemotherapy. After 6 months of follow-up, ORR was superior in the nivolumab cohort (32% vs 11%) and fewer grade 3 to 4 adverse events occurred (9% vs 31%).59 In another phase III clinical trial, nivolumab was compared with dacarbazine in patients without prior therapies and without BRAF V600 mutations. Nivolumab therapy was associated with a superior ORR (40% vs 14%), median PFS (5.1 vs 2.2 months), and OS at 1 year (72.9% vs 42.1%; $P < .001$ for all comparisons).38

Pembrolizumab

Pembrolizumab (MK-3475) is a fully humanized IgG4 monoclonal antibody to PD-1 that has also been extensively tested in melanoma and other cancers. Pembrolizumab was initially evaluated in a large phase I clinical trial with 411 patients with melanoma.40,41 Among patients treated following failure of ipilimumab therapy, the response rate was 26%. Fatigue was the only grade 3 adverse event occurring in more than 1 patient. A phase II trial of patients who had experienced failure of prior ipilimumab therapy randomized participants between 2 doses (10 mg/kg and 2 mg/kg) of pembrolizumab vs chemotherapy. A much improved PFS (HR, 0. 57) and response rate (24% vs 4%; $P < .001$) was observed in the pembrolizumab groups, with no difference between dose levels of pembrolizumab. Recent reports suggest that activity is higher in ipilimumab-naïve patients, with an observed ORR of 40%.60 Critically, responses were ongoing at the time of analysis in 88% of responding patients. Randomized phase III trials have completed accrual, and results are expected soon.

Mpdl3280a

MPDL3280A is a monoclonal antibody to PD-L1. A phase I clinical trial of this agent was conducted in melanoma, NSCLC, renal cell carcinoma, and other cancers. Among 43 patients with melanoma, the ORR was 30%, with an additional 12% experiencing stable disease for more than 24 weeks.42 Distinct from anti-PD-1, no episodes of pneumonitis were observed. Development of this agent has largely focused on NSCLC, bladder cancer, and other cancers. Several combination studies are ongoing in melanoma (see next subsection).

Combined Immune Therapy Strategies

Because ipilimumab and anti-PD-1–directed therapies remove negative T-cell regulators at distinct phases of T-cell activation, combining these therapies was suggested as a synergistic approach. Preclinical studies also demonstrated more effective antitumor activity in mouse models.61 This combination was then taken to phase I clinical trial development. Among the first 53 patients, 40% responded including 53% at the chosen phase II dose level (ipilimumab 3 mg/kg and nivolumab 1 mg/kg).43 All responses at this dose level occurred within 12 weeks, and all involved a more than 80% reduction in tumor size by Response Evaluation Criteria in Solid Tumors, version 1.1. An additional 40 patients were treated at this dose level with a 39% response rate observed.62 Critically, grade 3 to 4 toxic effects occurred in 53% of patients. These most commonly involved asymptomatic and reversible increases in liver and pancreatic enzyme levels, although severe pneumonitis, colitis, and other immune-related events also

occurred, including 1 treatment-related death from colitis. An ongoing phase III study is comparing nivolumab vs ipilimumab vs nivolumab plus ipilimumab (NCT01844505).

Ipilimumab has also been evaluated with other combination agents with promising results. In a randomized phase II trial, ipilimumab with granulocyte-macrophage colony-stimulating factor improved median OS (17.5 vs 12.7 months) and decreased grade 3 to 5 adverse events (44.9% vs 58.3%) compared with ipilimumab alone.63 Of interest, the ORR and median PFS were equivalent in this study. Ipilimumab and bevacizumab also produced a 17.4% ORR with a 12-week disease control rate of 67.4%.64 Although most patients tolerated the combination therapy, 23% withdrew as a result of toxic effects, including temporal arteritis, colitis, hypertension, and proteinuria. Ipilimumab and vemurafenib therapy was not tolerated, but ipilimumab and dabrafenib appears to have a reasonable toxicity profile in early phase I results thus far.65,66

The encouraging activity of these combination regimens has also led to a number of other anti-PD-1/PD-L1 combination approaches now being evaluated in early-phase trials, largely involving other immune modulators or targeted therapies. Ongoing nivolumab trials include combinations with lirilumab (anti-KIR), IL-21, and anti-LAG-3, respectively (NCT01714739, NCT01968109, NCT01629758). Pembrolizumab is also being evaluated with pegylated interferon alfa, dabrafenib and trametinib, and a 4-1BB agonist (NCT02089685, NCT02130466, NCT02179918). MPDL3280A is being combined with cobimetinib with or without vemurafenib, a CD40 agonist, and other immune modulators (NCT01656642, NCT02304393, NCT02174172). The relative efficacies of these approaches are not known, but results are awaited with anticipation.

Immune Biomarkers

In contrast to BRAF and MEK inhibitors, no clearly defined biomarkers exist for predicting the outcome of immune therapies although there are several promising candidate approaches. High levels of lactate dehydrogenase, visceral disease, and low absolute lymphocyte count decrease the likelihood of response to ipilimumab and/or IL-2.37,67 Conversely, a recent elegant study has suggested that total mutational burden and, in particular, specific resulting peptide changes may predict benefit from ipilimumab therapy.68 Intriguingly, many of these mutationally induced neoantigens are homologous to known viral or bacterial sequences. The translation of these findings for anti-PD-1 and for other malignant neoplasms is being investigated.

Tumor expression of PD-L1 seems to correlate with response to both nivolumab and pembrolizumab therapy.

39,57 Interestingly, a recent study implicated PD-L1 expression on infiltrating immune cells (rather than tumor cells) as more predictive for response for MPDL3280A.42 Melanomas lacking PD-L1 on the tumor or infiltrating immune cells, however, may still respond to therapy at a lower rate. Furthermore, technical aspects and multiple different available assays may also hinder the widespread use of this marker in clinical practice. T-cell receptor next-generation sequencing studies have also yielded intriguing findings. Increasing clonality (decreased diversity) of T-cell receptor sequences in tumor-infiltrating CD8+ T cells correlated with response to pembrolizumab.69 Serial biopsies further demonstrated more robust clonal expansion in responders. This study also suggested that preexisting CD8+ T cells at the invasive margin and expansion following treatment correlates with response to therapy. The role of these biomarkers in guiding clinical decision making is still being elucidated.

Future Strategies

Melanoma therapeutics continue to rapidly evolve. Combinations of targeted therapies to prevent and overcome resistance are being evaluated. Inhibitors of CDK4/6, MDM2, and ERK1/2 are particularly intriguing, especially in combination with MEK and/or BRAF inhibitors (ongoing or soon-to-open trials include NCT01781572, NCT02065063, NCT02110355).70,71 A novel antibody-drug conjugate to glycoprotein NMB (glembatumumab

vedotin) recently demonstrated activity in advanced melanoma and is being developed further.72 Directly injectable agents, including oncolytic viruses, cytokines, and rose bengal, may also be effective, particularly for patients with low-volume in-transit disease or subcutaneous metastases.73,74 Combined talimogene laherparepvec and ipilimumab therapy demonstrated a 41% ORR in early results, and a trial evaluating pembrolizumab with talimogene laherparepvec is planned.75 Finally, combinations of immune therapies, particularly involving anti-PD-1/PD-L1 with other agents as discussed herein, are drawing intense interest from physicians and patients alike. Developing immune biomarkers will be a critical objective to improve clinical trial design and treatment decision making.

Conclusions

Melanoma therapeutics have evolved at an incredibly rapid pace. Remarkable and nearly simultaneous advances have occurred over the last several years for both immune and targeted therapies. One major question in the short term is how immunotherapy or targeted therapy should be selected and prioritized in patients with BRAF V600–mutant melanoma. This will be assessed in a planned trial. Understanding how to sequence, combine, and manage these expanding treatment options will be a critical challenge alongside developing even more effective treatment options.

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