The Role of Systemic Therapy in Advanced Cutaneous Melanoma of the Head and Neck

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KEYWORDS

• Melanoma • BRAF • MEK • Immunotherapy • Checkpoint inhibitor

KEY POINTS

- Immunotherapy and BRAF/MEK targeted therapy have improved survival in advanced unresectable melanoma.

INTRODUCTION

The treatment of advanced melanoma has dramatically changed over the last decade. With the discovery of activating *BRAF* mutations and the advent of targeted therapies and checkpoint inhibitors, the overall survival of patients with advanced melanoma has increased. Survival for advanced unresectable melanoma previously averaged less than 1 year. In the era of checkpoint inhibitors such as antibodies against cytotoxic T-lymphocyte antigen (CTLA)-4 and programmed death (PD) receptor-1, and targeted therapies, such as BRAF and MEK inhibitors, 5-year overall survival rates as high as 55% have been reported.[1,2] Indeed, the most recent update of the American Joint Committee on Cancer staging system deferred major revisions in the stage IV category owing to the dramatic improvement in outcomes and the need for ongoing evaluation.[3] Here we provide an overview of systemic therapies, including the pivotal agents that have led to these advances. Advanced unresectable melanoma refers to patients with melanoma involving nodal and/or in-transit disease or distant metastases not amenable to complete resection. It is important to distinguish this population from the resected stage III/IV population, for whom adjuvant therapy can be considered. Neoadjuvant paradigms are also being studied intensely. Unfortunately, not all patients respond to these treatments and relapses still occur. Noncutaneous melanomas (uveal and mucosal) have not shown the same degree of response, and ongoing research seeks to improve outcomes for all subsets of melanoma.

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SYSTEMIC THERAPY

Melanoma, typically of cutaneous origin in the United States, often affects the head and neck. Head and neck melanomas carry a worse prognosis compared with other primary sites.[4] In 2020, there will be an estimated 100,350 new cases and 6850 deaths.[5] However, over the last decade there has been a dramatic decrease in mortality owing to advancements in systemic therapies.

Chemotherapy and immunotherapies were a mainstay of treatment of advanced melanoma before more recent advances. A number of chemotherapy regimens exist that offer clinical response and palliation, but no regimen has demonstrated improvement in overall survival. The first treatment approved by the US Food and Drug Administration (FDA) for metastatic melanoma was dacarbazine (DTIC), an alkylating agent, in 1975 based on phase I and II studies that demonstrated a maximum 28% response rate[6] (**Fig. 1**). Temozolomide, an analog of DTIC, has also been used in the treatment of melanoma and has similar activity to DTIC. A randomized phase III trial demonstrated no difference in response rate between patients with melanoma treated with DTIC (12.1%) and temozolomide (13.5%) ($P = .20$).[7] The major advantage to temozolomide is its oral administration and ability to cross into the central nervous system, which is attractive in advanced melanoma given the high incidence of brain metastases.[8] A number of additional single-agent chemotherapies have been used, including carmustine, carboplatin, taxanes, and combination platinums and taxanes.[9–12]

Combination regimens of chemotherapies and chemotherapies with immunotherapies have been investigated and include CVD (cisplatin, vinblastine or vindesine, DTIC), the Dartmouth regimen (carmustine (BCNU), DTIC, cisplatin, and tamoxifen), and biochemotherapy (cisplatin, vinblastine or vindesine, DTIC + Interferon -α + Interleukin-2).[13–15] Although smaller trials seemed to favor combination regimens, results from larger randomized trials did not demonstrate reproducibly increased response rates or overall survival, and DTIC remained the standard of care. Chemotherapy remains a treatment option for patients with relapsed or refractory melanoma after newer approved standard therapies.

Immunotherapies have been a foundation of treatment for melanoma for years based on an intimate relationship between the immune system and melanoma, including reports of spontaneous regression of tumors and vitiligo.[16,17] Before checkpoint inhibitor development, immunotherapies included cancer vaccines, cytokine

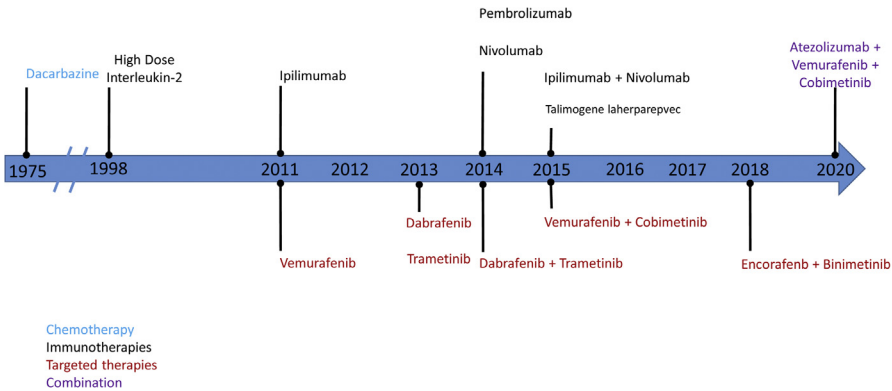

Fig. 1. Timeline of FDA-approved agents, coded by drug category: chemotherapy, immunotherapy, targeted therapy, and combination immunotherapy and targeted therapy.

therapies such as IFN and IL-2, and adoptive T-lymphocyte therapy.[18–21] High-dose IL-2 received FDA approval in 1998 (see **Fig. 1**). IL-2, an activator of T-lymphocytes as well as of other immune effector cells, administered at high doses yields response rates of approximately 16%, including 6% complete response rates (where response rate is composed of complete responses and partial responses).[20,21] Although the numbers were low, the durability of response was notable. Unfortunately, this treatment is challenging to administer and receive owing to capillary leak syndrome, multiorgan dysfunction that requires inpatient management, and strict eligibility criteria; other IL-2 molecules are in development.[22,23]

Molecularly Targeted Therapies

Genetic and molecular studies have discovered a number of somatic mutations involved in the pathogenesis of melanoma. These mutations have been identified at various stages of melanoma progression, including early tumor development, tumor metastasis, or both. These breakthroughs have led to an understanding of the mechanisms involved in melanoma tumorigenesis and to the development of targeted therapy in the treatment of melanoma.[24] Notable somatic mutations identified in melanoma include *BRAF*, *NRAS*, *KIT*, *PTEN*, and *GNA11/GNAQ*.

BRAF is mutated in 40% to 60% of melanomas, with the most common *BRAF* mutation at codon 600, resulting in substitution of glutamic acid for valine (V600 E).[25] The *BRAF* V600 E mutation results in constitutive kinase activity of BRAF and subsequent signaling through the downstream mitogen-activated protein kinase (MAPK) pathway.[26] Additional *BRAF* V600 mutations have been observed in melanoma tumor samples and melanoma cell lines.[27,28] Occasionally, mutations have been identified in *BRAF* in the loop domain (exon 11).[27] Interestingly, *BRAF* has been shown to be mutated in a significant percentage of benign nevi, suggesting that *BRAF* mutations are early events in the progression to melanoma.[29] *BRAF* mutations are associated with truncal melanomas and younger age, although *BRAF* V600 K have been associated with older patients and in areas of increased sun exposure.[30]

Activating mutations in *NRAS* have been identified in approximately 15% to 20% of melanoma tumors.[31,32] The most common *NRAS* mutation is in exon 3 at codon 61, specifically substitution of leucine for glutamine (Q61 L), although other amino acid changes are observed.[33] Q61 mutations result in a constitutively active form of the protein leading to uncontrolled cellular proliferation. Additional *NRAS* mutations have been identified in exon 2 at codons 12 and 13.[34] *NRAS* mutations are associated with nodular melanomas, chronically sun-damaged skin, thicker melanomas, and an increased mitotic rate.[35]

KIT mutations have been demonstrated to be associated with melanomas arising from acral skin, mucosa, and chronically sun-damaged skin.[36] *KIT* is mutated or amplified in approximately 30% of these melanoma tumor types. There is no one predominant *KIT* mutation and mutations are found in exons 9, 11, 12, 13, and 17. Data indicate that not all mutations result in functional dependence on *KIT* or correspond with sensitivity to KIT inhibitors.[37]

Recent clinical trials have demonstrated the benefit of targeting mutant *BRAF* with specific inhibitors, vemurafenib and dabrafenib.[38,39] Moreover, the use of MEK inhibitors, either alone or in combination with BRAF inhibitors, has demonstrated clinical response in patients with the *BRAF* V600 mutation.[40–42] After the dose-finding phase I study, the BRIM phase II trial (*BR*AF *i*n *m*elanoma) demonstrated an impressive 53% response rate in a population of pretreated patients with melanoma.[43] The BRIM 3 study was a randomized phase III clinical trial with 675 previously untreated patients with melanoma investigating vemurafenib (960 mg orally twice daily) versus DTIC,

1000 mg/m^2 intravenously (IV) every 3 weeks.[38] Treatment with vemurafenib resulted in a response rate of 48% compared with a 5% response rate for DTIC; moreover, at 6 months, the overall survival for patients treated with vemurafenib was 84% compared with 64% in patients treated with DTIC, and a relative reduction of risk of death of 63% (P<.001). An extended survival analysis of BRIM3 later reported a median overall survival of 13.6 months for patients treated with vemurafenib compared with 9.7 months for patients treated with DTIC.[44] Interestingly, the overall survival curves converged over time (>3 years), thought to be due to treatment crossover and subsequent therapies.

Dabrafenib was also evaluated in patients with metastatic melanoma with a *BRAF* V600 E or K mutation (BREAK studies). The single arm, phase II BREAK-2 trial evaluated safety and response of dabrafenib at 150 mg orally twice daily.[45] Seventy-six patients with *BRAF* V600 E melanoma and 16 patients with *BRAF* V600 K melanoma were enrolled and treated with tolerable toxicities. In the *BRAF* V600 E patients, the median progression-free survival was 6.3 months and the median overall survival was 13.1 months, although these rates were lower in the *BRAF* V600 K patients: the median progression-free survival was 4.5 months and the median overall survival was 12.9 months. Dabrafenib in *BRAF* V600 E/K mutant melanoma was further evaluated in a phase III randomized clinical trial of 250 treatment-naïve patients randomized (3:1) to dabrafenib or DTIC.[39] The median progression-free survival was 5.1 months for patients treated with dabrafenib compared with 2.7 months for patients treated with DTIC (hazard ratio [HR], 0.3; P<.0001). The long-term follow-up analysis of the BREAK-2 and BREAK-3 studies demonstrated that some patients maintained lasting responses with 5-year overall survival rates of 24% and 22% for dabrafenib and DTIC, respectively.[46] All DTIC patients progressed and received subsequent treatment.

Trametinib was first developed as a single agent to target MEK in solid tumors. MEK is a molecule in the MAPK pathway, located directly downstream of BRAF. In vitro studies demonstrated that inhibition of MEK decreased cell proliferation and increased apoptosis. MEK inhibitors are not mutation dependent and inhibit the wild-type MEK protein. An initial phase I study evaluated the safety and toxicity of trametinib and determined the recommended phase II dose via escalation and cohort expansions in select tumor types.[40,41] Patients with melanoma were enrolled in all cohorts, 97 in total, and 36 were *BRAF* mutant. Of the *BRAF* mutant patients, 30 had no prior treatment with a BRAF inhibitor. In this subgroup, 2 patients experienced a complete response, 8 patients experienced a partial response, and 19 patients experienced reduction in their tumors with a median duration of response of 5.6 months.[40] The most common side effect was rash, but gastrointestinal side effects (nausea, vomiting, and diarrhea), fatigue, peripheral edema, and decreased left ventricular ejection fraction (n = 7) were also reported. A phase III study in patients with *BRAF* mutant melanoma compared the recommended trametinib dose of 2 mg/d orally with chemotherapy, either DTIC 1000 mg/m^2 IV every 3 weeks or paclitaxel 175 mg/m^2 IV every 3 weeks; 322 patients with up to 1 previous line of therapy were randomized 2:1.[47] Trametinib improved the median progression-free survival to 4.8 months compared with 1.5 months in chemotherapy-treated patients and the 6-month overall survival to 81% compared with 67%, respectively. Common side effects included rash, diarrhea, and peripheral edema. Rare side effects included ocular toxicity and decreased ejection fraction.

Even though patients with *BRAF* mutant melanoma experienced benefits from treatment with single agent BRAF and MEK inhibitors, disease relapse and progression occurred in almost all patients. Research identified a number of mechanisms of

treatment resistance, including MEK reactivation and reactivation of the MAPK pathway. Thus, investigation of the combination of the BRAF inhibitor, dabrafenib, and the MEK inhibitor, trametinib was begun. A combined phase I and phase II clinical trial evaluated pharmacokinetics and safety of this combination with a cohort expansion at the recommended phase II dosing and compared it with single agent dabrafenib.[42] The maximum tolerated dose of the combination of dabrafenib and trametinib was 150 mg orally twice daily and 2 mg/d orally, respectively. Pyrexia was observed more frequently in patients receiving the combination compared with single agent dabrafenib (71% vs 26%, respectively), whereas the development of cutaneous squamous cell carcinoma was decreased with the combination (7% vs 19%). Outcomes were improved in patients who received combination dabrafenib and trametinib compared with single agent dabrafenib with a median progression-free survival of 9.4 months compared with 5.8 months, respectively (HR, 0.39; $P<.001$). Improved response rate and survival rates with combination dabrafenib and trametinib were also demonstrated when compared against the FDA-approved single agent BRAF inhibitor, vemurafenib.[48] Seven hundred and four patients were randomized in this open-label, phase III trial. At the preplanned interim analysis, the 12-month overall survival was 72% for the combination compared with 65% for the single agent (HR; 0.69; $P = .005$). A median progression-free survival of 11.4 months was also improved for the combination compared with 7.3 months for vemurafenib. Analyses in various disease subsets all favored treatment with combination with side effects being similar in both cohorts. A 5-year overall survival rate of 34% was reported for a combined 563 patients from these 2 trials who received combination dabrafenib and trametinib.[1]

The addition of the MEK inhibitor, cobimetinib, to the BRAF inhibitor, vemurafenib, also increased progression-free survival to 9.9 months compared with single agent vemurafenib at 6.2 months as well as response rates (68% vs 45%) in a randomized phase III trial.[49] There was increased toxicity observed in patients receiving combination vemurafenib and cobimetinib treatment, however, compared with single agent vemurafenib. Recently, a third BRAF and MEK inhibitor combination was shown to be superior to single agent BRAF inhibitor. The combination of encorafenib (a BRAF inhibitor) and binimetinib (a MEK inhibitor) demonstrated an improved median progression-free survival of 14.9 months compared with a median progression-free survival of 7.3 months with single agent vemurafenib (HR, 0.54; $P<.0001$).[50] Treatment with this combination is tolerable with increased gamma glutamyl transferase and creatinine kinase, and hypertension as common side effects, but decreased pyrexia and photosensitivity compared with each single agent, encorafenib or vemurafenib. Overall, treatment with *BRAF* mutant-specific inhibitors led to an increase in overall survival in patients with melanoma, which had been lacking with previous melanoma therapies.

The targeting of mutations other than *BRAF* has not achieved the same success in melanoma. *NRAS* mutations signal through multiple intracellular pathways including the MAPK pathway. MEK inhibitors have been used most recently in clinical trials in an attempt to target *NRAS* mutant melanoma.[51–53] In a recent study, patients with melanoma with an *NRAS* mutation were randomized to treatment with single agent binimetinib or DTIC.[51] Results demonstrated that median progression-free survival for patients treated with binimetinib was 2.8 months compared with 1.5 months in patients treated with DTIC, with an objective response rate of 15% compared with 7%, respectively. These results highlight the need for ongoing development in the treatment of *NRAS*-mutant melanoma. The use of KIT inhibitors, imatinib, dasatinib, and nilotinib has demonstrated responses in some isolated cases, primarily stable disease

and partial responses.[37,54–56] The continued discovery of somatic mutations in melanoma will allow for the ongoing development of specific therapies directed toward individual mutations and for the development of personalized medicine.

Checkpoint inhibitors

Tumor cells attempt to evade detection and destruction by the immune system through a variety of mechanisms.[57,58] CTLA-4 is a protein that can translocate to the cell surface of T lymphocytes to inhibit T-cell costimulation and activation when bound to B7.1 (CD80) and B7.2 (CD86).[57] Programmed death receptor ligand (PD-L1) (B7-H1) is expressed on many cell types, including multiple types of cancer, and negatively regulates antitumor cytotoxic T-cell responses when bound by PD-1.[58] Checkpoint inhibitors refer to therapies that interfere with these regulatory mechanisms of T cell activation. The current agents approved by the FDA for the treatment of advanced melanoma are antagonistic antibodies against CTLA-4, PD-1, and PD-L1 and are administered IV.

Ipilimumab, a human IgG1 monoclonal antagonistic antibody against CTLA-4, was the first agent to show an improvement in overall survival in melanoma in a randomized controlled trial that led to its FDA approval in 2011[59] (see **Fig. 1**). This trial randomized 676 patients 3:1:1 to ipilimumab in combination with a glycoprotein 100 (gp100) peptide vaccine versus ipilimumab alone versus gp100 alone. There was an increase in median overall survival from 6.4 months (95% confidence interval [CI], 5.5–8.7) for gp100 alone to 10 months (95% CI, 8.5–11.5) in patients who received ipilimumab with gp100 and to 10.1 months (95% CI, 8.0–13.8) with ipilimumab alone. The overall survival at 24 months was 14% for gp100 alone versus 24% and 22% for ipilimumab alone and with gp100, respectively. Ipilimumab is currently approved at a dose of 3 mg/kg every 3 weeks for 4 doses. Ipilimumab also has demonstrated activity in the brain.[60] The durability of benefit of ipilimumab was further supported in a pooled patient data analysis of 12 prospective and retrospective trials that included 1861 patients with melanoma.[61] Patients were treated at different doses and schedules of ipilimumab and included treatment-naïve and previously treated patients. The median overall survival was 11.4 months (95% CI, 10.7–12.1 months). A 3-year overall survival rate of 22% was reported for all patients that was accompanied by a plateau in the survival curve; notably, a 17% overall survival rate at 7 years was also reported. This finding supported the concept that, if a response was obtained, it would be maintained.

Two PD-1 inhibitors were studied simultaneously and received FDA approval for the treatment of advanced unresectable melanoma in 2014: pembrolizumab, a humanized IgG4 monoclonal antibody, and nivolumab, a human IgG4 monoclonal antibody (**see Fig. 1**). A multicenter phase Ib trial, Keynote-001, evaluated pembrolizumab in multiple cancers, including 655 patients with melanoma at 3 doses: 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks.[62–64] This trial included previously treated and treatment-naïve patients, as well as randomized and nonrandomized cohorts. The initial FDA approval was for previously treated patients at a dose of 2 mg/kg every 3 weeks based on the initial report of durable response rate. Several updates have been published to this study, including an objective response rate of 33% (95% CI, 30%–37%) with a median overall survival of 23 months (95% CI, 20–29) and a 24-month overall survival rate of 49% (95% CI, 44%–53%) for the entire melanoma population.[64] The most recent update for this study reported an estimated 5-year overall survival rate of 34% for all patients and a median overall survival of 23.8 months. At 55 months of follow-up, 73% of all responses were ongoing.[65]

Keynote 002, a randomized phase II trial, compared pembrolizumab with chemotherapy in ipilimumab-refractory patients with melanoma.[66] Five hundred forty

patients were randomized 1:1:1 to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks or investigator choice chemotherapy (ICC). This work demonstrated an improved progression-free survival (primary end point) and response rate for both pembrolizumab cohorts compared with ICC. Although not powered for comparison, the authors interpreted the data for the 2 pembrolizumab doses to be similar and 2 mg/kg every 3 weeks was recommended. Final analysis reported median overall survival and 2-year overall survival rates for the 3 respective arms of 13.4 months and 36%, 14.7 months and 38%, and 11.0 months and 30%.[67] Overall survival differences were not significant, possibly owing to crossover. Keynote 006, a randomized phase III trial, compared pembrolizumab at 10 mg/kg every 2 or 3 weeks or ipilimumab 3 mg/kg every 3 weeks for 4 doses in 834 patients with melanoma.[68] In this study, the 2 pembrolizumab-treated groups evidenced improved estimated 12-month overall survival rates (74.1% vs 68.4% vs 58.2%), response rates (33.7% vs 32.9% vs 11.9%), and estimated 6-month progression-free survival rates (47.3% vs 46.4% vs 26.5%), respectively. At a median follow-up of 57.7 months, the authors reported results for the 2 combined pembrolizumab arms and ipilimumab: a median overall survival rate of 32.7 months (95% CI, 24.5–41.6) and 15.9 months (95% CI, 13.3–22.0), respectively.[69] The FDA approval of pembrolizumab was later expanded to include first-line treatment.

Nivolumab was also evaluated in a large phase I study in multiple cancer types, which enrolled 107 patients with melanoma.[70] Nivolumab was administered every 2 weeks with doses ranging from 0.1 to 10.0 mg/kg. Across all doses, an overall response rate of 31% was seen in the patients with melanoma with an estimated median duration of response of 2 years. The median overall survival was 16.8 months with a 2-year overall survival rate of 43%. At the 3 mg/kg FDA-approved dose, the response rate was 41% with a median overall survival of 20.3 months. The most recent update reported an estimated 5-year overall survival rate of 34.2%.[71] A phase III trial, Checkmate 037, randomized (2:1) 405 patients with melanoma progressed through ipilimumab, and through BRAF inhibitor therapy if *BRAF* mutant, to nivolumab 3 mg/kg every 2 weeks versus ICC.[72] The objective response rate per independent radiologic review and overall survival were coprimary end points. This study reported an overall response rate of 31.7% versus 10.6% at the first interim analysis, which led to nivolumab receiving accelerated approval from the FDA for previously treated melanoma (see **Fig. 1**). The authors provided an updated report in 2017 with overall survival data.[73] The overall response rate was 27% versus 10% for nivolumab versus ICC, the median duration of response was 32 months versus 13 months, and the median overall survival was 16 months versus 14 months, respectively. Next, treatment-naïve, *BRAF* wild-type patients with melanoma were randomized in another phase III trial, Checkmate-066, to nivolumab or DTIC.[74] In this study of 418 patients, overall survival was the primary end point and a significant improvement in 1-year overall survival was reported: 72.9% (95% CI, 65.5–78.9) for nivolumab versus 42.1% (95% CI, 33.0–50.9) for DTIC. An improved response rate and progression-free survival were also reported for nivolumab.

Treatment with anti-PD1 agents typically is continued to maximal toxicity, progression, maximal benefit, or up to 2 years. PD-L1 expression in tumor tissue can be evaluated, but is not required for treatment with PD1 inhibitor therapy given limited predictive value.[75] Patients without PD-L1 expression can still respond to PD1 inhibitor therapy. Antagonistic PD-1/PD-L1 antibodies were evaluated as weight-based doses in trials. More recently, the FDA labels have been modified for flat dosing given simulations by a population pharmacokinetics model that determined that a clinically meaningful effect on safety and efficacy between the 2 doses was unlikely.[76] Pembrolizumab is

approved at 200 mg every 3 weeks and nivolumab at 240 mg every 2 weeks. Additional mathematical modeling has also led to approval of alternative doses and schedules: nivolumab 480 mg every 4 weeks and pembrolizumab 400 mg every 6 weeks.[77–79]

Combination immunotherapy with ipilimumab and nivolumab was then evaluated in a phase I study evaluating various doses and schedules (concurrent and sequential) in 8 cohorts.[80] Ipilimumab 3 mg/kg and nivolumab 1 mg/kg every 3 weeks for 4 doses, followed by single agent nivolumab was selected for further study because these were the maximum doses with an acceptable level of adverse events. Patients treated in this cohort evidenced an overall response rate of 53% (9/17), which included 3 complete responses; all 9 had a tumor reduction of 80% or greater at the first tumor assessment. This regimen has been further studied in phase II and phase III trials.[81,82] Checkmate 067, a phase III double-blind trial, randomized 945 treatment naive patients (1:1:1) to ipilimumab with nivolumab, nivolumab alone, or ipilimumab alone.[82] This study was designed to evaluate progression-free survival and overall survival as coprimary end points. The FDA-approved combination ipilimumab and nivolumab at this dosing schedule in October 2015 for the treatment of advanced, unresectable melanoma based on a significant improvement in median progression-free survival: 11.5 months (95% CI, 8.9–16.7) for ipilimumab with nivolumab versus 2.9 months (95% CI, 2.8–3.4) for ipilimumab alone with an overall response rate of 58% versus 19% for the combination versus ipilimumab alone (see **Fig. 1**). Further, nivolumab demonstrated an improved median progression-free survival of 6.9 months (95% CI, 4.3–9.5) compared with ipilimumab with an HR of 0.57 (99.5% CI, 0.43–0.76), as well as an overall response rate of 44%. The study was not designed for a formal statistical comparison of combination therapy to nivolumab.

Several updates of this study have been published. Notably, the 5-year overall survival rates were 52% for ipilimumab with nivolumab, 44% for nivolumab alone, and 26% for ipilimumab alone.[2] These response rates were similar to those initially reported and included complete response rates of 22%, 19%, and 6% for ipilimumab with nivolumab, nivolumab alone, and ipilimumab alone, respectively. The authors also reported outcomes after treatment: rates of subsequent systemic therapy (46% for ipilimumab with nivolumab, 59% for nivolumab alone, and 75% for ipilimumab alone), as well as the treatment-free interval, defined as the time from the last dose of the trial drug to subsequent systemic therapy or the last known date alive. The median treatment-free interval for ipilimumab with nivolumab was 18.1 months, 1.9 months for ipilimumab alone, and 1.8 months for nivolumab alone. Further, of the patients alive at 5 years, 74% of the combination treatment patients were not on treatment compared with 58% of the nivolumab group and 45% of the ipilimumab group. This result speaks to the durability of response after completing treatment, as well as to the risk/incidence of toxicities for each of these treatment groups, where more patients stop treatment in the combination arm owing to toxicity. This regimen has also shown intracranial responses in patients with asymptomatic, nonirradiated brain metastases.[83]

The majority of side effects related to checkpoint inhibitors are due to immune attack on normal parts of the body, termed immune-related adverse events.[84] There is ongoing research to understand the mechanisms of action and optimal management. These toxicities are unpredictable regarding severity, timing, and presentation, and require a high level of suspicion. Most commonly, the skin, bowels, and endocrine glands can be effected; however, any organ may be impacted. Most require holding immunotherapy, often temporarily, but sometimes permanently depending on the grade and the affected organ. They typically do not resolve on their own and require treatment with steroids, often at high doses, for no less than 4 weeks' duration.

Occasionally, additional immunosuppressive agents are needed and toxicities can rebound and can be fatal, although rarely. Guidelines have been developed to facilitate their management.[85] Side effects are graded according to the common toxicity criteria; grade 3 and 4 toxicities are more severe and grade 5 is fatal.[86] Patients with altered immune systems at baseline, such as patients with preexisting autoimmune conditions or immunosuppression, seem to be at greater risk.

The reported treatment related grade 3 or 4 toxicity rates for ipilimumab, nivolumab, and combination ipilimumab and nivolumab are 27%, 16%, and 55%, respectively.[82] The combination toxicity rate is for ipilimumab 3 mg/kg with nivolumab 1 mg/kg every 3 weeks for 4 doses followed by single agent nivolumab. Given this rate of toxicity, alternative combination regimens are under investigation. One phase IIIb/IV randomized, controlled trial, Checkmate 511, evaluated the rate of treatment-related grade 3 to 5 adverse events in patients with melanoma treated with 2 different regimens of ipilimumab with nivolumab.[87] Three hundred and sixty patients were randomized 1:1 to ipilimumab 1 mg/kg with nivolumab 3 mg/kg (I1N3) every 3 weeks for 4 doses or ipilimumab 3 mg/kg with nivolumab 1 mg/kg (I3N1—standard dosing) every 3 weeks for 4 doses. All patients who tolerated therapy then received nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity. This regimen showed a lower grade 3 to 5 immune-related adverse event rate for I1N3 of 34% compared with 48% for I3N1. The efficacy seemed to be similar, with an overall response rate of 46% and 51% for the 2 arms, respectively, but additional investigation is needed.

The optimal therapy sequence or combination across mechanisms of action is also an ongoing area of discussion and research. Many investigators believe that there is a greater potential for durable response and treatment-free period with immunotherapy and often recommend this in the first- line setting.[75] Combination regimens of BRAF/MEK inhibitors with PD1/PDL1 antagonistic antibodies are also being pursued. The FDA recently approved the regimen of vemurafenib, cobimetinib, and atezolizumab, a PD-L1 antagonistic antibody, for the treatment of *BRAF* V600–mutant melanoma given a significantly improved progression-free survival (15.1 months vs 10.6 months) compared with vemurafenib/cobimetinib alone[88] (see **Fig. 1**). This regimen and other combination regimens come with a high rate of grade 3 and 4 treatment-related adverse events (79%). How this regimen will fit into current practice is being determined. Most in the melanoma community agree that treatment decisions must be tailored to the features of the patient and their melanoma.

SUMMARY

Survival in advanced melanoma is consistently improving with the development and deployment of effective systemic therapies. However, there are still relapses and not all melanomas respond to these therapies. Ongoing research into novel pathways and combination strategies is continuing. Toxicities do come with these agents and must be balanced with cancer control.

CLINICS CARE POINTS

- Immunotherapy and BRAF/MEK targeted therapy have improved survival in advanced unresectable melanoma.
- Immunotherapy offers the potential for improved survival with time free from treatment.
- The optimal sequence or combination of therapies remain to be determined and is often tailored to patient and disease burden.

COI

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