

Current options and future directions in the systemic treatment of metastatic melanoma

Katja Schindler^a and Michael A. Postow^b

^aDermatology Service and ^bMelanoma and Sarcoma Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York

Systemic treatment options for metastatic melanoma have historically been limited, with conventional cytotoxic chemotherapies demonstrating only modest benefit. Recent advances, however, have dramatically changed the treatment landscape and can be considered in 2 general categories: immunotherapeutic approaches that enhance antitumor immunity, and targeted therapeutic approaches that block oncogenic driver mutations. Immunotherapy with antibodies that block cytotoxic T-lymphocyte antigen 4 and programmed death-1 receptor can result in durable responses in a subset of patients. These treatments may be considered for patients irrespective of their mutational status, and ongoing research continues to investigate biomarkers associated with clinical outcomes. Side effects of these agents result from immune-mediated reactions involving various organ sites and can include: diarrhea, rash, hepatitis, and endocrinopathies. For patients whose melanoma harbors a BRAF mutation, targeted therapy with BRAF and MEK inhibitors has the potential for rapid tumor regression in the majority of patients, and some patients with KIT mutations can also respond to appropriately targeted therapy. Unfortunately, most patients' responses to targeted agents are transient with disease progression ultimately ensuing owing to the emergence of a number of mechanisms of resistance. This review begins with a description of the traditional agents used to treat metastatic melanoma, then focuses on the mechanism of action, toxicity profile, and efficacy data for the recently approved immunotherapeutic and targeted therapeutic agents. Novel approaches in clinical development are also included because expectations are high that these new agents will ultimately have an important role in the treatment of advanced melanoma.

The incidence of melanoma, a highly aggressive tumor arising from melanocytes, continues to rise by approximately 3% a year in the United States with about 76,000 patients being diagnosed every year and 9,000 patients dying from their disease.¹ Complete surgical resection is the standard for localized melanoma, with surgical excision margins depending on tumor thickness. For patients with involved sentinel lymph nodes, complete lymphadenectomy is typically recommended,^{2,3} although the benefits of completion lymphadenectomy are being evaluated in an ongoing randomized trial (NCT00297895).

For patients with surgically resected, high-risk melanoma, the only approved adjuvant therapy is interferon- α (IFN- α).⁴ Use of interferon- α , however, remains controversial because of the associated side effects and controversial effects on overall survival (OS).^{5,6} Unfortunately, many patients with localized disease will ultimately recur, and the prognosis of patients with metastatic disease is poor with a historical 5-year survival rate of 10%.⁷

Chemotherapy and interleukin 2

For more than 3 decades, conventional cytotoxic chemotherapy was used to treat metastatic mel-

anoma. Typical agents included alkylating agents (dacarbazine, temozolomide, nitrosoureas), platinum analogs (cisplatin and carboplatin), and microtubular toxins (vinblastine and paclitaxel). Despite the clinical use and investigation of a number of these chemotherapies for patients with metastatic melanoma, the only treatment approved by the US Food and Drug Administration (FDA) is dacarbazine, which is administered intravenously every 3-4 weeks at a dose of 800-1,000 mg/m². Monotherapy with dacarbazine is generally well tolerated with only mild side effects such as nausea, myelosuppression, and fatigue. In a pooled analysis, the overall response rate for dacarbazine was approximately 9%.⁸ Temozolomide, the oral analog of dacarbazine, penetrates into the central nervous system and has been compared with dacarbazine in randomized trials. These agents are believed to have similar efficacy, but temozolomide has been associated with a higher rate of lymphopenia.^{9,10}

Investigation of chemotherapy combinations such as cisplatin, vinblastine, and dacarbazine or carboplatin and paclitaxel have shown promising response rates but unfortunately no prolongation of OS compared with single-agent dacarbazine.¹¹⁻¹³ Despite its modest efficacy, chemotherapy still has a

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place in the palliative treatment for some patients.

In addition to dacarbazine, the immunotherapeutic strategy, high-dose recombinant interleukin-2 (IL-2), had also been a mainstay treatment for advanced melanoma for many years. IL-2 is administered as an intravenous infusion every 8 hours at a dose of 600,000-720,000 IU/kg on days 1 to 5 and days 15 to 19, with a maximum of 14 such biphased cycles. Because of the significant acute toxicity profile, including capillary leak syndrome, cardiovascular complications, and seizures, IL-2 treatment requires hospitalization and is generally only performed at specialized centers for patients with good performance status. Though the overall response rate in pooled analysis was low at 16%, the durability of responses in some responders that appeared to last many years led to the FDA approval of IL-2 in 1998.^{14,15}

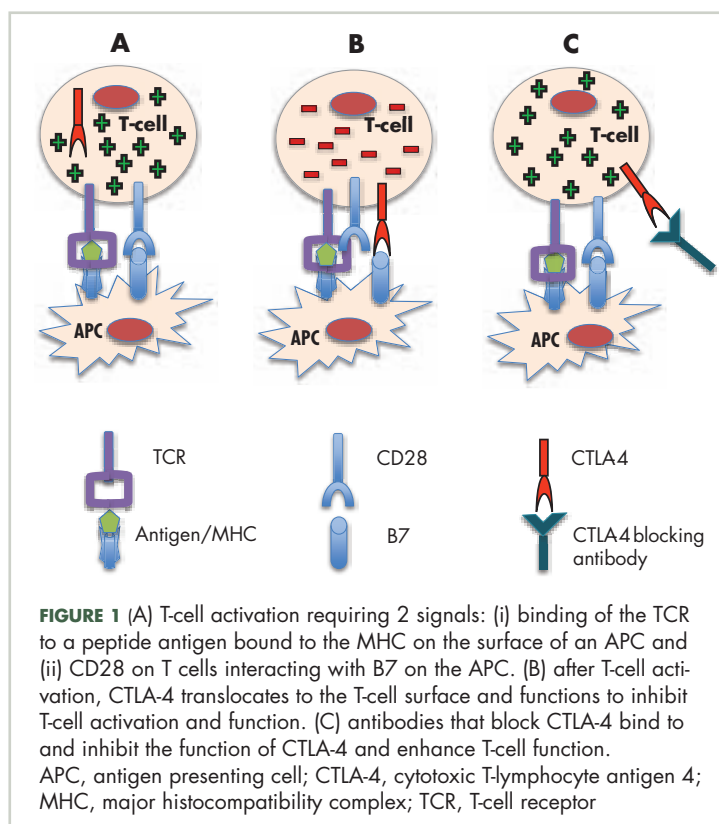
IL-2 continues to be investigated. In a randomized trial, an improved response rate and progression-free survival (PFS) were seen when IL-2 was combined with the glycoprotein 100 (gp100) peptide vaccine compared with IL-2 alone.¹⁶ Other approaches have sought to improve the safety of IL-2 by selectively delivering it to tumor sites. The fusion protein L19-IL2 couples IL-2 with the recombinant human vascular targeting antibody L19 and has preliminarily been shown to be safe in phase 1 evaluation and in combination with dacarbazine.^{17,18}

Antibodies that enhance antitumor immunity by blocking immunologic checkpoints

Melanoma has long been recognized as an immunogenic malignancy but the efficacy of immunotherapeutic strategies has generally been modest. The precise etiology of why immunotherapy historically was not more successful is not completely understood, but it is possible that patients with advanced malignancy have predominant immune inhibitory circuits that prevent otherwise effective antitumor immune responses. In recent years, research has illuminated some of these immunologic inhibitory elements, termed “immunologic checkpoints,” which includes cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1). Antibodies that target these checkpoints have resulted in durable responses in some patients and a unique pattern of immune-mediated side effects. Though an ongoing area of research, no pre- or on-treatment biomarkers have been sufficiently validated to enable specific patient selection for these therapies.

Antibodies blocking CTLA-4

Cytotoxic T-lymphocyte antigen (CTLA-4) is expressed on activated T cells and typically functions as a negative regulator of T-cell activity preserving normal immunologic homeostasis. Blocking CTLA-4 with therapeutic antibodies such as ipilimumab and tremelimumab prevents normal CTLA-4 mediated T-cell down regulation and thereby



enhances the ability of T cells to exert their full antitumor immune effects (Figure 1). Ipilimumab was the first drug in the management of metastatic melanoma to show an improvement in overall survival in phase 3 studies,^{19,20} and although a phase 3 study of tremelimumab did not demonstrate an improvement in overall survival, durable responses were similarly seen.²¹

The first phase 3 trial investigating ipilimumab randomized previously pretreated patients with advanced melanoma to ipilimumab at a dose of 3 mg/kg with or without the gp100 peptide vaccine. The median OS was 10.0 months among patients receiving ipilimumab plus gp100, compared with 6.4 months among patients receiving gp100 alone. There was no difference in OS between the ipilimumab groups.¹⁹ The outcome of this study has led to the approval of ipilimumab at a dose of 3 mg/kg in patients with advanced melanoma by regulatory agencies in the US, European Union, and Australia.

For treatment-naïve patients, a second phase 3 trial investigating dacarbazine in combination with ipilimumab compared with dacarbazine in combination with placebo also demonstrated improvement of OS for patients treated with dacarbazine in combination with ipilimumab.²⁰ The estimated 1-year, 2-year, and 3-year survival rates were 47.3%, 28.5%, and 20.8%, respectively, in the dacarbazine plus ipilimumab group, compared with 36.3%, 17.9%, and 12.2% in the dacarbazine alone group. This second trial

used a higher dose of ipilimumab (10 mg/kg) and though it confirmed ipilimumab's beneficial effects on OS, ipilimumab is not approved at 10mg/kg and is not routinely recommended to be used in combination with dacarbazine given hepatic toxicity concerns.

Though the median OS was improved in these phase 3 trials, perhaps the greatest activity of ipilimumab lies in the increased number of patients who can achieve long-term OS. In a recently published updated survival analysis, the 4-year survival rates for previously treated patients who received ipilimumab at 3 or 10 mg/kg were 18.2% and 19.7%-28.4%. For treatment-naïve patients receiving ipilimumab at 10 mg/kg, 4-year survival rates were between 37.7% and 49.5%.²² These values appear superior to historical data from prior chemotherapy trials.

An important consideration in the clinical use of CTLA-4 blocking antibodies is the possible occurrence of toxicities that differ from those associated with traditional chemotherapy. These side effects are termed immune-related adverse events (irAEs) and they most commonly manifest as diarrhea, dermatitis, hepatitis, and endocrinopathies but less commonly can involve other organs resulting in uveitis, nephritis, myopathy, and neuropathy. In general, the onset of irAEs follows a certain pattern with cutaneous manifestations often presenting early in treatment, followed by gastrointestinal and hepatic events occurring about 2 months into therapy and endocrinopathies appearing event later.²³ In rare cases, severe side effects (eg, perforating colitis, toxic

epidermal necrolysis) can occur and may require hospitalization.²⁴ Clinicians must be attentive to early signs of these side effects and promptly initiate immunosuppression with steroids or other immunosuppressive medications, which do not appear to diminish the antitumor immune effects.²⁵ Established management algorithms exist to guide clinicians. Given the occasional need for immunosuppression in this patient population, awareness of the possibility of opportunistic or rare infections is also important.

In phase 3 evaluation, the number of patients who had long-term survival exceeded the number of patients who had a classically defined disease response to treatment. Durable stable disease and late responses have been observed clinically and may be responsible for some of the beneficial outcomes.²⁶ If patients are asymptomatic and have minimal radiographic progression, it is reasonable to repeat imaging 1 to 2 months later to confirm progression before considering additional lines of therapy.

Antibodies blocking the programmed death-1 axis

Programmed death-1 (PD-1) is a receptor on the surface of T cells that is upregulated at later stages of T-cell activation as opposed to the early upregulation of CTLA-4. Normally, engagement of PD-1 attenuates T-cell activity at several phases of an immune response. Tumors are believed to escape immune attack by similarly inhibiting T-cell activity by upregulating one of the ligands of PD-1, PD-L1.^{27,28} Several antibodies that inhibit PD-1 activ-

TABLE 1 Selected ongoing trials investigating immunotherapeutic approaches in the treatment of advanced melanoma

Study drug	Trial no.	Treatment arms	Prior treatment	Phase
<i>Anti PD-1 antibodies</i>				
Nivolumab (BMS-936558)	NCT01844505	Ipilimumab alone Nivolumab alone Ipilimumab + nivolumab	Treatment naïve	3
	NCT01721772	Nivolumab Dacarbazine	Treatment naïve	3
	NCT01721746	Nivolumab chemotherapy (dacarbazine or carboplatin + paclitaxel)	Ipilimumab + RAF-I (if BRAF mutant)	3
	NCT01927419	Nivolumab + ipilimumab Ipilimumab	Treatment naïve	2
	NCT01783938	Nivolumab + ipilimumab sequentially	Treatment naïve and pretreated	2
MK-3475	NCT01866319	MK-3475 Ipilimumab	Treatment naïve	2
	NCT01704287	MK-3475 Chemotherapy	Ipilimumab pretreated	2
<i>Anti PD-L1 antibodies</i>				
MPDL3280A	NCT01656642	MPDL3280A + vemurafenib	Treatment naïve BRAF V600 mutant	1b
MEDI4736	NCT01693562	MEDI4736	Pretreated	1

PD-1, programmed death 1; PD-L1, programmed death ligand 1

ity, either by blocking the PD-1 molecule itself or PD-1's ligand, PD-L1, are demonstrating significant promise in ongoing clinical trials.

Nivolumab (previously, BMS-936558) is a fully human monoclonal antibody targeting PD-1. In a large phase I study in patients with a variety of malignancies, nivolumab demonstrated a 31% response rate in patients with advanced melanoma.²⁹ Subsequent follow-up data indicates these responses are generally durable with a median duration of response of 24 months and a 3-year OS rate of 40%.³⁰ Side effects of nivolumab appear less frequent than with CTLA-4 blockade but have included vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. Unique to PD-1 blockade appears to be the side effect of an inflammatory pneumonitis, which can present with a dry cough, dyspnea, and ground-glass opacities and can be potentially lethal.²⁹

On the basis of complementary regulatory roles of CTLA-4 and PD-1 checkpoint inhibition, a trial investigating combined nivolumab and ipilimumab was completed. In the small group of patients treated, a high response rate was seen with a generally acceptable safety profile.³¹ Ongoing phase 2 and 3 trials are assessing nivolumab alone and in combination with other agents for the treatment of advanced melanoma and other malignancies (Table 1).

Another PD-1 blocking antibody, MK-3475, has been evaluated in patients with advanced melanoma and promising response rates have been described.³² In a small group of patients, the confirmed response rate at a dose of 10 mg/kg every 2 weeks was 52% and appeared similar in patients who had and who had not been previously treated with ipilimumab. The side effects of MK-3475 seem to resemble nivolumab. MK-3475 is similarly being evaluated in large phase II and III trials for patients with melanoma but also in additional malignancies (Table 1).

In addition to antibodies targeting PD-1, clinical activity has also been observed with several different antibodies (BMS-936559, MPDL3280A, and MEDI4736) that target the ligand for PD-1, PD-L1. Though some data has been published for this therapeutic strategy,³³ ongoing trials will continue to clarify the role of targeting PD-L1 in patients with advanced melanoma.

Targeted therapies that block oncogenic signaling pathways

The mitogen-activated protein kinase (MAPK) pathway responds to extracellular growth signals and regulates cell proliferation and survival. In many patients with melanoma, the MAPK pathway is constitutively activated as a result of molecular alterations in genes encoding key regulators or components of the pathway such as BRAF, NRAS, and KIT.^{34,35} The most common mutation arising in melanoma is the BRAF mutation, occurring in nearly half of melanomas, and typically involves a missense mutation in

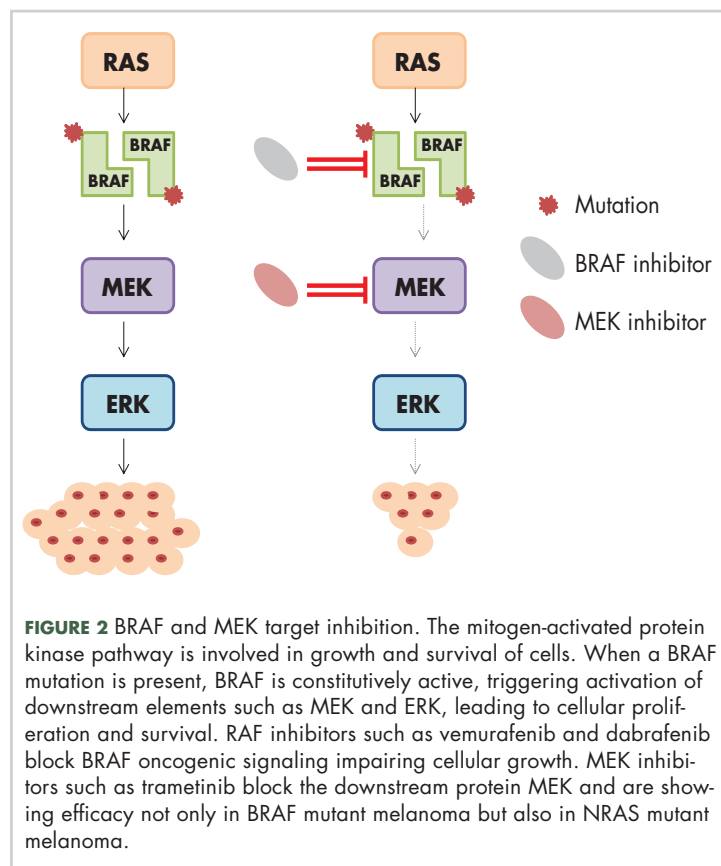


FIGURE 2 BRAF and MEK target inhibition. The mitogen-activated protein kinase pathway is involved in growth and survival of cells. When a BRAF mutation is present, BRAF is constitutively active, triggering activation of downstream elements such as MEK and ERK, leading to cellular proliferation and survival. BRAF inhibitors such as vemurafenib and dabrafenib block BRAF oncogenic signaling impairing cellular growth. MEK inhibitors such as trametinib block the downstream protein MEK and are showing efficacy not only in BRAF mutant melanoma but also in NRAS mutant melanoma.

which glutamic acid is substituted for valine at codon 600 (BRAF V600E mutation).³⁶ Less frequent BRAF mutations include V600K, V600R and K601E.³⁷ Strategies that directly inhibit oncogenic BRAF or disable downstream elements such as MEK have shown dramatic recent results in patients with melanoma (Figure 2).

BRAF inhibitors

Vemurafenib is a potent inhibitor of mutated BRAF with marked antitumor effects against melanoma cell lines with the BRAF V600E mutation.³⁸ The first striking results of tumor regression with this strategy in patients were seen in a phase 1 study in patients with melanoma characterized by a BRAF V600E mutation but not in patients whose melanomas do not have a BRAF mutation.³⁹ Subsequent phase 3 trials confirmed the high response rates of this agent in patients with BRAF mutant melanoma and demonstrated superiority in OS compared with dacarbazine chemotherapy.⁴⁰ The results of this phase 3 trial led to the approval of vemurafenib by the FDA in August 2011 with treatment exclusively limited to patients with BRAF mutant melanoma. Updated OS data from this phase 3 study revealed a median OS of 13.2 months for vemurafenib, compared with 9.6 months for dacarbazine, with an overall response rate in patients treated with vemurafenib of 57% and a

median PFS of 6.9 months.⁴¹ General side effects with vemurafenib include arthralgia, fatigue, aminotransferase elevations, nausea and vomiting, and decreased kidney function. In general, toxicities are manageable with dose reduction or temporary drug cessation.

One characteristic of vemurafenib and other BRAF-targeted agents is the frequent development of hyperproliferative skin side effects. Skin lesions including follicular and palmo-plantar hyperkeratosis, papillomas, and also cutaneous squamous-cell carcinomas and keratoacanthomas have commonly been observed under treatment with vemurafenib and close evaluation by a dermatologist is important.⁴² The mechanism of this phenomenon is believed to be a paradoxical activation of the MAPK pathway in nonmelanoma BRAF wild-type cells when systemic treatment with a BRAF inhibitor is administered.⁴³

The phenomenon of hyperproliferation of non-BRAF-mutant tissues with ongoing BRAF-inhibitor therapy has also been seen in patients with lymphoproliferative disorders and may be a mechanism involved in the discovery that patients have a high rate of new primary melanomas while on therapy.^{44,45} These findings warrant special attention, particularly as BRAF inhibitors are undergoing evaluation as adjuvant therapy.

Another active BRAF kinase inhibitor with a similar efficacy profile as vemurafenib is dabrafenib, which was approved in May 2013 based on the demonstration of improved PFS in a phase 3 trial comparing dabrafenib 150 mg orally twice daily and dacarbazine 1,000 mg/m² intravenously once every 3 weeks in previously untreated patients with BRAF V600E mutant melanoma. The median PFS times were 5.1 and 2.7 months in the dabrafenib and dacarbazine arms, respectively, with an objective response rate of 52% in patients treated with dabrafenib.⁴⁶ Follow-up time was too short to make a determination of the impact of dabrafenib on OS. In a separate study, dabrafenib was also shown to be effective for patients with brain metastases and remains an excellent therapeutic choice for this particular patient population.⁴⁷

Generally, dabrafenib is believed to have similar efficacy to vemurafenib. Nevertheless, adverse reactions of dabrafenib somewhat differ from those observed with vemurafenib: The rate of proliferative skin lesions including squamous cell carcinomas and keratoacanthomas appears to be lower for dabrafenib than vemurafenib. However, side effects particular to dabrafenib have been seen such as pyrexia, which were recorded in about 11% of patients.⁴⁶

MEK inhibitors

Though targeting oncogenic BRAF directly has been incredibly successful for patients with BRAF mutant metastatic melanoma, additional success has been observed by

blocking the MAPK pathway at a downstream component, MEK. Trametinib is an MEK inhibitor that was approved by the FDA in June 2013 as a single agent for patients with BRAF V600E or V600K mutant melanoma. Trametinib is administered at a dose of 2 mg once daily and was shown to improve PFS and OS compared with dacarbazine or paclitaxel chemotherapy.⁴⁷ Despite the improvement in PFS and OS compared with chemotherapy, the objective response rate for trametinib was somewhat lower (22%) than that seen with BRAF inhibitors.

Trametinib also is associated with a different side effect profile from BRAF inhibitors and includes diarrhea, peripheral edema, hypertension and fatigue, typical of other MEK inhibitors as well.⁴⁹ Asymptomatic and reversible reduction of the cardiac ejection fraction and ocular toxic effects also occur infrequently. Unlike with BRAF-inhibitor treatment, the development of cutaneous squamous-cell carcinomas or other hyperproliferative skin lesions was not noted.⁴⁸

Despite the significant benefits of targeted therapy disrupting overly active MAPK signaling in patients with BRAF mutant metastatic melanoma, almost all patients treated with these targeted inhibitors who achieve an initial response will ultimately progress. Several mechanisms of resistance have been proposed, and most relate to reactivation of the MAPK pathway.^{50,51} As a result, efforts to maintain suppression of the MAPK pathway have been pursued to delay the onset of resistance. In a phase 2 trial that combined dabrafenib with trametinib, there was a longer PFS than there was with dabrafenib monotherapy.⁵² Furthermore, the addition of trametinib to dabrafenib reduced the incidence of squamous cell carcinoma, providing further evidence that reactivation of the MAPK pathway is involved in these hyperproliferative skin lesions arising under BRAF directed therapy. A higher rate of febrile episodes was seen, however. An ongoing phase 3 study is looking at whether or not combining BRAF and MEK inhibitors results in improved overall survival compared with single-agent BRAF. It is premature at this juncture to recommend combining dabrafenib and trametinib until the results of the ongoing phase 3 studies more thoroughly describe the risks and benefits of this approach (Table 2).

KIT inhibitors

In a subset of melanomas, particularly those that arise from mucosal, acral, or chronically sun-damaged skin, mutations are found in the receptor-tyrosine kinase, KIT.³⁵ A number of agents directed against KIT such as imatinib have been tested in clinical trials. Initial phase 2 studies revealed poor response rates with KIT inhibition in molecularly unselected patients.⁵³⁻⁵⁵ Subsequent studies selected patients with KIT genetic aberrations including mutations and amplifications and some responses were seen.⁵⁶⁻⁵⁸ Importantly, not all

TABLE 2 Selected ongoing trials investigating targeted therapeutic approaches in the treatment of advanced melanoma

Study drug	Trial no.	Treatment arms	Prior treatment	Phase
<i>BRAF mutant</i>				
LGX818 MEK162	NCT01909453	Vemurafenib LGX818 LGX818 + MEK162	Treatment naïve	3
Vemurafenib Dabrafenib Trametinib	NCT01597908	Vemurafenib Dabrafenib + trametinib	Treatment naïve	3
LGX818	NCT01894672	LGX818 pulsatile	Pretreated	2
GDC-0973	NCT01689519	GDC-0973 + vemurafenib Vemurafenib	Treatment naïve	3
<i>NRAS mutant</i>				
MEK162	NCT01763164	MEK162 Dacarbazine	Treatment naïve and pretreated	3

KIT genetic aberrations are believed to be considered equal. Preliminarily, it appears that mutations in exon 11 (L576P) and exon 13 (K642E) appear to be most closely associated with response and may be true driver mutations. Other KIT mutations may have less functional significance but additional research is needed. Imatinib is a reasonable therapeutic choice in patients with a KIT mutation, particularly when an L576P or K642E mutation is present.

Summary and future directions

Since 2011, 4 new drugs – ipilimumab, vemurafenib, dabrafenib, and trametinib – have been approved for the treatment of metastatic melanoma. Exciting early data from PD-1 clinical trials suggest that agents that disrupt PD-1 may also become important therapeutic modalities. Future studies will continue to evaluate combinations of these therapeutic modalities, but caution should be exercised in combining these drugs prior to data from ongoing clinical trials revealing the true benefits and risks of combinatorial therapy. Excessive toxicity was seen in an early phase trial when vemurafenib was combined with ipilimumab.⁵⁹

Additional research will also explore biomarkers that may help clinicians apply immunotherapy to the most appropriate patients and better understand mechanisms of resistance to targeted therapies. Clinical trials of novel agents or combinations should be considered at every treatment juncture to continue the rapid pace of developing the most innovative and tailored treatment approaches.

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