Evolving therapeutic strategies maintain clinical momentum in melanoma

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The past 5 years have witnessed a watershed moment in the management of metastatic melanoma. The successes of molecularly targeted and immune-based therapies have transformed it from an aggressively lethal malignancy into one that is readily treatable. Here, we discuss continued efforts to find new therapies and broaden the clinical impact of existing options to maintain the unprecedented momentum of improving patient outcomes.

Taking aim at oncogenic drivers

Decades of intense research efforts in melanoma have enabled researchers to pin down some of the molecular drivers of this disease and unraveled its complex relationship with the immune system. This has dramatically altered the treatment landscape in the past 5 years, with almost a dozen new treatment options coming to market, many of which have had an unprecedented impact on patient survival, and with many more in clinical development.

The most significantly mutated gene in melanoma is *BRAF*, which encodes a serine-threonine protein kinase involved in the mitogen-activated protein kinase (MAPK) pathway (Figure 1), an important mediator of cell growth and proliferation. *BRAF* is mutated in about half of all patients with melanoma, generating a mutant kinase that is always active and drives aberrant MAPK signaling.

A number of other components of the MAPK pathway are altered in melanoma, including activating mutations in the upstream RAS enzyme, and loss of the neurofibromin 1 (*NF1*) gene, which is a negative regulator of RAS. The discovery of this pathway as a key oncogenic driver of melanoma prompted the development of drugs to specifically target it.[1,2]

First to arrive on the scene were vemurafenib and dabrafenib, two specific inhibitors of mutant BRAF kinase. Both drugs elicited impressive response rates and improved progression-free survival (PFS) in patients with *BRAF*-mutant disease compared with those receiving chemotherapy, which resulted in their approval by the US Food and Drug Administration (FDA) in 2011 and 2013, respectively.[3,4]

Attempts to target other components of the MAPK pathway culminated in the successful development of inhibitors of MEK kinase, which sits immediately downstream of BRAF. Trametinib was approved by the FDA in 2013 for the treatment of *BRAF*-mutant metastatic melanoma, based on a 4-month improvement in survival over chemotherapy.[5]

Though BRAF and MEK inhibitors represent transformative treatment options, not all patients have mutations in the MAPK pathway. They are common in melanomas arising from nonchronically sun-damaged skin, but significantly less so in other types of melanoma, such as acral, mucosal, and vulvo-vaginal melanomas. Activating mutations of *KIT* have been identified in a significant proportion of patients with these subtypes and multikinase inhibitors, such as imatinib, dasatinib and sunitinib, have shown clinical activity in these patients, with clinical trials ongoing (Table 1).[6]

Immunotherapy achieves durable control

Melanoma has been the poster child of immunotherapy – cancer drugs that boost the antitumor immune response rather than directly killing the tumor. The success is explained at least in part by the hypermutability of these tumors, which makes them strongly immunogenic.[2,7] Though numerous types of immunotherapy have been tested, the most promising are the immune checkpoint inhibitors that have now been widely embraced (Figure 2).

These drugs are designed to target one of the mechanisms cancer cells use to subvert the immune response mounted against them. Immune checkpoints are receptors expressed on the surface of immune cells that coordinate the activation of T cells in response to specific antigens. Cancer cells manipulate their expression to suppress T-cell activity, effectively masking themselves from the immune system.[8]

The drug that launched the immune checkpoint

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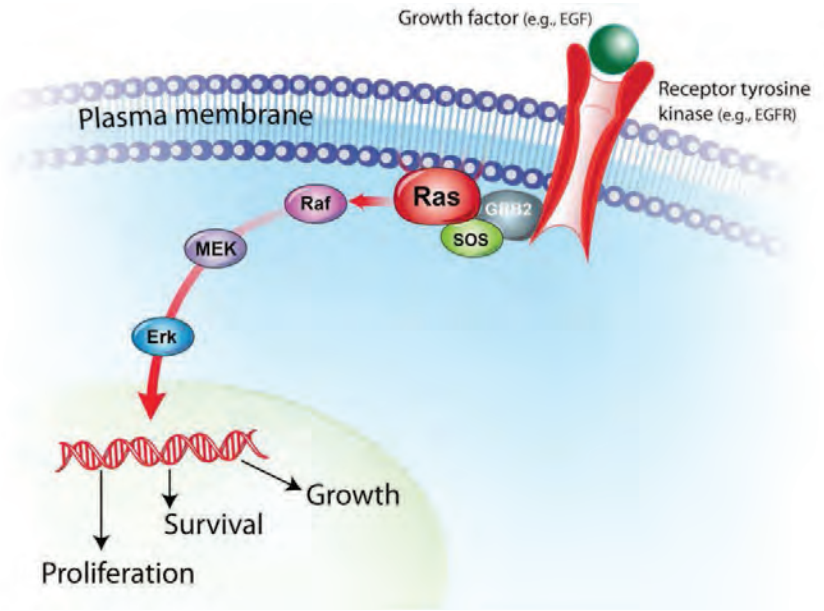

FIGURE 1 The mitogen-activated protein kinase pathway. The MAPK pathway converts extracellular signals into fundamental cellular processes, such as proliferation, growth and survival, through the activation of a series of kinases, culminating in the translocation of ERK1/2 to the nucleus, which stimulates the transcription of numerous gene targets involved in these cellular processes. This pathway is frequently deregulated in melanoma, most commonly via oncogenic mutations in the gene encoding the BRAF kinase. Reproduced with permission. Mochizuki H, Breen M. Vet Sci. 2015;2:231-245.

inhibitor era was ipilimumab, an inhibitor of cytotoxic T-lymphocyte antigen 4 (CTLA-4), which was awarded regulatory approval for the treatment of metastatic melanoma in 2011. Although the response rates were relatively low, they were astonishingly durable, with 60% of patients maintaining an objective response for at least 2 years.[9] That durability has been highlighted recently in long-term survival analyses. Pooled data from almost 2000 patients across different clinical trials demonstrated that more than 20% of patients survive 3 years after initiating treatment, and survival rates plateau after 2-3 years, with median 7-year overall survival (OS) of 17%, and some responses lasting up to 10 years. The plateau effect was observed in several different large-scale analyses and occurred regardless of the dose, the type of previous treatment received, or *BRAF* mutation status.[10,11]

Ipilimumab became the first check-

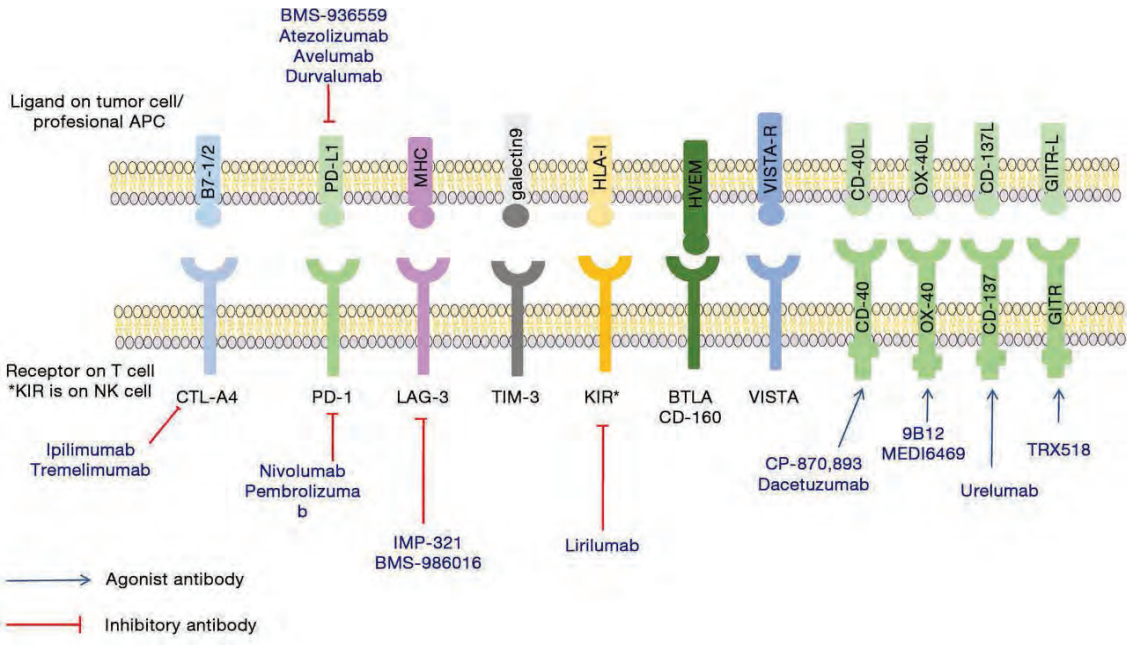

FIGURE 2 Immune checkpoints. The responses of T cells to foreign antigens are regulated by a balance between costimulatory and co-inhibitory signals that help to maintain self-tolerance. Inhibition of these immune checkpoints has been particularly successful in the treatment of melanoma, with the focus on two cell surface receptors – programmed cell death 1 (PD-1), and its ligands, and cytotoxic T-lymphocyte antigen 4 (CTLA-4). As understanding of immune checkpoint signaling has improved, the number of known T-cell modulators has grown and with it, the number of potential drug targets. These include lymphocyte activation gene (LAG3), T-cell immunoglobulin and mucin protein 3 (TIM3), and V-domain immunoglobulin suppressor of T-cell activation (VISTA). Reproduced with permission. Marquez-Rodas I, Cerezuela P, Soria A, et al. Ann Transl Med. 2015;3:267.

TABLE 1 A selection of therapies being evaluated in clinical trials for the treatment of melanoma

Agent	Manufacturer	Leading clinical trials (trial name)	Phase
MEK inhibitor			
Selumetinib	AstraZeneca	▪ Selumetinib + MEDI4736 in advanced solid tumors	1
Binimetinib (MEK162)	Array Biopharma	▪ Binimetinib + encorafenib in *BRAF*-mutant melanoma (COLUMBUS) ▪ Binimetinib vs dacarbazine in *NRAS*-mutant melanoma (NEMO) ▪ Binimetinib + encorafenib and a third agent (BKM120, LEE011, BGJ398, INC280) in *BRAF*-mutant melanoma (LOGIC-2)	3
Encorafenib (LGX818)	Array Biopharma	As above (COLUMBUS and LOGIC-2)	3
PI3K/Akt/mTOR inhibitors			
Buparlisib	Novartis	▪ Buparlisib monotherapy in patients with metastatic melanoma with brain metastases not eligible for surgery or radiosurgery	2
IPI-549	Infinity	▪ IPI-549 +/- pembrolizumab in advanced solid tumors	1
GSK2636771	GlaxoSmithKline	▪ GSK2636771 monotherapy in patients with advanced *PTEN*-deficient solid tumors	1/2
GSK2141795	GlaxoSmithKline	▪ Trametinib +/- GSK2141795 in metastatic uveal melanoma ▪ GSK2141795 + trametinib in *BRAF* wild-type melanoma ▪ GSK2141795 + dabrafenib and trametinib in *BRAF*-mutant melanoma	2
GDC-0994	Genentech	▪ GDC-0994 monotherapy in locally advanced or metastatic solid tumors ▪ GDC-0994 + cobimetinib in locally advanced or metastatic solid tumors	1
Everolimus (Affinitor)	Novartis	▪ Everolimus monotherapy in select patients with melanoma	2
Hsp90 inhibitors			
Onalespib (AT13387)	Astex	▪ AT13387 + dabrafenib and trametinib in recurrent melanoma	1
XL888	Exelixis	▪ XL888 + vemurafenib in *BRAF*-mutant melanoma ▪ XL888 + vemurafenib and cobimetinib in *BRAF*-mutant melanoma	1
CDK inhibitors			
Palbociclib (Ibrance)	Pfizer	▪ LEE011 + binimetinib in *NRAS*-mutant melanoma	1/2
SHR6390	Jiangsu HengRui	▪ SHR6390 monotherapy in Chinese patients with advanced melanoma	1
Durvalumab (MEDI4736)	MedImmune	▪ Durvalumab + trametinib +/- dabrafenib in metastatic melanoma ▪ IMCgp100 + durvalumab +/- tremelimumab in cutaneous melanoma ▪ Tremelimumab + durvalumab + polyICLC in advanced melanoma	1/2
KIT inhibitors			
Masitinib	AB Science	▪ Masitinib vs dacarbazine in *KIT*-mutant unresectable/metastatic melanoma	3
Regorafenib (Stivarga)	Bayer	▪ As second-line therapy in *KIT*-mutant metastatic melanoma	2
Imatinib (Gleevec)	Novartis	▪ Imatinib monotherapy in metastatic acral and mucosal melanoma	2
Sunitinib (Sutent)	Pfizer	▪ Sunitinib + nivolumab in metastatic *KIT*-mutant melanoma	2
Pexidartinib (PLX3397)	Plexxikon	▪ PLX3397 monotherapy in metastatic *KIT*-mutant acral and mucosal melanoma	2
Immune checkpoint inhibitors			
Tremelimumab	AstraZeneca	▪ Tremelimumab + MEDI3617 in unresectable stage III/IV melanoma ▪ Hypofractionated RT + durvalumab and tremelimumab in metastic melanoma ▪ Tremelimumab + durvalumab + polyICLC in advanced melanoma	1

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Agent	Manufacturer	Leading clinical trials (trial name)	Phase
Atezolizumab (MPDL3280A)	Genentech	▪ Atezolizumab + vemurafenib in BRAF-mutant melanoma ▪ Atezolizumab + CPI-444 in advanced cancers ▪ Atezolizumab monotherapy in advanced or metastatic solid tumors	1
Durvalumab (MEDI4736)	MedImmune	▪ Durvalumab + trametinib +/- dabrafenib in metastatic melanoma ▪ IMCgp100 + durvalumab +/- tremelimumab in cutaneous melanoma ▪ Tremelimumab + durvalumab + polyICLC in advanced melanoma	1/2
IMP321	Prima Biomed	▪ IMP321 + pembrolizumab in metastatic melanoma	1
LAG525	Novartis	▪ LAG525 +/- PDR001 in advanced solid tumors	1
MGA271	MacroGenics	▪ MGA271 monotherapy in refractory cancer ▪ MGA271 + ipilimumab in refractory cancer ▪ MGA271 + pembrolizumab in refractory cancer	1
Indoximod	NewLink Genetics	▪ Indoximod + ipilimumab/nivolumab/pembrolizumab in metastatic melanoma	1/2
Epacadostat	Incyte	▪ Epacadostat + vaccine therapy in advanced melanoma ▪ Epacadostat + durvalumab in advanced solid tumors ▪ Epacadostat + nivolumab in advanced cancers	2
TRX-518	GITR Inc.	▪ TRX518 in advanced melanoma	1
Vaccines			
Seviprotimut-L (POL-103A)	Polynoma	▪ Seviprotimut-L in postresection melanoma at high risk of recurrence	3
M-Vax	AVAX	▪ M-Vax + low-dose interleukin 2 in metastatic melanoma	3

RT, radiation therapy

point inhibitor approved in the adjuvant setting. The FDA approved the higher dose of 10 mg/kg on the basis of the EORTC 18071 trial, in which ipilimumab improved recurrence-free survival compared with placebo in patients who are at high risk of recurrence following surgery. The results of ongoing assessment of OS and the comparison of adjuvant nivolumab with interferon in the ECOG 1609 trial are eagerly awaited.[12]

A second CTLA4-targeting antibody, tremelimumab, has also been developed, but has not proved as successful. Despite promise in early clinical trials, it did not improve OS when compared with standard chemotherapy in a phase 3 trial.[13] Several clinical trials are ongoing, however, and a recent analysis of long-term survival in 143 patients treated with tremelimumab suggested a pattern of long-term survival similar to that of ipilimumab.[14]

Ipilimumab has largely been replaced in the front-line setting by antibodies that target a different immune checkpoint – the programmed cell death 1 (PD-1) receptor and its ligands, PD-L1 and PD-L2, largely as the result of the better safety profile and improved response rates observed with these drugs. Pembrolizumab and nivolumab were both originally approved in 2014 as second-line treatment options for patients who had progressed after treatment with ipilimumab or, in patients with *BRAF* mutations, after treatment with a BRAF inhibitor.[15,16]

In 2015, the FDA expanded the indications to allow their use in the front-line setting in *BRAF* wild-type patients, when both demonstrated improved efficacy compared with chemotherapy (in the nivolumab trial) and in a direct head-to-head comparison with ipilimumab in the case of pembrolizumab. The nivolumab indication was further expanded to include patients with *BRAF* mutations.[17-19]

More recently, researchers have begun to uncover more details of immune checkpoint signaling and the number of known modulators of T-cell function, and with it the number of potential drug targets, has grown. Drugs that target other inhibitory checkpoint pathways have been developed, but the alternative strategy of targeting stimulatory checkpoints, such as the lymphocyte activation gene (LAG3) and T-cell immunoglobulin and mucin protein 3 (TIM3), with agonists has also borne fruit, with numerous agents in the early stages of clinical testing (Table 2).[8]

Though immune checkpoint inhibition remains the most promising strategy, other ways of stimulating the immune system have been and continue to be evaluated. Therapeutic vaccines have been a major focus of research and a number of different approaches have been tested, including whole cell vaccines, dendritic cell vaccines, DNA vaccines, and peptide vaccines. Historically, vaccines have had limited efficacy in melanoma, however, a novel type of vaccine was recently approved by the FDA for the treatment of unre-

TABLE 2 Guideline-recommended front-line therapies for metastatic melanoma

Study	Drug	Manufacturer	Mechanism of action	Pivotal clinical trial data
Robert[19]	Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	*Ipilimumab-naïve* (n = 834) ORR, 34% (10 mg/kg every 2 wk mPFS, 5.5 mo (10 mg/kg every 2 wk)
Larkin[17] Robert[18]	Nivolumab (Opdivo)	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	*Previously untreated patients* (2 studies; n = 418 and n = 945) ORR, 34% and 40%, respectively mPFS, 5.1 mo and 6.9 mo
Hauschild[3]	Dabrafenib (Tafinlar)	GlaxoSmithKline	BRAF inhibitor	*Previously untreated patients* (n = 187) ORR, 52% mPFS, 5.1 mo
Chapman[4]	Vemurafenib (Zelboraf)	Genentech/ Daiichi Sankyo	BRAF inhibitor	*Previously untreated patients* (n = 675) ORR, 48.4% mPFS, 5.3 mo mOS, 13.6 mo
Larkin[17]	Nivolumab + ipilimumab	Bristol-Myers Squibb	Combination of PD-1-targeting and CTLA-4-targeting monoclonal antibodies with complementary and nonredundant mechanisms of action	*Previously untreated patients* (n = 945) ORR, 50% mPFS, 11.5 mo
Long[23]	Dabrafenib + trametinib	GlaxoSmithKline	Combination of BRAF inhibitor and MEK inhibitor targets 2 points in the MAPK pathway	*Previously untreated patients* (n = 162) ORR, 76%
Larkin[25]	Cobimetinib (Cotellic) + vemurafenib	Exelixis Genentech/ Daiichi Sankyo	Combination of BRAF inhibitor and MEK inhibitor targets 2 points in the MAPK pathway	*Previously untreated patients* (n = 495) ORR, 70% mPFS, 12.3 mo

CTLA-4, cytotoxic T-lymphocyte antigen-4; DRR, durable response rate; MAPK, mitogen-activated protein kinase; mPFS, median progression-free survival; mOS, median overall survival; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PFS, progression-free survival

sectable melanoma after initial surgery.

Talimogene laherparepvec (T-VEC) is an oncolytic herpes simplex virus type 1 (HSV-1)-based vaccine – the virus preferentially infects and destroys cancer cells by inducing immune responses against them and by directly disrupting metabolic processes. Among 436 patients, the durable response rate was higher in those receiving T-VEC than in those receiving granulocyte macrophage colony-stimulating factor (GM-CSF; 16.3% vs 2.1%, respectively). The primary survival analysis was recently published and demonstrated improved OS for T-VEC compared with GM-CSF (median OS, 23.3 vs 18.9 months).[20]

Combination therapy maintains momentum

Despite the significant advances in targeted and immune therapies, many patients still succumb to melanoma as a result of the clinical limitations of these agents. On the one hand, targeted therapy can lead to rapid responses in a significant proportion of patients, but these are generally short-lived responses and tumors inevitably regrow as patients develop resistance. Immunotherapy, on the other hand, can lead to long-term survival benefits, but only a minority of patients respond. The challenge now is to maintain momentum in melanoma research to not only develop new drugs, but to broaden the clinical impact of existing treatment modalities.

Significant research efforts have been focused on uncovering the mechanisms of resistance to targeted therapies. Best understood are changes that occur in the MAPK pathway that lead to reactivation of its effects, most commonly through alterations in the *BRAF* gene that prevent BRAF inhibitor binding. Alternatively, alterations in other components of the MAPK pathway, such as RAS or NF1, or activation of alternative pathways, including the phosphatidylinositol-3-kinase (PI3K) pathway, or of downstream effector proteins, most prominently the cyclin-dependent kinases (CDKs), can also drive resistance.[21]

A number of therapeutic strategies have been developed to help overcome resistance. Several next-generation, more potent and specific BRAF (eg, encorafenib) and MEK (eg, cobimetinib and binimetinib) inhibitors have been developed. The results from the ongoing phase 3 NEMO trial of binimetinib compared with dacarbazine in *NRAS*-mutant melanoma were recently reported, and the study met its primary endpoint of improved PFS (2.8 vs 1.5 months, respectively).[22] For the most part, however, these drugs are

being evaluated as part of combination regimens, which represents another important approach to overcoming resistance – by combined targeting of multiple points of the MAPK pathway or other related pathways.

Furthest along in clinical development is the combination of BRAF and MEK inhibitors. Trametinib and dabrafenib became the first FDA-approved combination for the treatment of metastatic melanoma in 2014, following the demonstration of an improvement in OS of more than 6 months in the phase 3 COMBI-d trial, compared with dabrafenib monotherapy.[23]

A second combination – cobimetinib and vemurafenib – was approved in 2015 on the basis of the phase 3 coBRIM trial. The combination improved PFS compared with vemurafenib alone (12.3 vs 7.2 months, respectively) and data presented at the 2015 Society for Melanoma Research Congress confirmed that OS was also improved (22.3 vs 17.4 months).[24,25]

The combination of encorafenib and binimetinib has recently demonstrated efficacy in the ongoing phase 2 LOGIC2 trial, according to results presented at the 2015 European Society of Clinical Oncology meeting. The response rate was 71% in previously untreated patients and 42% in patients who had received prior BRAF and/or MEK inhibitor therapy. Adverse events were mostly grade 1/2 and included diarrhea, nausea, fatigue, and retinopathy.[26] This combination is also being evaluated in the phase 3 COLUMBUS trial. Other targeted therapies have been shown to act synergistically with BRAF inhibitors, and combination approaches undergoing clinical testing include with both PI3K and CDK inhibitors.

Combination therapy has also been fruitful for improving outcomes with immune checkpoint inhibitors, although it comes at the price of increased cost and toxicity. Nivolumab and ipilimumab became the first combination immunotherapy to be awarded regulatory approval in 2015 and is approved for the same indications as nivolumab monotherapy. This combination has produced the highest response rates and OS to date in melanoma patients. In the CheckMate-069 study, it reduced the risk of progression or death by 60% compared with ipilimumab monotherapy, and the CheckMate-067 trial subsequently showed that those benefits were independent of *BRAF*-mutation status.[17]

Many other combinations are being evaluated in clinical trials, including pairing drugs with different mechanisms of action, such as targeted therapy in combination with immunotherapy. Some studies are even investigating the potential of triplet therapy, though the efficacy has to be carefully weighed against the potential for increased toxicity. The focus is on BRAF, MEK, and immune checkpoint drug combinations, but other rational groupings are being examined. In the second part of the LOGIC2 trial, the combination of encorafenib and binimetinib is being tested with other targeted drugs, including PI3K and CDK inhibitors, to determine potentially effective triplets.

A question of timing

BRAF, MEK, and immune checkpoint inhibitors, along with several combinations all now provide potential options for front-line therapy of patients with melanoma (Table 2). The treatment landscape has evolved faster than guideline recommendations and important questions remain to be answered. A key consideration is which of these drugs is the optimal front-line therapy and whether it matters in what order the drugs are administered as first-, second-, third-line, and so on, therapy.

Head-to-head comparisons have been limited thus far, and it is unclear which drugs should be the preferred choice in the front line. There are also no clear data about optimal sequencing – indeed, arguments can be made for and against each possible scenario. Findings from one study suggested that using targeted therapy first can negatively influence the response to an immune checkpoint inhibitor in the second-line, while the reverse is not true. Other findings have proposed that BRAF inhibitors help to reduce the size of the tumor, making subsequent immunotherapy more effective.[27-29]

The situation is likely to be more nuanced and will need to be tailored to each situation and patient. The current consensus is that patients with aggressive, high-volume, symptomatic disease are best treated with BRAF inhibitors first, whereas those with indolent, low-volume, asymptomatic disease could be treated with upfront immunotherapy, but the availability of combination therapy now further complicates the situation. Sequencing and comparative studies are ongoing that should help to provide clarification.

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