BRAF Inhibitors and the "Lazarus Syndrome"
An Update and Perspective

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Abstract

Identification of the BRAF mutation as an effective therapeutic target in approximately 50% of patients with metastatic melanoma has dramatically impacted the landscape of melanoma treatment. These therapies have not only impacted progression-free survival, but overall survival as well. They are, however, not without flaws. While these drugs have a very rapid onset of action and can quickly reverse a clinical decline of a patient with metastatic melanoma, their flaw lies in the limited duration of activity. Although there have been cases of long durable responses, the majority of tumors will develop resistance within months of treatment, and tumors will again progress. Combining dual targets such as BRAF and MEK inhibitors has improved the time to progression and survival, but has not demonstrated consistent long-term durability of responses. Continued research with multiple targeted therapies and targets with immunotherapy are under way. These agents have salvaged patients from impending death, which is revolutionary in the treatment of melanoma; however, this comes with new psychological impacts for the patient, family, and healthcare team, as patients are transiently resurrected but ultimately succumb to this disease within a few short months.

Key words: Metastatic melanoma, BRAF inhibitors, MEK inhibitors, targeted therapy

State of the Art Update

The identification of BRAF as a therapeutic target has changed the landscape of melanoma therapy and impacted many patient lives. Since this driver mutation is expressed in approximately 50% of all melanomas, many patients will receive therapeutic benefit from targeted agents. Response rates to these therapies range between 20% and 50%, which is truly impressive considering that chemotherapy response rates are less than 15%. These responses, however dramatic, have a tendency to be of limited duration, and therein lies our challenge.

Pathways for Melanoma Metastasis

The **Figure** shows pathways for melanoma metastasis. Vemurafenibis an oral, highly selective inhibitor of the oncogenic V^{600E} mutant BRAF kinase, which showed promising results in early clinical studies. In a dose-finding phase I trial, 11 of 16 patients (68%) with *BRAF*-mutated metastatic melanoma achieved a partial response (PR) and 4 patients had minor responses, leading to a progression-free survival (PFS) of 8 to 9 months.[1] A dose-extension phase I trial with 32 patients demonstrated an objective response rate of 81% (2 complete responses [CRs], 24 PRs). The median PFS among these patients was more than 7 months. Vemurafenib was generally well tolerated, with the most common side effects being rash, photosensitivity, arthralgia, and nausea. Of note, 31% of patients developed grade 3 squamous cell carcinoma (SCC), keratoacanthoma (KA) type. The median time to the appearance of a cutaneous SCC was 8 weeks with no reported involvement of other organs. Treatment with vemurafenib was not interrupted by the appearance of these skin lesions, and the majority of them were resected.[2]

The phase II trial of vemurafenib 960 mg orally twice daily administered to patients with previously treated melanoma (BRIM 2) demonstrated an overall survival (OS) of 16.9 months, which is unprecedented in melanoma trials.[3] The phase III trial (BRIM 3) comparing vemurafenib 960 mg orally twice daily to dacarbazine 1000 mg/m^2 IV in untreated patients with *BRAF* V^{600E}-mutant metastatic melanoma demonstrated improvement in PFS and OS for patients receiving vemurafenib. Due to the significant advantage of vemurafenib, the trial was amended to allow patients randomized to dacarbazine to crossover to the vemurafenib arm.[4]

The data from the previously treated patients in the phase II trials mirrored the results of the untreated patients in the phase III trial, confirming that order of therapy does not impact response rate or survival.[3] The robust data generated in this phase III trial was the basis for FDA approval of vemurafenib in patients with *BRAF* V^{600E}-mutated metastatic melanoma in 2011.[4]

Dabrafenib is another oral, highly potent, and selective BRAF $V^{600E/K/D}$ inhibitor that has shown similar effectiveness to vemurafenib. In a phase I/II study, treatment with dabrafenib 150

mg orally twice daily led to a decrease in FDG-PET metabolic uptake, with 11 of 14 patients (79%) with melanoma showing a decrease from baseline (range, 5% to 100%) and 18 of 30 patients (60%) demonstrating a greater than 20% tumor decrease by RECIST at first restaging (8-9 weeks).[5] Most of the side effects, including low-grade nausea, pyrexia, vomiting, fatigue, and headaches, were predominantly transient and mild in severity, making dabrafenib very well tolerated. Similar to vemurafenib, patients also experienced increased rates of low-grade SCC lesions; however, this side effect was found to be much less prevalent with dabrafenib. A phase III study of dabrafenib as initial therapy in patients with unresectable stage III or metastatic disease demonstrated improved PFS compared with chemotherapy.[6] Although confounded by crossover, this study was later updated to show improved OS with dabrafenib, 18.2 months versus 15.6 months.[7] Following these results, the FDA added dabrafenib to the melanoma treatment repertoire in 2013.

One of the factors that initially set dabrafenib apart from vemurafenib was the extensive data regarding its effects on brain metastases. Dabrafenib was first found to have activity in a phase I dose escalation trial, in which a small subgroup of 10 patients with brain metastases had a significant reduction in the size of their brain lesions.[8] This was further supported by a phase II multicenter, open-label trial that evaluated dabrafenib therapy in 172 patients with melanoma with both previously treated and untreated brain metastases. Dabrafenib therapy resulted in a 31% and 39% response rate, respectively.[9] Recently, similar outcomes were found with vemurafenib. A small open-label pilot study involving 24 patients with previously treated brain metastases showed a PR in 10 patients and stable disease in 9 patients with vemurafenib therapy.[10]

MEK Inhibitors

Trametinib is a potent and selective inhibitor of the MEK1/2 enzymes, which are found downstream from BRAF. A phase I clinical trial resulted in a response rate greater than 70% in patients with advanced melanoma with known *BRAF* mutations, including 1 patient who was previously treated with vemurafenib.[11] A phase II study further supported the activity of trametinib in patients with *BRAF*-mutated disease, with the greatest effect observed in patients who were BRAF-inhibitor naïve.[12] This was followed by a phase III open-label trial that compared chemotherapy (dacarbazine or paclitaxel) with trametinib and found improved median PFS and OS in the trametinib group; median PFS was 4.8 months in the trametinib group versus 1.5 months in the chemotherapy group.[13] The study revealed that even though 74% of patients had some tumor regression with trametinib, only 22% had a response that met RECIST. Although these results are not as robust as with BRAF inhibitors, it still provides significant benefit to patients when compared with previous chemotherapy treatment options. Similar to other targeted therapies, trametinib is well tolerated; however, the side effect profile is different from BRAF inhibitors and includes papulopustular rash, diarrhea, and peripheral edema.

Practical Application

- Differentiating between both BRAF inhibitors and MEK inhibitors
- Realizing the different potential adverse effects of BRAF, MEK, and dual-targeted therapy
- Understanding the benefits and limitations of targeted therapy

Dual Targeted Therapy

Emerging data at the time of these studies disappointingly revealed that the dramatic responses to single-agent BRAF inhibition were of limited duration. Research has shown none of the mechanisms of resistance to be through the MAPK pathway, making the idea of dual blockade an intuitive option to pursue. Dabrafenib and trametinib were combined in a phase I dose escalation trial, and the phase II recommended dosages of these medications were identified at 150 mg orally twice daily for dabrafenib and 2 mg orally daily for trametinib.[14]

The phase II trial published in 2012 demonstrated that this combination provided improved PFS and increased the proportion of patients alive at 1 year compared with dabrafenib monotherapy.[15] The subsequent phase III trial published in *The New*

FIGURE. Pathways For Melanoma Metastasis

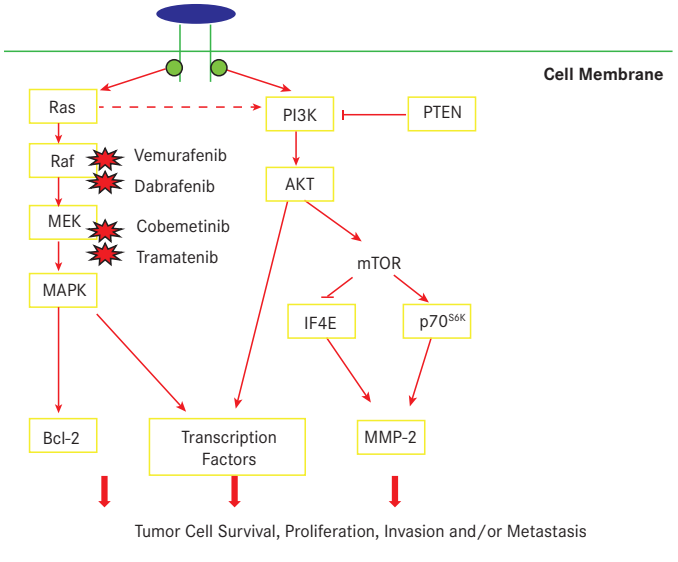

TABLE 1. Efficacy of Combination BRAF and MEK Inhibitors

Endpoint	Vemurafenib[17]	Vemurafenib and Cobimetinib[17]	Dabrafenib[16]	Dabrafenib and Tramatenib[16]
Objective response (%)	45	68	51	67
Complete response (%)	4	10	9	10
Median PFS (months)	6.2	9.9	8.8	9.3
Survival at 6 months (%)	NR	NR	77	85
Survival at 9 months (%)	73	81	NR	NR
AEs leading to treatment discontinuation (%)	12	13	5	9

AE indicates adverse event; NR, not reported; PFS, progression-free survival.

England Journal of Medicine in 2014 additionally demonstrated improved PFS in the combination group of 9.3 months versus 8.8 months. In addition to increased PFS, combination therapy significantly decreased the development of SCC.[16] There are, however, a small group of patients who will achieve complete or partial responses that are sustained for greater than 12 months. While these prolonged responses do occur, we cannot predict which patients will derive this benefit de novo. This long-term follow-up data of the phase I and II trials was recently presented at the 2014 American Society of Clinical Oncology Annual Meeting, with updated results showing a median OS of 23.8 months with the combination treatment.[25]

Concurrently, trials evaluating vemurafenib combined with cobimetinib were being conducted. A phase III trial published in *The New England Journal of Medicine* evaluated 495 patients who were randomly assigned to either the combination group or single-agent vemurafenib group. Results not only showed improved PFS, but revealed an OS benefit in the combination group. There was an 81% survival rate at 9 months in the combination group versus 73% in the single-agent group. Although the combination did show increased grade 3 adverse events, similar to previous combination studies, there was a significant decrease in SCC rates.[17] **Tables 1** and **2** detail single-agent versus dual-agent efficacy and toxicity.

Future Research on Combination Therapy

Although targeting the MAPK pathway is a promising new therapeutic approach for the treatment of melanoma, and treatment with selective BRAF and MEK inhibitors can induce high response rates, the limited duration of these responses in most patients, most likely because of emerging resistance to these inhibitors, represent a significant clinical challenge. Molecular redundancy, in part due to the existence of RAF isoforms and signaling through alternative oncogenic pathways such as PI3K/AKT/mTOR pathway,[18,19] receptor tyrosine kinase (PDGFR)-dependent pathway,[20] and COT (MAP3K8),[21] may provide the melanoma cells escape mechanisms to specific pathway inhibitors, and underscore their ability to adapt to pharmacologic challenges. In preclinical models, it has been reported that acquired resistance of melanoma cells to the BRAF inhibitors was associated with rebound activation of the RAF/MEK/ERK pathway.[19] In line with this finding, activating signals to downstream MEK/ERK has been shown to switch to ARAF[22] or CRAF[22,23] via N-RAS upregulation[20] to overcome the effect of BRAF inhibition. Moreover, the majority of melanoma cells harboring the *BRAF*^{V600E} mutation retained the wild-type *BRAF* allele, which could be rescued from the effects of BRAF knock-down by extracellular growth factors such as basic fibroblast growth factor, hepatocyte growth factor, or endothelin-1.[24] These mechanisms of resistance may not apply to immunotherapy with checkpoint inhibitors, which may lead to less frequent responses, but can be of longer duration compared with BRAF and MEK inhibition.

Continued research exploring multi-targeted inhibitors and immunotherapy is currently under way. These trials will explore important questions of drug sequencing and scheduling.

Clinical Perspective

Despite the majority of significant responses lasting several months, there is a subset of patients who experience what we have termed the "Lazarus Syndrome." I have coined this term because Lazarus was raised from the dead simply by God calling his name, and these drugs resurrect deathly ill patients with melanoma this quickly. It is an unbelievable feeling for the patient, their family, and the medical staff—a sense of vindication occurs, and patients and families stop planning funerals and start planning vacations. Unfortunately, some of the most miraculous responses in deathly ill patients are also the shortest-lived, with most responses lasting no more than months.

Clinical Cases of the "Lazarus Syndrome"

A 26-year-old Hispanic female with *BRAF*-mutated metastatic melanoma status post-4 cycles of ipilimumab with no response and rapid progression of disease presented to the clinic via ambulance transport on a stretcher. Physical examination demonstrated an extremely cachectic young woman in moderate distress, with multiple massive subcutaneous masses over trunk and extremities, severe abdominal distention due to liver metastases, bilateral 4+ pitting, and weeping lower-extremity edema and shallow breathing due to bilateral pleural effusions.

She was treated with vemurafenib 960 mg orally twice daily and was instructed to return for follow-up in 1 week.

Her response was dramatic. One week after initiating vemurafenib, her leg edema resolved, her abdomen was no longer distended, and she was eating normally. She walked into the clinic 1 week later modeling her size 4 jeans with a pair of platform shoes! It was a wonderfully emotional day for the patient, family, and staff.

She did extremely well for 8 weeks until she called to report a new "lump" on the right side of her neck, which appeared "overnight." It was the beginning of the end. Within 2 weeks, she became severely debilitated and bedridden with recurrent abdominal distention and leg edema. She died 10 weeks after that dramatic response.

Another such case was that of a 57-year-old male who developed a large necrotic mass on his right posterior shoulder. A biopsy was nondiagnostic due to the extensive necrosis. He had a distant history of stage I melanoma 12 years prior. Magnetic resonance imaging (MRI) demonstrated extensive necrotic tumors in the right shoulder, liver, lungs, subcutaneous nodes, and brain. His brain lesions were treated with gamma knife surgery. The pathology returned, identifying his tumor as a *BRAF*-mutated melanoma. On the same day the information regarding his pathology was revealed, he was hospitalized for progressive shortness of breath that required CPAP ventilation. Within 72 hours of starting vemurafenib, he was discharged from the ICU and was sent home 24 hours later. Within 1 week, he also had a notable improvement in the large, right-shoulder mass.

He did well for approximately 9 weeks, but required dose delays and dose reductions due to liver function test elevations. Reimaging demonstrated stable treated brain metastases and 75% reduction in his disease burden. Since he was having difficulty tolerating the targeted therapy but had dramatically improved clinically and was neurologically stable, his therapy was changed to immunotherapy with ipilumumab. He received 1 dose of ipilimumab and 14 days later developed mental status changes and headaches. MRI revealed innumerable, hemorrhagic brain metastases and leptomeningeal disease. Systemic scans also documented rapid progression in visceral organs.

He was immediately started on dabrafenib and trametinib, but had no response to treatment and became severely debilitated from the rapid progression of disease complicated by his whole-brain radiation therapy. He died 12 weeks after the initiation of dual-targeted therapy.

These cases represent the "roller coaster" that some patients and their families endure with this disease. They prepare for death, then a "miracle drug" salvages them and gives them hope that survival is possible. Unfortunately, far too often and far too quickly, this hope is crushed with the rapid progression of disease and demise of the patient. The mental anguish that patients, families, and healthcare professionals experience during this time needs to be acknowledged. This roller coaster of hope deceives patients, family members, and health care providers into believing that "everything is going to be okay." This period of hope must be tempered with the reality that it may only be a transient hiatus and that the patient is going to die from their disease. It is an area where psychosocial support can have a tremendous impact.

We must always keep in mind our limitations as well as the limitations of these drugs. These are life-changing drugs whose impact has been felt worldwide, but now we are faced with the challenge to make these responses durable. We have to approach our patients by hoping for the best, but always being prepared for the worst. Most important, we have to continue to enroll pa-

TABLE 2. Toxicity Associated With BRAF Inhibitors

Adverse Event (grade 3-4)	Vemurafenib[17]	Vemurafenib and Cobimetinib[17]	Dabrafenib[16]	Dabrafenib and Trametinib[16]
Pyrexia (%)	0	2	34	32
Fatigue (%)	3	4	2	6
Rash (%)	5	6	1	0
Peripheral edema (%)	0	0	1	1
Elevated LFT (%)	8	19	5	3
Myalgia/arthralgia (%)	5	2	1	0
SCC (%)	11	2	4	2
Retinopathy (%)	0	1	0	0
Photosensitivity (%)	0	2	0	0

LFT indicates liver function test; SCC, squamous cell carcinoma.

tients onto clinical trials so that we can continue to improve on our successes and work to resolve the "Lazarus Syndrome," and provide all of our patients with long-term durable responses. We have made huge strides in combating this disease, but more work still needs to be done.

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