# Guest Editorial

## New Melanoma Treatments: A Panacea or a Pandora's Box?

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The outlook for patients with stage IV melanoma has remained relatively unchanged[1] over the last 40 years, until this last year when ipilimumab and vemurafenib were introduced for patients with unresectable and metastatic melanoma. But are these wonder drugs all they promise to be? The answer is complex. According to the most recent Surveillance, Epidemiology, and End Results data from the National Cancer Institute, the fact remains that 1 in 51 men and women will be diagnosed with melanoma of the skin in their lifetime,[2] and of these patients, an estimated 9180 will die from the disease in 2012. In the past, treatments have increased periods of remission but none have increased overall survival, which is the most promising aspect of both new drugs. On the other hand, although the initial data from both medications are positive, the side effects are not as straightforward as nausea and vitiligo but rather immune-related adverse events that can result in death and the development of tumor resistance. To understand if these drugs represent a panacea or a Pandora's box, it is important to understand the mechanism of action of both.

Although tumors generally are considered antigenic, over time they learn how to evade immune control, resulting in cancer progression in a process known as immune editing. Limited success with high-dose IL-2, which has shown durable remission in 5% to 15% of metastatic melanoma patients,[3] prompted researchers for the last 2 decades to focus on modulating the immune system to combat disease rather than target the tumor itself.

In March 2011, the US Food and Drug Administration approved ipilimumab (Yervoy) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a human monoclonal antibody directed against cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which is a negative regulator of T-cell mediated immune response. Under normal circumstances, CTLA-4 maintains peripheral tolerance and prevents unwanted autoimmunity and tissue damage from unrestricted T-cell activation. In the case of tumors, although T cells are constantly being presented antigen, CTLA-4 also is upregulated, thus turning these activated T cells "off." The idea is that if the negative regulation of T cells by CTLA-4 can be interrupted, the primed T cells are then free to target the tumor. Ipilimumab disrupts CTLA-4 cell signaling by competitively binding with B7 ligand molecules, thus it potentiates T cells.

In the study published by Hodi et al[4] (N=676), ipilimumab showed an overall median survival of 10.1 months with an overall survival of 45.6%, 33.2%, and 23.5% at 12, 18, and 24 months, respectively. In addition, ipilimumab alone showed a 36% reduction in the risk for disease progression.[4] Interestingly, treatment responses were variable with some patients noticing results during treatment while others experienced disease progression before improvement and yet others had success after the treatment period.[5] Although the numbers are positive, in all of the clinical trials (phases 1–3) more than 2000 patients have been treated with ipilimumab and more than half did not respond.[6] In addition, one should not dismiss the fact that the medication is a T-cell potentiator. In suppressing CTLA-4, one is essentially allowing T cells free reign that can be seen in the side-effect profile, including vitiligo, hypothyroidism, adrenal insufficiency, hypophysitis, hepatitis, dermatitis (including toxic epidermal necrolysis), and colitis. Of the 14 deaths reported in the phase 3 trial, 7 were from these immune-related adverse events.[4] Still, when one considers that the overall median survival for patients with stage IV melanoma is less than a year, the data for ipilimumab gives hope where there previously was little. And more importantly, the success in melanoma opens the pathway for this medication to be used to combat other tumors such as non–small cell lung cancer.

The US Food and Drug Administration approved vemurafenib (Zelboraf) for the treatment of unresectable or metastatic melanoma in August 2011. The medication is a BRAF inhibitor indicated for patients with melanomas containing V600E mutations in the v-raf murine sarcoma viral oncogene homolog B1 gene, *BRAF*.[7] This mutation occurs in an estimated

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The author reports no conflict of interest.

50% of melanomas and vemurafenib blocks the function of the V600E-mutated BRAF protein. The medication was approved along with a test known as the cobas® 4800 BRAF V600 Mutation Test, which specifically tests for the mutation in biopsy specimens.

Normally, the mitogen-activated protein kinase pathway transmits signals from the cell surface to the nucleus. *BRAF* is a kinase that upregulates transcription factors when phosphorylated by adenosine triphosphate that lead to cellular proliferation. In melanomas with $BRAF^{V600E}$ point mutations, the tumor is able to evade negative feedback mechanisms and continues to activate antiapoptotic pathways. Vemurafenib works by binding to the adenosine triphosphate phosphorylation site on the mutated *BRAF* gene and halt the mitogen-activated protein kinase pathway itself.

In the BRIM-3 (BRAF Inhibitor in Melanoma 3) trial (N=2107), patients receiving vemurafenib had a 74% reduction in the risk for progression (or death) compared to patients receiving dacarbazine chemotherapy, which currently is a standard chemotherapeutic agent used for advanced melanoma. Mean time to progression was 5.3 months in the vemurafenib group compared to 1.6 months in the dacarbazine group. At 6 months, estimated overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group, though these estimates are unreliable as they were calculated at the 3-month interval analysis.[8]

The early data from the BRIM-3 trial were so convincing that the data safety monitoring board recommended that the trial be halted and all patients be given the option to switch to vemurafenib.[8] Recently published phase 2 data showed a response rate of 53% with median overall survival of 16 months.[9] Unfortunately, the tumor can be subject to drug resistance and regrowth is possible. Patients also may require dose modification due to toxicity. In the dermatology world, we have witnessed the eruption of keratoacanthomas in patients taking vemurafenib that then required surgical intervention.[10,11] Nonetheless, the ability to target the tumor based on genomic characteristics represents a milestone in oncologic treatment. The drug also is a testament to the collaborative effort underway in oncology, as it was only 9 years ago that the V600E mutation was even reported in melanoma.

However, the question still remains: Are these medications a panacea or a Pandora's box? The answer is yes for both, but I remain cautiously optimistic. Both drugs represent hope for patients with unresectable and metastatic melanoma, though there is a price. Although overall survival is improved with ipilimumab, the cost is unrestricted T-cell activation, which can lead to death if immune-related adverse events are not recognized and intervention provided early. With vemurafenib, numerous squamous cell carcinomas can occur and tumors can become resistant, which would then require high-dose IL-2 or perhaps ipilimumab (combination trials currently are underway). However, patients clearly are surviving longer. But for patients with stage IV disease, few other options exist. The science behind these medications is fascinating and heralds a new era in tailoring oncologic therapy. For patients with inoperable disease, the extra months and maybe more than a year (from what the latest data show[9]) can be priceless.

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