Melanoma — An Unlikely Poster Child for Personalized Cancer Therapy

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Personalized medicine has long been a mainstay of the treatment of localized melanoma, involving surgical decisions that are individualized on the basis of measured differences as small as 0.01 mm, as well as other biomarkers of metastatic potential, such as the presence of ulceration or mitoses.1 Once melanoma spreads beyond the regional nodes, however, the lack of validated molecular targets hampers efforts to individualize therapy.

In this issue of the Journal, Flaherty and co-workers2 provide clinical proof that mutations in the gene encoding the serine–threonine protein kinase B-RAF (BRAF) are bona fide therapeutic targets in melanoma. A remarkable 81% of patients whose melanomas had an activating mutation in BRAF had a response to treatment with the new BRAF kinase inhibitor PLX4032 in a multicenter, phase 1, dose-escalation trial. Responses to PLX4032 were dependent on mutation status, with no complete or partial responses (according to the Response Evaluation Criteria in Solid Tumors [RECIST]) seen in patients with melanomas carrying wild-type BRAF. These results represent a major breakthrough and provide proof of the principle that the treatment of metastatic melanoma can be individualized for a substantial percentage of patients.

Over the past decade, great strides have been made in unraveling the unique biology of melanoma, and the research investment is paying off. The discovery in 2002 that approximately 50% of human melanomas harbor an activating mutation in BRAF resulting in a substitution of glutamic acid for valine at amino acid 600 (the V600E mutation) first raised the possibility that melanoma may be amenable to targeted therapy.3 Since then, extensive preclinical data have validated the V600E mutation as an important therapeutic target in melanoma. In parallel studies, activating mutations in the human KIT gene (encoding the v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue) were identified in a small minority of melanomas, and there is now evidence that imatinib therapy leads to tumor regression in this group of patients.4 But the very low frequency of KIT mutations in melanoma limited the impact of this discovery.

BRAF is an upstream component of the growth-promoting mitogen-activated protein (MAP) kinase pathway, and it is known that melanoma cells containing mutant BRAF are dependent on MAP kinase signaling for their growth and survival.5 Flaherty and colleagues confirmed this in paired-biopsy studies and showed that PLX4032 effectively blocked intratumoral MAP kinase activity, leading to reduced expression of cyclin D1 and the proliferation marker Ki-67. Responses to PLX4032 occurred in patients who had previously received multiple chemotherapy regimens, as well as at organ sites such as bone and liver that are typically refractory. Overall, PLX4032 had moderate toxicity, with rash of grade 2 or 3, fatigue, and arthralgia being the major dose-limiting toxic effects. Somewhat unexpectedly, cutaneous squamous-cell carcinomas, mostly of the keratoacanthoma type, developed in a significant percentage of patients. Even after accounting for the facts that such tumors have been seen with the use of other kinase inhibitors and patients with one cu-
taneous neoplasm are at high risk of others, the incidence of this type of squamous-cell carcinoma was quite high.

PLX4032 is not the first agent aimed at BRAF to be evaluated for the treatment of melanoma. The most thoroughly investigated anti-BRAF agent to date is the multikinase inhibitor sorafenib (Nexavar). Unlike PLX4032, sorafenib has little single-agent activity in melanoma, and two large trials of sorafenib and chemotherapy, as compared with the same chemotherapy alone, showed no significant effect of the addition of the inhibitor (ClinicalTrials.gov numbers, NCT00111007 and NCT00110019). This led many to question the validity of BRAF as a target in melanoma, and had the more specific inhibitors of mutant BRAF been a clinical failure, the approach might well have been abandoned.

Instead, the future holds the promise that patients with metastatic melanoma will undergo screening, before the initiation of therapy, for the presence of mutations in BRAF, KIT, and probably other key genes. An important reason to confirm the BRAF mutational status of patients comes from the surprise finding that BRAF inhibitors paradoxically stimulate MAP kinase–mediated cell proliferation in cell lines lacking BRAF mutations. Mechanistically, this seems to occur because BRAF inhibitors have the ability to transactivate RAF1 (the v-raf-1 murine leukemia viral oncogene homologue 1, also known as CRAF), and this may well underlie the frequent development of keratoacanthomas in patients receiving PLX4032. Clearly, the administration of PLX4032 or similar BRAF inhibitors to patients whose melanomas do not carry BRAF mutations should be avoided for the time being.

The impressive responses seen in the study by Flaherty and colleagues do not necessarily persist for extended periods, although the median duration of progression-free survival was not yet reached at the time of publication and will probably exceed 7 months. This pattern of initial response and eventual resistance is similar to that seen with targeted therapy in other tumors. Although we currently know little about the mechanisms of resistance to PLX4032 therapy, Flaherty and colleagues did not find that any tumors had new or novel BRAF mutations (such as the “gate-keeper” mutations found in the epidermal growth factor receptor after erlotinib therapy). The mechanisms of PLX4032 resistance may be diverse; personalized therapy may equal personalized failure. Studies in vitro indicate that exogenous growth factors or cytokines rescue melanoma cells from apoptosis when BRAF is knocked down by small interfering RNA, and that resistance to BRAF inhibitors can be mediated through pathway switching, wherein MAP kinase signaling is routed from BRAF to RAF1 (Fig. 1A). Melanoma cells that are resistant to BRAF inhibitors seem to remain reliant on MAP kinase signaling, and this may direct future efforts: preclinical data already suggest that combined inhibition of BRAF and MEK (a component of the MAP kinase pathway) abrogates the emergence of resistance, and a clinical trial is currently under way to investigate this dual approach to treating melanoma (NCT01072175).

Although much attention has focused on acquired PLX4032 resistance, in the extension cohort in the study by Flaherty and colleagues, 19% of the patients with melanomas carrying the V600E BRAF mutation showed evidence of intrinsic resistance (i.e., did not have an objective response on the basis of RECIST criteria). A number of mechanisms probably underlie this intrinsic resistance; melanoma cells that either lack phosphatase and tensin homologue (PTEN) function or possess cyclin D1 amplification may be able to survive and proliferate when BRAF is inhibited (Fig. 1B). These and other “escape routes” could limit dual-inhibitor approaches as well; thus, even more novel strategies may be needed. The recent observation that ipilimumab, a monoclonal antibody directed against the inhibitory cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) molecule on T cells, improves survival in patients with metastatic melanoma suggests the possibility of combining CTLA4 blockade with BRAF inhibition. CTLA4 blockade also offers a viable alternative therapy for patients who do not have a defined mutation to target. Even for patients whose melanomas contain mutant BRAF, decisions about therapy with an inhibitor versus ipilimumab will have to be individualized, since the overall effect of PLX4032 therapy on survival is still undefined.

Nonetheless, the data provided by Flaherty and colleagues represent a major advance in the treatment of metastatic melanoma. But what’s next? How much can we improve on these results — especially in terms of extending the duration of dis-
ease control — through combination therapy or even by manipulating the dose and schedule of single-agent therapy? When should this therapy be moved to the adjuvant setting? How can we achieve similar success in treating patients with wild-type BRAF? The prospects for patients with metastatic melanoma have never been brighter, but the need for further progress through laboratory research and well-conducted clinical trials is as great as — or greater than — ever.

Disclosures forms provided by the authors are available with the full text of this article at NEJM.org.

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