Melanoma is the most aggressive of the common forms of skin cancer. A landmark event in this disease was the discovery of somatic mutations that cause substitutions at the V600 residue of the BRAF protein (BRAFV600 mutations). The BRAFV600 mutation is detected in 40% to 45% of cutaneous melanomas, making it the most common oncogenic event in this disease. Substitutions at the V600 position [most frequently glutamic acid (V600E) or lysine (V600K)] of the BRAF protein markedly increase its serine–threonine kinase activity, and melanomas with these mutations demonstrate constitutive activation of the RAS–RAF–MEK–ERK signaling pathway. Early preclinical studies confirmed that BRAFV600 mutations promote the growth and survival of human melanoma cells. The role and significance of the RAS–RAF–MEK–ERK signaling pathway in melanoma is reinforced by the presence of hotspot mutations in NRAS in approximately 20% of melanomas in a mutually exclusive pattern with BRAFV600 mutations. Recent whole-exome studies have demonstrated that virtually all cutaneous melanomas harbor at least one mutation predicted to activate BRAFV600 mutations. The relevance of these findings was bolstered by the identification of other somatic mutations in the extracellular domain of BRAF (BRAFex) that can drive melanoma cell growth and survival and contribute to resistance to BRAF inhibition (1).

The clinical management of melanoma is rapidly evolving due to the development of potent inhibitors of the RAS–RAF–MEK–ERK signaling pathway (reviewed in ref. 2). To date, three small-molecule inhibitors have been approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic melanoma with BRAFV600 mutations on the basis of positive phase III clinical trials. Vemurafenib (approved in 2011) and dabrafenib (approved in 2013) are BRAF inhibitors with a higher affinity for BRAF proteins with substitutions at the V600 site than wild-type BRAF proteins. Both vemurafenib and dabrafenib achieve Response Evaluation Criteria in Solid Tumors (RECIST) criteria clinical responses in >50% of patients with BRAFV600 mutations; many other patients achieve minor responses or stabilization of disease. Trametinib, an inhibitor of MAP–ERK kinase 1/2 (MEK1/2), was approved as a single-agent treatment for patients with metastatic melanoma with BRAFV600 mutations. Concurrent treatment with dabrafenib and trametinib was approved for these same patients in 2014.

Preclinical studies have demonstrated that vemurafenib and dabrafenib both potently inhibit mitogen-activated protein kinase (MAPK) pathway activation and in vivo growth in melanomas with BRAFV600 mutations. Surprisingly, preclinical studies also showed that these agents cause tumors with wild-type BRAF to grow faster in vitro and in vivo, particularly in tumors with activating RAS mutations (3). Molecular characterization of this phenomenon showed that this increased growth correlated with hyperactivation of MAPK pathway signaling due to the formation of heterodimers between wild-type BRAF proteins and other RAF kinases (CRAF and ARAF). These protein dimers interact in a multiprotein complex at the cell membrane with activated RAS proteins to activate MEK and ERK, thereby driving cellular proliferation. This unexpected effect of the BRAF inhibitors on the MAPK pathway in BRAF-wild-type cells has been termed paradoxical activation. Clinically, this finding has reinforced the critical need to test for the presence of BRAFV600 mutations before using vemurafenib or dabrafenib in patients with melanoma, as it suggests that these agents may accelerate tumor growth in the absence of such a mutation. In addition, paradoxical activation provides a mechanism and explanation for one of the most common and unexpected side effects of the mutant-selective BRAF inhibitors.

Up to 20% of patients with metastatic melanoma treated with vemurafenib or dabrafenib develop secondary malignancies, most commonly cutaneous squamous cell carcinomas or keratoacanthomas. Molecular characterization of these lesions demonstrated that the majority harbor alterations in RAS family genes and demonstrate hyperactivation of the RAS–RAF–MEK–ERK pathway (4). Preclinical studies showed that although the BRAF inhibitors alone were not sufficient to induce such lesions, treatment with these agents accelerated the growth of premalignant lesions that were already present. Concurrent treatment with a MEK inhibitor blocked the proliferation of these lesions, validating the role of paradoxical

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activation of the MAPK pathway in this phenomenon (4). This result added to the rationale for clinical testing of combined treatment with BRAF and MEK inhibitors, which was also supported by the identification of multiple acquired resistance mechanisms to BRAF inhibitors that result in reactivation of, and maintained dependence upon, MEK signaling (2). A subsequent randomized phase II study reported that combined treatment with dabrafenib and trametinib resulted in higher response rates, increased response duration, and reduced incidence of cutaneous squamous cell carcinomas and keratoacanthomas compared with treatment with dabrafenib alone (5).

In 2012, Callahan and colleagues (6) reported an interesting case of a patient with metastatic melanoma with a BRAF<sup>V600K</sup> mutation. Less than 1 month after starting treatment with vemurafenib, the patient presented with a noticeably smaller subcutaneous melanoma metastasis, but also with marked fatigue and new leukocytosis. Evaluation of the leukocytosis led to the diagnosis of a chronic myelomonocytic leukemia (CMML) with an activating NRAS<sup>G12R</sup> mutation. Consistent with the hypothesis that the proliferation of the leukemia was augmented by the vemurafenib treatment, withholding treatment quickly and markedly reduced the patient’s white blood cell (WBC) count. Providing more direct evidence, treatment with a BRAF inhibitor stimulated the MAPK pathway and increased colony formation efficiency of the leukemic cells in vitro. Further in vitro testing demonstrated that a MEK inhibitor reduced MAPK pathway activation and colony formation of the CMML cells and was able to prevent the increases induced by the BRAF inhibitor treatment. On the basis of these observations, the authors speculated that combined treatment with a BRAF inhibitor and a MEK inhibitor might control the patient’s leukemia and melanoma (6). However, the lack of a clinically available MEK inhibitor at that time precluded the testing of this hypothesis.

In this issue of Cancer Discovery, further follow-up is provided about the treatment and outcomes of this patient (7). Specifically, the effects of intermittent therapy with vemurafenib with cobimetinib, an experimental MEK1/2 inhibitor, in this same patient are described. The combination treatment was started after approximately 50 weeks of single-agent vemurafenib treatment. During the subsequent 35 weeks, the patient was monitored for symptoms, WBC and absolute monocyte counts, and radiographic changes in tumor size. In addition, circulating DNA was assessed for levels of BRAF<sup>V600K</sup> (from the melanoma) and NRAS<sup>G12R</sup> (from the leukemia) mutations after each demonstrated strong correlation with melanoma tumor volume and WBC count, respectively.

As presented in Fig. 1 in the article (7), the patient achieved durable control of both the melanoma and the CMML. The dosing and scheduling of vemurafenib and cobimetinib were adjusted several times over the course of treatment. Importantly, the control of the CMML demonstrated dose-dependence. When the cobimetinib dose was reduced from 40 mg to 20 mg daily, the total WBC and absolute monocyte counts both increased, but resumption of the 40-mg daily dose successfully reduced both measures. This effect is reminiscent of the relationship observed among dose, MAPK pathway inhibition, and antitumor activity observed in the phase I clinical trial of vemurafenib (8). As multiple combinations of BRAF and MEK inhibitors are now being used and tested in patients, this observation highlights that dose selection and adjustments likely make an important contribution to clinical outcomes, in addition to our improving understanding of molecular heterogeneity and resistance mechanisms.

The direct demonstration of the suppression of the NRAS-mutant CMML with vemurafenib and cobimetinib may also have implications for the treatment of this patient’s melanoma. Although BRAF<sup>V600E</sup> and hotspot NRAS mutations are virtually mutually exclusive in treatment-naïve melanomas, they are observed concurrently in approximately 20% of melanomas that have developed acquired resistance to single-agent BRAF inhibitor treatment. In contrast to the marked activity observed in BRAF inhibitor-naive patients, combination therapy with BRAF and MEK inhibitors achieves clinical responses in only 15% to 20% of patients with acquired resistance to single-agent BRAF inhibitors (2, 9). To date, there have been no reports describing the resistance mechanisms that were present in the patients that achieved these responses. The observed control of the NRAS-mutant leukemia in this patient supports the rationale to evaluate whether the presence of mutations in RAS family members predicts sensitivity to combined BRAF and MEK inhibition after progression on BRAF inhibitor monotherapy, as well as their prevalence in patients who progress after up-front treatment with the combination. Although it is intriguing to hypothesize that the durable control of stage IV melanoma achieved in this patient reflects the suppression of RAS-mediated resistance mechanisms, the patient’s treatment is also notable for the use of frequent drug holidays and a resulting intermittent dosing schedule. Recent preclinical studies suggest that such intermittent dosing may also be an effective strategy to prevent the onset of resistance to MAPK pathway inhibition (10). The continued melanoma control achieved by this patient suggests that clinical testing of this strategy is at least feasible, although results from additional patients are needed to make conclusions about its potential benefit.

The treatment of melanoma is evolving rapidly. After decades of discouraging results, investigators are now in the midst of an era in which exciting insights and new clinical strategies are emerging on a regular basis. Although many of the advances that have been made are attributable to the analyses of large randomized clinical trials, this case report demonstrates that careful study of even a single patient can also provide interesting and potentially important new information to drive further advances against this disease.

Disclosure of Potential Conflicts of Interest

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