Conjunctival Melanomas Harbor BRAF and NRAS Mutations—Response

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In our recently published study (1), we describe genetic similarities between conjunctival and cutaneous melanoma and propose that the treatment rationale for patients with metastasized conjunctival melanoma should be adapted to that for metastasized cutaneous melanoma. Weber and colleagues (2) responded to this, reporting that a BRAF V600E–mutant metastasized conjunctival melanoma patient treated with the BRAF inhibitor vemurafenib demonstrated only a mixed response, primarily with disease progression. Weber and colleagues interpret this finding as possible evidence that BRAF inhibitors may be less effective in metastasized conjunctival than cutaneous melanoma.

In contrast to their experience, we observed a partial response in a 43-year-old male patient with metastasized conjunctival melanoma treated with the BRAF inhibitor dabrafenib. The patient’s conjunctival melanoma, diagnosed in 2001, involved the caruncle of the right eye and had developed from a preexisting nevus. Initial treatment was surgical with adjuvant ruthenium therapy. Recurrences in 2003 and 2007 were treated surgically and by proton therapy. Metastatic disease with intramuscular and pulmonary metastasis was diagnosed in 2010. Disease progressed under dacarbazine (DTIC) chemotherapy. Having developed two small brain metastases (left frontal lobe <5 mm), the patient was admitted to the GlaxoSmithKline BRF113929 study and received dabrafenib (3). The patient’s tumor showed a partial response [Response Evaluation Criteria in Solid Tumors (RECIST) 1.0] (Fig. 1), most pronounced 4.5 months after therapy initiation with target lesions demonstrating a 61.6% cumulative tumor reduction. Dabrafenib was discontinued after 6 months when progressive disease with appearance of additional pulmonary and lymph node metastases were observed.

Although also only a single patient, our report clearly shows that BRAF inhibitors can be of value in the treatment of patients with metastasized BRAF V600–mutant conjunctival melanoma. Experience has taught us that not all patients with BRAF V600–mutant metastasized cutaneous melanoma respond to BRAF inhibitors (4, 5). As such, individual patients with metastatic conjunctival melanoma not responding to therapy is not that surprising and cannot necessarily be assumed to be representative of the overall situation in conjunctival melanoma.

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The genetic evidence we presented in our article strongly supports a link between conjunctival and cutaneous melanoma (1). In addition, our report on a patient with metastasized conjunctival melanoma who clearly profited from BRAF inhibitor therapy is further confirmation that patients with metastasized conjunctival melanoma can benefit from receiving treatment modalities available for metastasized cutaneous melanoma. Treating larger, representative numbers of patients (preferably in the context of prospective clinical trials) will be essential before allowing any objective assessment regarding which of the therapies available for metastasized cutaneous melanoma are also effective in metastasized conjunctival melanoma.
Disclosure of Potential Conflicts of Interest

B. Schilling has honoraria from the Speakers Bureau of Roche. E. Livi-
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Roche, Amgen, Boehringer-Ingelheim, Merck, Sharp & Dohme, and Merck
and has supplied expert testimony for Bristol-Myers Squibb. L. Zimmer
has honoraria from the Speakers Bureau of Bristol-Myers Squibb and Roche,
is a consultant/advisory board member of Bristol-Myers Squibb and Roche,
and has supplied expert testimony for Bristol-Myers Squibb and Roche. D.
Schadendorf has honoraria from the Speakers Bureau of Roche, Bristol-
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References

et al. Conjunctival melanomas harbor BRAF and NRAS mutations and
 copy number changes similar to cutaneous and mucosal melanomas.
2. Weber J, Smalley K, Sondak V, Geoffrey G. Conjunctival melanomas
 harbor BRAF and NRAS mutations—letter. Clin Cancer Res
3. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman
PB, et al. Dabrafenib in patients with V600Glu or V600Lys
BRAF-mutant melanoma metastatic to the brain (BREAK-MB):
 a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:
1087–95.
Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl
et al. Improved survival with vemurafenib in melanoma with BRAF V600E
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