Conjunctival malignant melanoma treated successfully with BRAF inhibitor: encorafenib plus binimetinib

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To the Editor:

Conjunctival malignant melanoma (MM) is very rare, and its prognosis is worse than that of the cutaneous form [1]. *BRAF* V600 mutations are present in 14-50% of cases of conjunctival MM, whereas *NRAS* and *KIT* mutations are present in 18% and 7%, respectively. On the other hand, *GNAQ* mutations, known to be associated with uveal melanoma, are almost absent [1].

An 89-year-old woman was admitted to our hospital because of recurrence of a conjunctival MM. Two years previously, she had developed MM on the right palpebral conjunctiva (**Figure 1A**) and this had been resected by an ophthalmologist. On admission, the tumor measured 30×25×30mm and had already invaded the eyeball (**Figure 1B**). Distant metastasis was also detected. The patient opted for pharmacological treatment and a *BRAF* gene test of the primary lesion demonstrated V600E mutation. Given her advanced age and deterioration of performance status related to fever, we started treatment with a combination of encorafenib (450mg once daily) plus binimetinib (45mg twice daily), which induces a low incidence of fever. The primary lesion decreased in size soon after the start of treatment and six months after the end of treatment, the tumor was further reduced (**Figure 1C**). Distant metastases shrank as well. Unfortunately, complete response of primary and metastatic lesions was not achieved. She had no adverse events during treatment and the dose of the drug continued unchanged. At the time of writing, one year after the start of treatment, both the primary and metastatic lesions remain at the same size as at 6 months.

Immune checkpoint inhibitors are one option for pharmacological treatment of melanoma, but they are known to be less effective against mucosal and uveal MM than against the cutaneous form [2]. Currently, there are no data on the efficacy of immune checkpoint inhibitors for treatment of

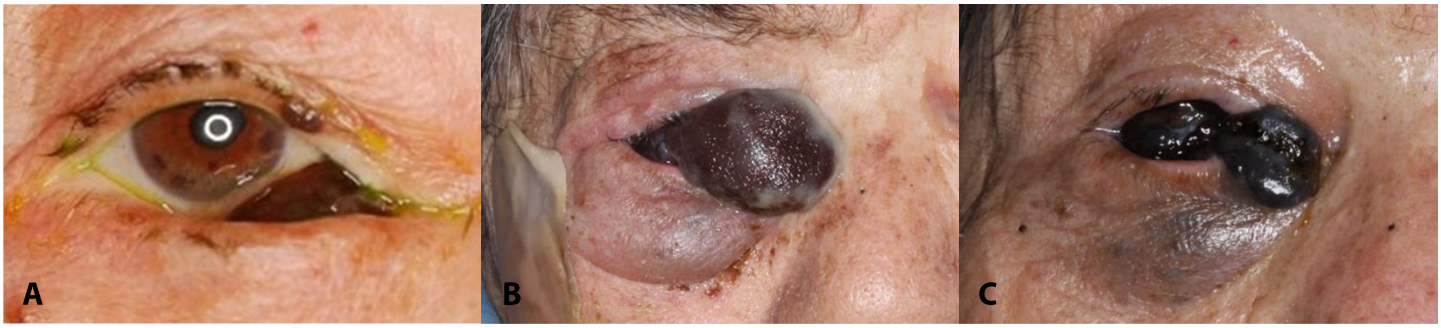

Figure 1. ***A)*** *The melanoma, originating from the palpebral conjunctiva.* ***B)*** *Two years after surgery, the recurrent lesion had spread from the palpebral conjunctiva to the parenchyma of the eye.* ***C)*** *Six months after the start of therapy with encorafenib plus binimetinib, the tumor had shrunk.*

conjunctival MM, which is a rare malignancy. However, one report has indicated that nivolumab, a monoclonal anti-PD1 antibody, elicited a positive response in a patient with conjunctival MM metastatic to the breast [3]. As conjunctival MM expresses PDL1, and thus appears to have greater genetic similarity to cutaneous MM than to uveal MM [2], there is a possibility that immune checkpoint inhibitor therapy might be effective.

There have been 9 reported cases of conjunctival MM for which BRAF inhibitors were used. The patients received only vemurafenib or dabrafenib plus trametinib and most responded to the treatment [4]. As the number of cases was small, no clear conclusion could be made as to whether the treatment response was comparable to that of cutaneous MM. This suggests that BRAF inhibitor therapy would be sufficiently effective against a wide range of cancers harboring *BRAF* mutations. However, it has been reported that colon carcinomas carrying the *BRAF* V600E mutation show a poor response to vemurafenib therapy [5]. Therefore, it is difficult to conclude whether BRAF inhibitors would be truly effective for conjunctival MM. The present case of conjunctival MM treated successfully with encorafenib plus binimetinib is the first of its kind to have been reported, to the best of our knowledge, and our findings are informative when considering the safety and efficacy of encorafenib plus binimetinib in this setting.

Potential conflicts of interest

The authors declare no conflicts of interest.

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