LETTER TO THE EDITOR

Comment on: Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib

To the Editor,

We are writing in response to a recent publication entitled “Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib” by Marks et al.¹

We describe a 9-year-old female child with an optic pathway glioma diagnosed by magnetic resonance imaging at 5 months of age after experiencing bilateral nystagmus. She underwent multiple lines of treatment including vincristine/carboplatin, weekly vinblastine, and bevacizumab/irinotecan. A biopsy at 5 years of age confirmed pilocytic astrocytoma with a BRAF V600E mutation and trametinib was initiated.

She was referred to our center at 7 years of age after failing trametinib therapy, with worsened imaging and vision noted on serial ophthalmological exams (Figure S1A-D).

She was trialed on vemurafenib but experienced generalized maculopapular rash after 2 weeks. Vemurafenib was held for 2 weeks and was re-administered with a dose reduction. Within 3 h of administration, the patient again experienced a full body rash with intense pruritus. Due to the possibility of an anaphylactic reaction occurring with further administrations, vemurafenib was permanently discontinued.

We formulated a desensitization plan using dabrafenib at 35% of recommended dosing in combination with trametinib (Table 1) after review of literature suggested lower incidence of skin toxicity with combination therapy.¹⁻⁴ No adverse events were observed and dabrafenib was slowly escalated over 3 weeks without the need of premedications. Both medications continue to be well tolerated, with imaging and visual improvements, now 18 months into therapy (Figure S1E-G).

BRAF inhibitors were originally approved to treat melanomas with the BRAF V600E mutation after demonstrating improved survival in patients with unresectable or metastatic melanoma.⁵,⁶ BRAF V600E mutations occur in 5-16% of pediatric patients with pilocytic astrocytoma, the most common type of pediatric brain tumor.⁷ This alteration is associated with high recurrence rates, despite conventional chemotherapy, and poor progression-free survival.⁸⁻¹⁰ BRAF V600E inhibitors not only produce dramatic imaging responses but also may halt or reverse tumor-induced functional impairments.¹¹,¹² Despite the promising efficacy of BRAF inhibitors in a variety of BRAF-mutant cancers, dabrafenib or vemurafenib frequently causes intolerable adverse effects, such as severe cutaneous reactions.⁵ Combination therapy with MEK inhibitors, such as trametinib or cobimetinib, increase progression-free survival and overall survival by decreasing resistance and cutaneous reactions in patients with melanoma.¹,¹³⁻¹⁵ To date, only one pediatric publication describes tolerance and response to dabrafenib and trametinib combination therapy in a patient with previous vemurafenib intolerance.¹

Radiation therapy was considered, but due to her young age and the potential for long-term neurocognitive and endocrine sequelae, a desensitization approach with dabrafenib with addition of trametinib was pursued to prevent recurring cutaneous or more severe allergic reactions. She continues to experience a positive tumor response and improved vision without further reactions. In conclusion, our report endorses the approach taken by Marks et al¹ supporting the use of an alternate BRAF inhibitor with concurrent MEK inhibitor in the presence of severe hypersensitivity to vemurafenib and adds to the limited literature on this topic.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ETHICAL STATEMENT
Informed consent was obtained from the patient.

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Melissa S. Bourque¹
Marta Salek²
Noah D. Sabin³
Meredith Canale⁴
Santhosh A. Upadhyaya⁴

¹ Department of Pharmaceutical Services, St. Jude Children’s Research Hospital, Memphis, Tennessee
² Department of Hematology/Oncology, St. Jude Children’s Research Hospital, Memphis, Tennessee

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**TABLE 1**

Clinical summary including treatment, dabrafenib desensitization and dose escalation schedule, and serial visual assessment findings

<table>
<thead>
<tr>
<th>Age(years, months)</th>
<th>Treatment</th>
<th>Desensitization</th>
<th>Dabrafenib dose</th>
<th>OD near</th>
<th>OD distance</th>
<th>OS near</th>
<th>OS distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4, 0</td>
<td>Bevacizumab and irinotecan</td>
<td>–</td>
<td>20/70</td>
<td>20/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6, 0</td>
<td>Trametinib</td>
<td>–</td>
<td>20/100</td>
<td>20/125</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7, 7</td>
<td>Single-agent vemurafenib</td>
<td>–</td>
<td>20/100</td>
<td>20/200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7, 9</td>
<td>Dabrafenib desensitization initiated and trametinib started*</td>
<td>1</td>
<td>2 mg/kg QD</td>
<td>20/100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3 mg/kg QD</td>
<td>20/100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2 mg/kg BID</td>
<td>20/125</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>5 mg/kg/day (dosed twice daily)</td>
<td>20/100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>Successfully tolerated desensitization</td>
<td>20/100</td>
<td></td>
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</tr>
</tbody>
</table>

**Note:** The recommended pediatric dose is 5.25 mg/kg/day (orally administered, divided twice daily). The patient received trametinib at the recommended pediatric dose of 0.025 mg/kg (orally administered, daily).

**Abbreviations:** AM, daily dose in the morning; BID, twice daily; OD, oculus dexter (i.e., right eye); OS, oculus sinister (i.e., left eye); PM, daily dose in the evening.

**References**


**Correspondence**

Melissa S. Bourque, Department of Pharmaceutical Services, St. Jude Children’s Research Hospital, 262 Danny Thomas Place, Mail Stop 150, Memphis, TN 38105.

Email: Melissa.Bourque@stjude.org

Funding: NIH; Grant Number: CA21765; ALSAC.

**ORCID**

Melissa S. Bourque [https://orcid.org/0000-0003-4741-6102](https://orcid.org/0000-0003-4741-6102)

Santhosh A. Upadhyaya [https://orcid.org/0000-0001-6101-149X](https://orcid.org/0000-0001-6101-149X)


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