

## Peer Review File

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### Reviewer A

The commentary gives an overview over the current knowledge on pediatric LGG and the challenges / sequelae / side effects of therapy children have to face with conventional (chemo)therapy. It then refers to molecular data that we now know on this single pathway disease and the influence of MEK/BRAF/CRAF inhibition as "logical" targeted therapies. Comparative data on other entities (melanoma) is given as well. In the next part the study of Bouffet et al is summarized and the question on what we can learn from the data is asked. The authors correctly state that BRAF inhibition enhances the efficacy of MEK inhibition in BRAF V600E mutant LGG but the proof of the vice versa (Tram enhancing the efficacy of BRAF inhibition) is missing. The difficulty in how defining responses in the long-term disease of inoperable LGG is referred to, a problem pediatric neurooncologist know well. The study comparing trametinib + dabrafenib to chemotherapy in newly diagnosed BRAF V600E mutant LGG that was published by Bouffet et al in 2023 in the NEJM is referred to, the paper is highly acknowledged in the community. In Europe final approval for the drugs in pediatric BRAF V600E mutant LGG is still pending. Even with targeted therapy we do not expect cure our patients from inoperable pediatric LGG but it seems the best therapy available, less toxic, but more effective than the chemotherapy we have given for decades. Still we do not know enough about longterm toxicities with these drugs nor on scenarios on how to stop therapy in young adults (tumor senescence occurs) - so there are more questions to come, as they came with imatinib therapy in CML. The commentary broadens the perspective on targeted therapy in pediatric V600E mutant LGG.

**Response: No changes were recommended**

### Reviewer B

This manuscript is well-written and, in my opinion, acceptable in its current format. I only found an extra space on line 126, that needs to be fixed.

Line 16 - Needs an extra space between "system" and [1]

Line 30 – II should be 2 "(grades 1 and 2)"

**Response: 1. I could not identify the 'extra space' mentioned on line 126**

**2. Line 16, space between 'system and [1]' added; 3. II changed to 2 as requested.**