

# Response to: Correspondence on "G-CSF as a suitable alternative to GM-CSF to boost dinutuximab-mediated neutrophil cytotoxicity in neuroblastoma treatment" by Mora *et al*

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#### Correspondence to

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Dear Editor,

We appreciate the interest of Dr Mora and Dr Chantada<sup>1</sup> in our recently published work proposing granulocyte colony-stimulating factor (G-CSF) as a suitable alternative to improve antibody treatment of patients with high-risk neuroblastoma.<sup>2</sup> The authors strongly advocate finding ways to increase accessibility of granulocyte-monocyte colony-stimulating factor (GM-CSF, sargramostim), used in combination with dinutuximab in North America, also in countries where this treatment is currently not available. We fully agree that all relevant stakeholders should participate in finding a permanent solution to prevent potentially suboptimal treatment of patients with high-risk neuroblastoma in the absence of sargramostim. Part of this solution might be identification of another suitable cytokine with potential to increase neutrophil-mediated killing of neuroblastoma cells as the inaccessibility of sargramostim may remain a problem in the future.

As neutrophils have been shown to be the main effector cells in the destruction of dinutuximab-opsonized GD2<sup>+</sup> cells,<sup>3</sup> the choice for a cytokine that increases production, release, and activation state of these immune cells is a highly reasonable one. Dr Mora and Dr Chantada urge for caution in using G-CSF as an alternative as this cytokine is not interchangeable with GM-CSF and may pose safety risks as previously suggested.<sup>4-6</sup> We agree that G-CSF cannot fully recapitulate the biological properties of GM-CSF, but it is in our opinion the next closest alternative and deserves proper evaluation in follow-up clinical studies. Two of the studies reporting detrimental effects of G-CSF in patients with

neuroblastoma were published by the same group<sup>5,6</sup> and suggest caution in administering G-CSF during chemotherapy cycles. These findings triggered opposed responses in the clinical field.<sup>7</sup> The main argument was that concentrations of G-CSF used in preclinical studies were much higher than equivalent dosages used in patients. Also, use of G-CSF to support intensive induction chemotherapy regimens had been shown to be safe and not affecting overall tumor response to therapy.<sup>7</sup> We have shown in our study that long-term in vitro exposure to G-CSF in high concentrations does not alter the phenotype of neuroblastoma cell lines and primary cells, nor their sensitivity to dinutuximab-mediated killing, further suggesting safety of such a treatment for patients with neuroblastoma.

As proposed in our study, a thorough clinical evaluation of safety, clinical efficacy and effect on overall survival of G-CSF in combination with dinutuximab in patients with high-risk neuroblastoma should be performed, ideally in a randomized and multicenter clinical trial.

Sincerely,

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