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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Dear Editor,

We appreciate the interest of Dr Mora and Dr Chantada¹ 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.² 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⁺ cells,³ 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.⁴⁻⁶ 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^{5,6} and suggest caution in administering G-CSF during chemotherapy cycles. These findings triggered opposed responses in the clinical field.⁷ 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.⁷ 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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REFERENCES

- 1 Mora J, Chantada GL. Correspondence on "G-CSF as a suitable alternative to GM-CSF to boost dinutuximab-mediated neutrophil cytotoxicity in neuroblastoma treatment" by Martinez Sanz *et al.* *J Immunother Cancer* 2021. doi:10.1136/jitc-2021-003751
- 2 Martinez Sanz P, van Rees DJ, van Zogchel LMJ, *et al.* G-CSF as a suitable alternative to GM-CSF to boost dinutuximab-mediated neutrophil cytotoxicity in neuroblastoma treatment. *J Immunother Cancer* 2021;9:e002259.
- 3 Barker E, Mueller BM, Handgretinger R, *et al.* Effect of a chimeric anti-ganglioside GD2 antibody on cell-mediated lysis of human neuroblastoma cells. *Cancer Res* 1991;51:144–9.
- 4 Gay AN, Chang S, Rutland L, *et al.* Granulocyte colony stimulating factor alters the phenotype of neuroblastoma cells: implications for disease-free survival of high-risk patients. *J Pediatr Surg* 2008;43:837–42.
- 5 Hsu DM, Agarwal S, Benham A, *et al.* G-CSF receptor positive neuroblastoma subpopulations are enriched in chemotherapy-resistant or relapsed tumors and are highly tumorigenic. *Cancer Res* 2013;73:4134–46.
- 6 Agarwal S, Lakoma A, Chen Z, *et al.* G-CSF promotes neuroblastoma tumorigenicity and metastasis via STAT3-dependent cancer stem cell activation. *Cancer Res* 2015;75:2566–79.
- 7 Maris JM, Healy J, Park J, *et al.* G-CSF is a cancer stem cell-specific growth Factor-Letter. *Cancer Res* 2015;75:3991.