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Response to comment on: "Immune checkpoint therapy in pediatric and adolescent lymphomas".

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MSC conceptualized and supervised the response. *DJH* and *ACX* wrote the response.

Disclosures

DJH is a consultant for both Merck Pediatric Hematology and Oncology Scientific Advisory Committee and Ymabs (SERB) Radiopharmaceutical Protocol Steering Committee. MSC serves as a consultant for Jazz Pharmaceuticals and Abbvie; Speakers Bureau for Jazz Pharmaceuticals and Amgen, Inc.; and receives research funding from Jazz Pharmaceuticals, Abbvie, Merck, Miltenyi Biotec, Servier, Omeros, and Janssen.

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To the Editor,

We thank Jaing and Chen for their thoughtful comments(1) regarding our recent review, Immune checkpoint therapy in pediatric and adolescent lymphomas, published in *Haematologica*(2), and for highlighting important clinical and biological nuances.

We strongly agree with the author's perspective on immune checkpoint blockade in pediatric lymphoma. As these agents are increasingly incorporated into earlier lines of therapy, understanding how prior checkpoint exposure effects subsequent allogeneic immunity, graft failure, and graft-versus-host disease remains a key consideration for prospective pediatric studies conducted before AlloHSCT. In addition to the relevant reports highlighted by Jaing and Chen, Perales et al reported for the CIBMTR and EBMT a retrospective review of the effect of prior checkpoint blockade inhibitor (CPI) before AlloHSCT in patients with classical Hodgkin Lymphoma (cHL).(3) Approximately 600 patients with cHL received CPI prior to AlloHSCT. While there was a notable increase of grade II-IV AGVHD in patients who received CPI prior to AlloHSCT (HR 1.26) ($p=0.02$), this did not result in decreased overall survival. Importantly, the use of CPI prior to AlloHSCT increased non-relapse mortality but also resulted in a significant improvement of PFS ($p=0.03$) and a significantly lower risk of relapse ($p<0.001$). This data in cHL suggests that CPI prior to AlloHSCT may lead to both increased risk of AGVHD but also increased graft vs lymphoma effect.

We also fully agree with the authors that aggressive NK-cell leukemia (ANKL) and extranodal NK/T-cell lymphoma (ENKTL) remain distinct clinicopathological entities under current World Health Organization (WHO) and International Consensus Classification (ICC) classifications.(4, 5) Moreover, we appreciate the opportunity to clarify that in our original review, the term "aggressive NK-cell leukemia/lymphoma" was inadvertently used synonymously with "NK-cell leukemia/lymphoma".

Given the extreme rarity of ANKL and the profound lack of prospective studies dedicated strictly to this entity, initial systemic management of ANKL frequently mirrors that of advanced ENKTL, utilizing L-asparaginase-based combination chemotherapy regimens followed by prompt consolidation with allogeneic hematopoietic stem cell transplantation (allo-SCT).(6) However, despite these shared therapeutic strategies, important distinctions lie in their precise genomic landscapes. ANKL studies describe recurrent *overlapping* abnormalities in JAK-STAT signaling with MYC expression and transcriptional activities, rather than reproducible TSIM, MB or HEA ENKTL genomic clusters. For instance, an integrated genomic analysis of ANKL patient samples identified a great proportion of *JAK-STAT* mutations (48%), followed by *TP53* (34%), *TET2* (28%), *CREBBP* (21%) and *MLL2/KMT2D* (21%).(7) Accordingly, describing ANKL with "TSIM-like or MB-like biological features" will serve strictly as a descriptive research analogy rather than a recognized subtype diagnosis. While clinical treatment protocols currently overlap out of therapeutic necessity, ENKTL-derived subtype frequencies, prognostic associations, and targeted treatment predictions (such as response to PD-1 blockade post L-

asparaginase failure) should not be transferred to ANKL without formal prospective validation, remaining hypothesis-generating, as well stated by Jaing and Chen.

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