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Different definitions in intention-to-treat analysis for chimeric antigen receptor T-cell therapy depend on research scope

Blood Cancer Journal (2025)15:33 ; https://doi.org/10.1038/s41408-025-01246-4

Dear Editor,

Milrod et al. have reported some interesting insights that can fuel the debate on how to analyze the data of patients who undertake the CAR T pathway starting from our recently published article [1, 2].

We would like first of all to respond to the two points raised by the Authors and then add considerations regarding the analysis intention-to-treat (ITT) to discuss that the type of research is conducted and its corresponding purpose bring several and different important messages.

Regarding the use of bridging therapy (BT), we have performed metaregression, which led to the conclusion that rate of patients who underwent BT had a significant influence on complete response rate in both per protocol (PP) and ITT populations. In particular, a negative value of the coefficient b indicating that when the percentage of patients who underwent BT increase, the response rate decreases by about 60% thus BT could be a potential driver of the observed differences. Adjusting analyses for BT was out of our scope as we aimed at reporting what actually occurs in the everyday clinical practice. Nevertheless, in our opinion there other hidden/unknown variables that can influence different efficacy and survival outcomes and research must continue in this direction.

This brings us to the second point of discussion, i.e the starting point of the therapeutic pathway of CAR T -cell must be defined on the basis of the scope of the research. For efficacy/effectiveness we proposed the date of leukapheresis as well as for the economic burden for hospitals [3].

The Authors suggested that ITT definition could begin earlier such as the time of referral but we think this time is not suitable for efficacy considerations. On contrary we think time to referral should be considered for other scope such as the identification of barriers to access to this kind of therapy and to assess the lack of a shared consensus both for referral and patients' eligibility assessment.

To investigate barriers in the real-world other factors must be considered e.g. poor understanding of the therapy or lack of care giver support. This kind of investigation has the aim to facilitate more eligible patients in receiving CAR T. In fact, other definitions were set as time to "decision-to-vein" and "vein-to-vein" [4]. To date, this two times can have an impact also on patients survivals [4].

This is the first study that analyzed and compared the benefit of CAR T-cell in real-world in both ITT and PP modalities on the same datasets, considering also patients who started CAR T pathway without reaching infusion timepoint. We reiterate that our main message is to always conduct analyses in both ITT and PP modalities as each brings valuable information and conclusions that also arise from their comparison.

The debate should continue to improve therapy and disease national registries, patient management at both clinical and logistics level and to provide payers, clinicians, patients and national health services useful insights as CAR T-cell therapy indications are rapidly increasing. The starting point for the analyses must be shared with the different actors of the therapeutic pathway and chosen on the basis of the key messages.

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AUTHOR CONTRIBUTIONS

LA and PLZ conceived the Letter. LA and BC co-wrote the paper draft. All authors wrote and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Received: 23 January 2025 Revised: 11 February 2025 Accepted: 27 February 2025
Published online: 07 March 2025