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Reply to comment by Arber C, et al. on: Real-world expenditures and survival time after CAR-T treatment for large B-cell lymphoma in Switzerland

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We would like to thank the Swiss Blood Stem Cell Transplant and Cellular Therapies (SBST) group for their thoughtful comments [1], and for the valuable time and effort spent evaluating our article describing healthcare expenditure after CAR-T therapies in Switzerland.

We would also like to thank the editor for the opportunity to respond to the concerns raised in the letter.

" These data include only a fraction of patients who underwent CAR-T therapy for relapsed or refractory large B-cell lymphoma (LBCL) in Switzerland as their third-line treatment between October 2018 and June 2021."

Response: The participating companies provided mandatory insurance to approximately 78% of Swiss residents in 2021. While this is a sizeable fraction of the market, a larger sample size or an analysis of the total population would always be better. We are not aware of evidence showing that our sample is a poor representation of the total population treated with CAR-T cells for LBCL in Switzerland, which if true would represent a potential source of bias in the results. Evidence based on the SBST registry [2] reports the following CAR-T cell therapy recipient numbers: 24 in 2019, 48 in 2020, and 49 in 2021 ([2], table 61, page 203). The estimated recipient number until our treatment identification cut-off (June 2021) can be calculated as 24 + 48 + (0.5 * 49) = 96.5. Our sample represents 84% (81/96.5) of the estimated recipients.

"Insurance claim databases lack important data granularity and critical medical information."

Response: While this statement is correct, insurance claim databases are the only comprehensive source of healthcare expenditure data, combining resource utilisation data across various healthcare settings. There is no single dataset combining all relevant clinical and economic data of Swiss patients. It is essential to publish diverse data analyses, each emphasising distinct aspects, to achieve a more comprehensive understanding of the subject.

"Trottmann et al. indicate that CAR-T therapy is considered a "one and done" treatment approach. With a failure rate of 50-60% in third-line treatment, this seems unrealistic and requires rethinking at the level of insurance companies. In addition, the majority of patients require relatively intense monitoring and supportive care measures in the months following CAR-T therapy, especially those who do not achieve long-lasting responses."

Response: The SBST group raises a very important point. The value message of CAR-T therapies hinges on long-term patient benefits and cost-offset effects. The latter arise from the elimination of the need for additional treatment regimens following successful curative therapy. The observation of a 50–60% failure rate and intensive monitoring and supportive care measures after CAR-T therapy is in line with our findings of high treatment costs after administration. These aspects are important for price negotiations considering the global trend towards high prices for new treatments. This challenge extends beyond CAR-T cell therapies. Rather, potential cost-offset effects are commonly used by manufacturers to justify high prices for new therapies, yet the extent of these effects remains highly uncertain. Swiss health insurers encourage public debate on this societal challenge, welcoming fresh ideas.

"Trottmann et al. also compared CAR-T-related healthcare expenditure with previously published healthcare expenditure for lymphoma patients in their last year of treatment. The comparison to analyses published in 2011 and 2014 does not seem pertinent. At the time, most novel treatment regimens and immunotherapies that are now part of standard care were unavailable. Thus, those cost estimates do not reflect current practice and are misleading."

Response: The SBST group raises a very important point. Comparisons to historical data may not be accurate in a rapidly evolving medical field. Still, such comparisons are frequently found in the literature (see, for example, references [3] and [4]). At the time of our study, there was no established standard of care for patients after CAR-T therapy. It is unclear to us what a better comparison would have been, or whether cost data on the most novel treatments would have been available. It is important to keep in mind that prices of new therapies are confidential in many countries.

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"SBST fully recognises that beyond clinical effectiveness, costs and benefits are an integral part of efficacy analysis of new treatments. We clearly support the analysis of economic aspects of new treatments. However, in answering those questions we believe it is imperative to consider all costs and not just those of selected insurance companies. The federal office of public health (FOPH) has conducted a health technology assessment with the objective to understand clinical efficacy, safety and cost-effectiveness of tisagenlecleucel and axicaptagene ciloleucel compared to current standard of care [7]. The report clearly highlights the difficulties encountered answering these questions with the available data, based on single arm clinical registration trials and real-world datasets. In particular, the economic evaluation was hampered by limited and low certainty evidence when comparing CAR-T cell therapies to historic controls as no randomized clinical trials are available and will likely never be. Thus, current studies lack relevant comparators and as a result, are not conclusive. A deeper and more thorough assessment of healthcare expenditure for novel therapies is required. Insurance companies are invited to collaborate with hospitals and clinicians and contribute with their data to future collaborative studies addressing the economic impact of these novel innovative treatments. The field would also benefit from an improved understanding of biological correlates of response and non-response in CAR-T therapy. Identification of objective parameters that allow for risk stratification in the CAR-T setting may help improve patient outcomes and cost-effectiveness."

Response: We endorse the need for further analyses, and we are open to collaborations of this nature.

Again, we would like to express our gratitude to the SBST group for their careful reading and valuable insights.

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Potential competing interests

Most authors work for health insurers providing mandatory insurance in Switzerland. N. Meier regularly advises different Swiss health insurers on topics related to health technology assessment and pricing. M. Pletscher advised different Swiss health insurers during the writing of the study.

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