COMMENTARY

blood advances

TO THE EDITOR:

Need for risk adjustment in comparative effectiveness and cost-effectiveness studies in r/r follicular lymphoma

John Gribben,[1] M. Lia Palomba,[2] Anik R. Patel,[3] Myrna Nahas,[3] and Sattva S. Neelapu[4]

[1]Barts Cancer Institute, Queen Mary University of London, United Kingdom; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Kite, A Gilead Company, Santa Monica, CA; and [4]The University of Texas MD Anderson Cancer Center, Houston, TX

Follicular lymphoma (FL) is an indolent and generally incurable disease. Therapeutic options range from relatively low-cost chemotherapies to intensive high-cost therapies including stem-cell transplant that vary in administration duration from less than 1 month to 2 years or more. Given this landscape, we commend Potnis et al for conducting a cost-effectiveness analysis (CEA) of axicabtagene ciloleucel (axi-cel) comparing it with other available treatments in r/r FL.[1] However, their CEA compared standard of care outcomes from an all-risk population to those from the high-risk population enrolled in ZUMA-5 without risk-adjustment. The comparative outcomes of axi-cel and other treatments from Potnis et al diverge from our own recently published SCHOLAR-5 analyses primarily due to a lack of risk-adjustment during the comparison to the external LEO CReWE control cohort.[2,3] Hence, the cost-effectiveness of axi-cel may be understated in such an analysis.

In SCHOLAR-5, risk-adjustment using propensity score methods revealed the impact of high-risk features on clinical outcomes: the response and survival outcomes decreased in the comparison group after risk-adjustment, demonstrating the need for a balanced outcomes analysis with ZUMA-5. Providers are mindful of high-risk features when making treatment decisions using novel therapies, including CAR T-cell therapy. As the comparator cohort's PFS and OS data are key drivers of the final QALY estimates in a CEA, they greatly influence the final incremental cost-effectiveness ratio. Use of risk-adjusted outcomes in the Potnis et al study would more accurately reflect the real-world use of axi-cel and potentially impact findings. Potnis et al suggest the inclusion of experimental treatments in SCHOLAR-5 was a key barrier to use the data in their CEA. However, clinical trials are a recommended treatment option for r/r FL in the NCCN guidelines and are one of several real-world treatment options available to patients in modern practice.

Questions about the cost-effectiveness of CAR T-cell therapy are important to consider as global health systems continue to implement these transformative treatments. To date, 2 CAR-T products have been approved in third line and later r/r FL in the US and further cost-effectiveness analyses will be needed as the number of cell therapy options increase. It is therefore critical that these analyses focus on populations most likely to benefit from axi-cel so that the value is not understated during policy making, reimbursement, and treatment-selection decisions. We strongly believe that risk-adjustment is an important step in comparative effectiveness and cost-effectiveness analyses to ensure the true unmet need and economic value are reflected in the final outputs.

Contribution: All authors participated in results interpretation, writing the manuscript, and approving the final submitted version.

Conflict-of-interest disclosure: J.G. has received honoraria from AbbVie, Amgen, Bristol Myers Squibb, Janssen, and Kite/Gilead, and has received grant funding from AstraZeneca and Janssen. A.R.P. and M.N. are employees of Kite Pharma, a Gilead Company. L.P. holds individual stocks and stock options from Seres

Submitted 5 December 2022; accepted 9 January 2023; prepublished online on *Blood Advances* First Edition 20 January 2023; final version published online 2 June 2023. https://doi.org/10.1182/bloodadvances.2022009469.

and Notch; has received consulting fees from Novartis, Kite, PCYC, and BeiGene; research funding from Seres; and patents and royalty fees from Seres, Juno, Wolters, and Kluwer. S.S.N. has received honoraria from Kite, Merck, Bristol Myers Squibb, Novartis, Celgene, Pfizer, Allogene Therapeutics, Cell Medica/Kuur, Incyte, Precision BioSciences, Legend Biotech, Adicet Bio, Calibr, Unum Therapeutics, and bluebird bio; patents and royalty fees from Takeda Pharmaceuticals; research funding from Kite, a Gilead Company, Bristol Myers Squibb, Merck, Poseida, Cellectis, Celgene, Karus Therapeutics, Unum Therapeutics (Cogent Biosciences), Allogene, Precision BioSciences, Acerta, and Adicet Bio; and personal fees from Kite, a Gilead Company, Merck, Bristol Myers Squibb, Novartis, Celgene, Pfizer, Allogene, Kuur, Incyte, Precision BioSciences, Legend, Adicet Bio, Calibr, and Unum Therapeutics.

ORCID profiles: J.G., 0000-0002-8505-7430; A.R.P., 0000-0001-9091-8904; M.N., 0000-0002-6864-0931; S.S.N., 0000-0003-1045-4914.

Correspondence: John Gribben, Barts Cancer Institute, Queen Mary University of London, London EC1M6BQ, United Kingdom; email: j.gribben@qmul.ac.uk.

References

1. Potnis KC, Di M, Isufi I, et al. Cost-effectiveness of chimeric antigen receptor T-cell therapy in adults with relapsed or refractory follicular lymphoma. *Blood Adv*. 2023;7(5):801-810.
2. Ghione P, Palomba ML, Patel AR, et al. Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma. *Blood*. 2022;140(8):851-860.
3. Casulo C, Larson MC, Lunde JJ, et al. Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study. *Lancet Haematol*. 2022;9(4):e289-e300.