

Correspondence

Salaam, Tanzania, ³Department of Haematology, Cambridge Institute for Medical Research, ⁴Department of Haematology, University of Cambridge, ⁵Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, UK and ⁶University of Florence, Firenze, Italy.
E-mail: icalauraabia@gmail.com

Keywords: fever, severe congenital neutropenia, childhood, granulocyte-colony stimulating factor, elastase, neutrophil expressed gene

First published online 1 November 2021

doi: 10.1111/bjh.17924

References

- Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. *Nat Rev Dis Primers*. 2017;3:17032.
- Kostmann R. Infantile genetic agranulocytosis; agranulocytosis infantilis hereditaria. *Acta Paediatr Suppl*. 1956;45:1–78.
- Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis*. 2011;6:26.
- Link DC. Mechanisms of leukemic transformation in congenital neutropenia. *Curr Opin Hematol*. 2019;26:34–40.
- Bessler M, Mason PJ, Link DC, Wilson DB. Inherited bone marrow failure syndromes. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, editors. *Hematology and oncology of infancy and childhood*, vol. 1. Philadelphia: Elsevier, 2015; p. 243–7.
- Horwitz MS, Corey SJ, Grimes HL, Tidwell T. ELANE mutations in cyclic and severe congenital neutropenia: genetics and pathophysiology. *Hematol Oncol Clin North Am*. 2013;27:19–41, vii.
- Germeshausen M, Deerberg S, Peter Y, Reimer C, Kratz CP, Ballmaier M. The spectrum of ELANE mutations and their implications in severe congenital and cyclic neutropenia. *Hum Mutat*. 2013;34:905–14.
- Rydzynska Z, Pawlik B, Krzyzanowski D, Mlynarski W, Madzio J. Neutrophil elastase defects in congenital neutropenia. *Front Immunol*. 2021;12:653932.
- Chen X, Peng W, Zhang Z, Wu Y, Xu J, Zhou Y, et al. ELANE gene mutation-induced cyclic neutropenia manifesting as recurrent fever with oral mucosal ulcer: a case report. *Medicine (Baltimore)*. 2018;97:e0031.
- Bellanné-Chantelot C, Schmaltz-Panneau B, Marty C, Fenneteau O, Callebaut I, Clauin S, et al. Mutations in the SRP54 gene cause severe congenital neutropenia as well as Shwachman-Diamond-like syndrome. *Blood*. 2018;132:1318–31.
- Rosenberg PS, Zeidler C, Bolyard AA, Alter BP, Bonilla MA, Boxer LA, et al. Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. *Br J Haematol*. 2010;150: 196–9.
- Shu Z, Li XH, Bai XM, Zhang ZY, Jiang LP, Tang XM, et al. Clinical characteristics of severe congenital neutropenia caused by novel ELANE gene mutations. *Pediatr Infect Dis J*. 2015;34:203–7.
- Chong LA, Josephine P, Ariffin H. Malignant myeloid transformation in a child with severe congenital neutropenia (Kostmann's syndrome). *Med J Malaysia*. 2006;61:236–8.
- Thomas M, Jayandharan G, Chandy M. Molecular screening of the neutrophil elastase gene in congenital neutropenia. *Indian Pediatr*. 2006; 43:1081–4.
- Iancovici-Kidon M, Stoecker D, Abrahamov A, Wolach B, Beutler E, Gelbart T, et al. A new exon 9 glucose-6-phosphate dehydrogenase mutation (G6PD "Rehovot") in a Jewish Ethiopian family with variable phenotypes. *Blood Cells Mol Dis*. 2000;26:567–71.

Synthetic control arms in studies of multiple myeloma and diffuse large B-cell lymphoma

Within the past year, several publications have compared the outcomes of clinical trials in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or R/R multiple myeloma (MM) against retrospective real-world datasets.^{1–4} Two such datasets include the SCHOLAR-1 cohort in DLBCL (comprising 636 patients analysed between 2001 and 2014) and the MAMMOTH cohort in MM (comprising 275 patients analysed between 2017 and 2018).^{5,6} When these observational datasets are compared against single-arm trials in such a manner, their use has been described as constituting a 'synthetic control' arm.^{7,8}

However, synthetic control arms may be inadequate substitutes for true control arms generated via randomised controlled trials (RCTs). Specific critiques of SCHOLAR-1 and MAMMOTH as synthetic controls involve differences in patient eligibility due to (i) slight but significant variations in definitions of R/R status and (ii) general exclusion of unfit patients from trials *versus* their general inclusion in observational datasets.^{9,10} Furthermore, the generalisability of historical observational results as controls for more recent trials is

uncertain. Lastly, whether potential conflict of interests exist in these analyses has not been described.

We thus characterised all studies using SCHOLAR-1 or MAMMOTH as synthetic controls by comprehensively reviewing relevant publications or abstracts available on PubMed or Google Scholar before the data cut-off of 30 September 2021. As shown in Fig 1, a total of four studies in DLBCL^{3,4,11,12} and five studies in MM^{1,2,13–15} were included in our present analysis. These included four peer-reviewed publications and five conference abstracts (Table I).^{1–6,11–6,19,20}

In DLBCL, the novel-agent arm in all four studies enrolled patients during more recent intervals than the SCHOLAR-1 dataset.^{3,4,11,12} All four studies adjusted for key potential confounders using individual patient data. However, one study did not adjust for differences in the specific definitions of R/R status in SCHOLAR-1 *versus* the JULIET trial of tisagenlecleucel.^{5,12,16} Similarly, one study did not adjust for slight differences in clinical response definitions between the TRANSCEND trial of lisocabtagene maraleucel (Lugano

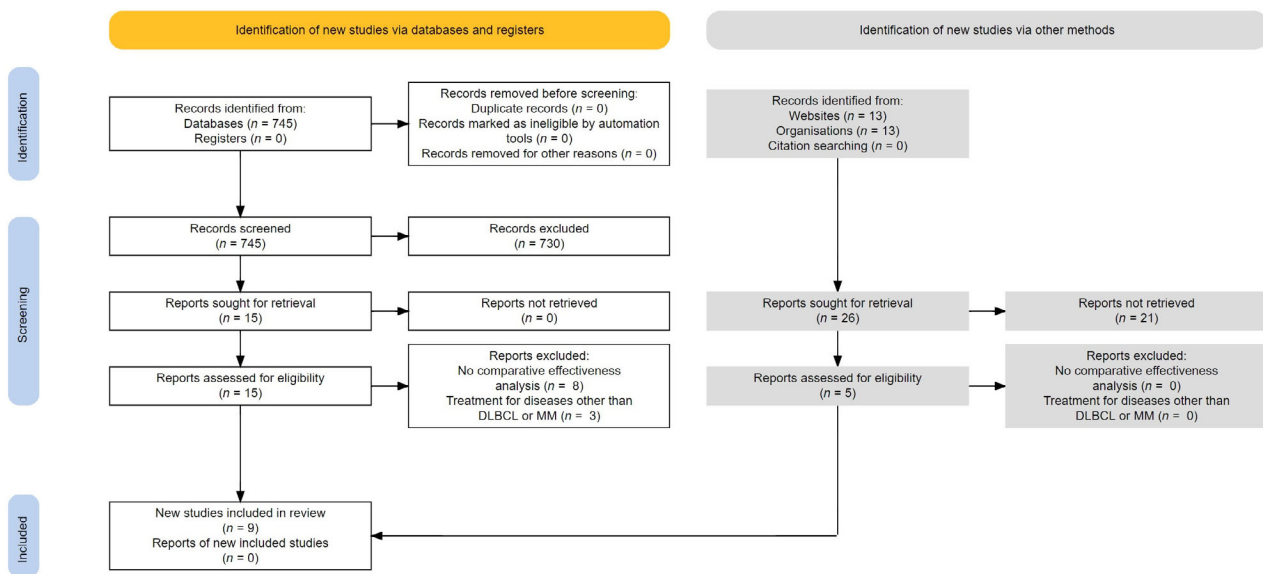


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma. [Colour figure can be viewed at wileyonlinelibrary.com]

criteria) *versus* SCHOLAR-1 (original International Working Group 2007 criteria).^{4,17,18}

Three of four DLBCL studies reported improved overall survival (OS) with the novel agent.^{3,4,11} In the fourth study, the authors acknowledged a statistical difference in OS but did not report further details because they felt that this incremental improvement was clinically insignificant.¹² Of note, this negative study did not report any potential conflicts of interest. Among the three studies that showed a benefit to the novel agent, all three reported potential conflicts of interest such as funding or medical-writing assistance by the manufacturer of the novel agent.

In MM, the novel agent arms in all five studies were contemporaneous with the MAMMOTH dataset and analyzed similar patient cohorts.^{1,2,13–15} However, unlike the MAMMOTH dataset, the DREAMM-2 trial of belantamab mafodotin included treatment intolerance as a determinant of R/R status.^{6,19} This variation in the definition of R/R status was not commented upon in the corresponding synthetic control analysis.¹³ Finally, while two studies used regression modeling to compare arms, they did not report any statistical adjustments based on individual patient data.^{1,15}

All five studies in MM reported significantly improved OS with the novel agents. Two studies noted a comparative benefit in OS but no corresponding benefit in progression-free survival.^{13,15} Similarly, three studies did not find any significant improvement in overall response rates with the novel agent.^{1,13,15} All five studies reported potential conflicts of

interest, most typically in the form of authorship by employees of the manufacturer of the novel agent.

In our present review of studies using the SCHOLAR-1 and MAMMOTH datasets as synthetic control arms, we thus noted several potential items of concern. Firstly, several studies (primarily in DLBCL) compared more recent trials against older control arms. Secondly, statistical adjustments using individual patient data were employed in most but not all studies. Thirdly, most studies reported potential conflicts of interest with the pharmaceutical manufacturers of the novel agent being analysed. In contrast, the only study without any conflicts of interest was also the only study to determine that the novel agent in question did not meaningfully improve OS.¹²

In addition to these specific issues raised by our present study, broader issues with synthetic control arms include the presence of unmeasured confounders. For example, patients with significant comorbidities are generally included in registries but excluded from trials.⁹ Similarly, patients in registries only need to be alive at the time of eligibility; in contrast, clinical trials only characterise patients who survived until treatment initiation. This, in turn, may select for more indolent disease among clinical trial participants *versus* synthetic controls.²⁰ Landmark analyses can potentially correct for these differences in ‘time zero’ but were not performed in any of the studies we identified. Lastly, performing multiple *post hoc* comparisons against the same static dataset can raise the risk of generating false-positive signals.^{21,22}

Limitations of our present study include our specific emphases on SCHOLAR-1 and MAMMOTH and not any other observational datasets. We were not able to determine how much study results were meaningfully influenced (if at all) by differences in years of enrolment, R/R status, or the presence of potential conflicts of interest. Lastly, regarding

[Correction added on 13 January 2022, after first online publication: The data and reference citations in Paragraph 6 were corrected and reference 19 was deleted in this version.]

Table I. Characteristics of included studies.

Novel agent in DLBCL	Enrolment for trial of novel agent*	R/R status differences versus SCHOLAR-1	Adjustment using IPD	Response metrics	Survival metrics	Potential conflicts of interest†
Axicabtagene ciloleucel ¹¹	2015–2016	None	Propensity score matching	ORR improved	6-month OS improved	Authors include employees of manufacturer
Axicabtagene ciloleucel ³	2015–2016	None	Propensity score matching	ORR improved	2-year OS improved	Funding and writing by manufacturer
Lisocabtagene maraleucel ⁴	2016–2019	None, after eligibility adjustment	Matching-adjusted indirect comparisons	ORR improved	3-year OS improved	Funding and writing by manufacturer
Tisagenlecleucel ¹²	2015–2017	PD after first-line therapy not allowed in JULIET ^{5,16}	Restricted mean survival times	Not reported	No ‘clinically relevant’ improvement	None reported
Novel agent in MM	Enrolment for trial of novel agent	R/R status differences versus MAMMOTH	Adjustment using IPD	Response metrics	Survival metrics	Potential conflicts of interest†
Belantamab mafodotin ¹³	2018–2019	Treatment intolerance allowable in DREAMM-2 ^{6,20}	Matching-adjusted indirect comparisons	ORR not improved	OS but not PFS improved	Authors include employees of manufacturer
Ciltacabtagene autoleucel ²	2018–2019	CD38 mAb exposure (alone) allowable in CARTITUDE-1 ^{6,19}	Propensity score matching	ORR improved	12-month PFS and OS improved	Authors include employees of manufacturer
Idecabtagene vicleucel ¹⁴	2017–2018	None, after eligibility adjustment	Matching-adjusted indirect comparisons	ORR improved	PFS and OS improved	Authors include employees of manufacturer
Melflufen ¹⁵	2016–2019	None, after eligibility adjustment	None reported	ORR not improved	OS but not PFS improved	Authors include employees of manufacturer
Selinexor ¹	2015–2018	None, after eligibility adjustment	None reported‡	ORR not improved	OS improved	Funding and writing by manufacturer

CD38 mAb, cluster of differentiation 38-directed monoclonal antibody (daratumumab or isatuximab); IPD, individual patient data; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed or refractory.

*When specific dates were not provided, these were derived from related publications of the novel agent.

†Defined as any listed contribution from the pharmaceutical manufacturer of the novel agent.

‡While Cox regression was performed, no specific techniques using IPD were employed to account for heterogeneity in underlying patient populations.

the ZUMA-1 trial of axicabtagene ciloleucel, the use of SCHOLAR-1 as a synthetic control may have been pre-planned in ways that we are unable to fully characterise.²³

Nevertheless, when true RCTs are not feasible, we suggest that appropriate steps be taken to ensure the validity of synthetic control arms. For example, as is being done with the observational KarMMa-RW dataset *versus* the KarMMa trial of idecabtagene vicleucel,²⁴ a contemporaneous study-specific control arm can be compiled prospectively (even if not randomised) to reflect the changing status quo more accurately for standard-of-care therapies. Additionally, observational datasets should be governed by neutral co-operative groups and specialty societies to encourage pre-planned comparisons and to minimise conflicts of interest.

In summary, our present findings highlight several problems with the use of observational datasets as synthetic

control arms in malignant haematology. While these analyses may provide additional context regarding novel therapeutic agents, they cannot serve as replacements for RCTs.

Author contributions

Aaron Goodman, Vinay Prasad, and Ghulam Rehman Mohyuddin conceptualised the study. Rahul Banerjee, Shonali Midha, and Amar H. Kelkar performed the research. All authors analysed the data and contributed substantially to writing the manuscript.

Conflict of interest

Rahul Banerjee reports the following disclosures: Guidepoint Global (consulting), Pack Health (research), Sanofi

(consulting), SparkCures (consulting). Aaron Goodman reports the following disclosures: EUSA Pharma (consulting), Seattle Genetics (consulting). Vinay Prasad reports the following disclosures: Arnold Ventures (research), Johns Hopkins Press (royalties), United Healthcare (consulting), Evicore (honoraria). The remaining authors do not have any conflicts of interest to report.

Rahul Banerjee¹ 

Shonali Midha²

Amar H. Kelkar³

Aaron Goodman⁴

Vinay Prasad¹

Ghulam Rehman Mohyuddin⁵

¹Division of Hematology/Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA, ²Division of Myeloma, Department of Medical Oncology, Dana-Farber Cancer Institute, ³Division of Transplantation and Cellular Therapies, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, ⁴University of California San Diego, San Diego, CA and ⁵University of Utah, Salt Lake City, UT, USA.

E-mail: g.mohyuddin@hci.utah.edu

Keywords: myeloma therapy, malignant lymphomas, clinical studies

First published online 8 November 2021

doi: 10.1111/bjh.17945

References

- Cornell R, Hari P, Tang S, Biran N, Callander N, Chari A, et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. *Am J Hematol*. 2021;**96**:E5–8.
- Costa LJ, Lin YI, Martin TG, Chhabra S, Usmani SZ, Jagannath S, et al. Ciltacabtagene autemcel versus conventional treatment in patients with relapse/refractory multiple myeloma. *J Clin Oncol*. 2021;**39**(Suppl):8030.
- Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. *Blood Adv*. 2021;**5**:4149–55.
- Salles G, Spin P, Liu FF, Garcia J, Kim Y, Hasskarl J. Indirect treatment comparison of Liso-Cel vs. salvage chemotherapy in diffuse large B-cell lymphoma: TRANSCEND vs. SCHOLAR-1. *Adv Ther*. 2021;**38**:3266–80.
- Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;**130**:1800–8.
- Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;**33**:2266–75.
- Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and external controls in clinical trials – a primer for researchers. *Clin Epidemiol*. 2020;**12**:457–67.
- Kanapuru B, Gong Y, Mishra-Kalyani PS, Menefee ME, Sridhara R, Farrell AT, et al. Project switch: lenalidomide and dexamethasone (Len-Dex) as a potential synthetic control arm (SCA) in relapsed or refractory multiple myeloma (rrMM). *J Clin Oncol*. 2019;**37**(Suppl):8047.
- Rutherford SC, Leonard JP. Lymphoma “benchmark” or “bench-smudge”? *Blood*. 2017;**130**:1778–9.
- Shah N, Sussman M, Crivera C, Valluri S, Benner J, Jagannath S. Comparative effectiveness research for CAR-T therapies in multiple myeloma: appropriate comparisons require careful considerations of data sources and patient populations. *Clin Drug Investig*. 2021;**41**:201–10.
- Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, et al. A comparison of one year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). *Blood*. 2017;**130**(Suppl 1):579.
- Messori A, Damuzzo V, Leonardi L, Agnoletto L, Chiumente M, Mengato D. CAR-T treatment: determining the survival gain in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2020;**20**:490–1.
- Suvannasankha A, Kapetanakis V, Prawitz T, Sarri G, Hughes R, Wang F, et al. Assessing efficacy via indirect comparison of single-agent belantamab mafodotin (Belamaf; GSK2857916) in DREAMM-2 versus STORM or MAMMOTH studies in relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma Myeloma Leuk*. 2020;**20**(Suppl 1):S300–1.
- Shah N, Ayers D, Davies FE, Cope S, Mojeib A, Parikh K, et al. A matching-adjusted indirect comparison of efficacy outcomes for idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy versus conventional care in triple-class-exposed relapsed and refractory multiple myeloma. *Blood*. 2020;**136**(Suppl 1):6–7.
- Blade Creixenti J, Mateos M-V, Oriol A, Larocca A, Cavo M, Rodríguez-Otero P, et al. HORIZON (OP-106) versus MAMMOTH: an indirect comparison of efficacy outcomes for patients with Relapsed/Refractory Multiple Myeloma Refractory (RRMM) to anti-CD38 monoclonal antibody therapy treated with melflufen plus dexamethasone versus conventional agents. *Blood*. 2020;**136**(Suppl 1):2–4.
- Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-Cell lymphoma. *N Engl J Med*. 2019;**380**:45–56.
- Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;**32**:3059–68.
- Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;**25**:579–86.
- Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol*. 2020;**21**:207–21.
- Collignon O, Schritz A, Spezia R, Senn SJ. Implementing historical controls in oncology trials. *Oncologist*. 2021;**26**:e859–62.
- Gay ND, Tao D, Prasad V. Multiplicity and the marginal benefits of bevacizumab in malignant solid tumours. *Curr Oncol*. 2019;**26**:e791–2.
- Albers C. The problem with unadjusted multiple and sequential statistical testing. *Nat Commun*. 2019;**10**:1921.
- Papadoulis I, Mueller-Berghaus J, Beuneu C, Ali S, Hofner B, Petavy F, et al. EMA review of axicabtagene ciloleucel (Yescarta) for the treatment of diffuse large B-cell lymphoma. *Oncologist*. 2020;**25**:894–902.
- Jagannath S, Lin YI, Goldschmidt H, Reece D, Nooka A, Senin A, et al. KarMMa-RW: comparison of idecabtagene vicleucel with real-world outcomes in relapsed and refractory multiple myeloma. *Blood Cancer J*. 2021;**11**:116.