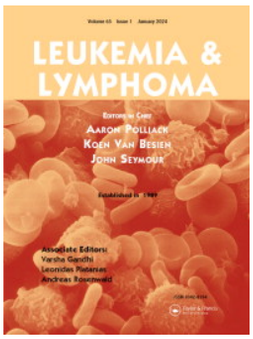

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

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To cite this article: Georg Hess, Martin Dreyling, Lucie Oberic, Eva Gine, Pier Luigi Zinzani, Kim Linton, Adam Vilmar, Mats Jerkeman, Jenny M. H. Chen, Anke Ohler, Stephan Stilgenbauer, Catherine Thieblemont, Jonathan Lambert, Vittorio Ruggero Zilioli, Juan-Manuel Sancho, Ana Jimenez-Ubieto, Luca Fischer, Toby A. Eyre, Sam Keeping, Julie E. Park, James J. Wu, Ana Nunes, John Reitan, Sally W. Wade & Gilles Salles (2024) Indirect treatment comparison of brexucabtagene autoleucel (ZUMA-2) versus standard of care (SCHOLAR-2) in relapsed/refractory mantle cell lymphoma, Leukemia & Lymphoma, 65:1, 14-25, DOI: 10.1080/10428194.2023.2268228

To link to this article: https://doi.org/10.1080/10428194.2023.2268228

LEUKEMIA & LYMPHOMA
2024, VOL. 65, NO. 1, 14–25
https://doi.org/10.1080/10428194.2023.2268228

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ORIGINAL ARTICLE

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Indirect treatment comparison of brexucabtagene autoleucel (ZUMA-2) versus standard of care (SCHOLAR-2) in relapsed/refractory mantle cell lymphoma

Georg Hess[a], Martin Dreyling[b], Lucie Oberic[c], Eva Gine[d], Pier Luigi Zinzani[e], Kim Linton[f], Adam Vilmar[g], Mats Jerkeman[h], Jenny M. H. Chen[i], Anke Ohler[a], Stephan Stilgenbauer[j], Catherine Thieblemont[k], Jonathan Lambert[l], Vittorio Ruggero Zilioli[m], Juan-Manuel Sancho[n], Ana Jimenez-Ubieto[o], Luca Fischer[b], Toby A. Eyre[p], Sam Keeping[i], Julie E. Park[i], James J. Wu[q], Ana Nunes[q], John Reitan[r], Sally W. Wade[s] and Gilles Salles[t]

[a]Department of Hematology, Oncology and Pneumology, Comprehensive Cancer Center, University Medical School of the Johannes Gutenberg-University, Mainz, Germany; [b]Medizinische Klinik III, LMU Klinikum, Munich, Germany; [c] Department of Hematology, University Hospital Centre Toulouse, Service d'Hématologie, Toulouse, France; [d]GELTAMO, Hematology Department, Hospital Clínic of Barcelona, Barcelona, Spain; [e]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [f]The Manchester Cancer Research Center, Manchester, UK; [g]Odense University Hospital, Odense, Denmark; [h]Department of Oncology, Skane University Hospital and Lund University, Lund, Sweden; [i]PRECISIONheor, Vancouver, BC, Canada; [j]Department of Internal Medicine III, Ulm University, Ulm, Germany; [k]APHP, Hôpital Saint-Louis, Hemato-oncologie, Université de Paris, Paris, France; [l] Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK; [m]Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [n]GELTAMO, Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [o]GELTAMO, Hospital Doce de Octubre, Madrid, Spain; [p]Haematology and Cancer Centre, Oxford, UK; [q]Kite, a Gilead Company, Santa Monica, CA, USA; [r]RJM Group, LLC, Crown Point, IN, USA; [s]Wade Outcomes Research & Consulting, Salt Lake City, UT, USA; [t]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

ABSTRACT

The SCHOLAR-2 retrospective study highlighted poor overall survival (OS) with standard of care (SOC) regimens among patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) who failed a covalent Bruton tyrosine kinase inhibitor (BTKi). In the ZUMA-2 single-arm trial, brexucabtagene autoleucel (brexu-cel; autologous anti-CD19 CAR T-cell therapy) demonstrated high rates of durable responses in patients with R/R MCL who had previous BTKi exposure. Here, we compared OS in ZUMA-2 and SCHOLAR-2 using three different methods which adjusted for imbalances in prognostic factors between populations: inverse probability weighting (IPW), regression adjustment (RA), and doubly robust (DR). Brexu-cel was associated with improved OS compared to SOC across all unadjusted and adjusted comparisons. Hazard ratios (95% confidence intervals) were 0.38 (0.23, 0.61) for IPW, 0.45 (0.28, 0.74) for RA, and 0.37 (0.23, 0.59) for DR. These results suggest a substantial survival benefit with brexu-cel versus SOC in patients with R/R MCL after BTKi exposure.

ARTICLE HISTORY
Received 21 July 2023
Revised 18 September 2023
Accepted 2 October 2023

KEYWORDS
CAR T-cell therapy; brexucabtagene autoleucel; indirect treatment comparison; mantle cell lymphoma; non-Hodgkin lymphoma; standard of care

Introduction

Mantle cell lymphoma (MCL) is an uncommon B-cell malignancy, accounting for less than 10% of non-Hodgkin lymphomas (NHL). Although response rates to first-line therapies are high, almost all patients diagnosed with MCL will eventually relapse and require multiple lines of therapy [1–3]. Advancements have been made in the treatment landscape for MCL over the past decade, such as the introduction of covalent Bruton tyrosine kinase inhibitors (BTKi) [4,5]; however, no standard therapeutic approach or established standard of care (SOC) exists for relapsed/refractory (R/R) MCL after BTKi treatment. Therefore, an unmet therapeutic need remains for patients with R/R MCL.

Limited published data from retrospective, non-comparative, observational studies indicate especially poor outcomes in patients with R/R MCL who experience disease progression following BTKi therapy. Median overall survival (OS) has been shown to range

CONTACT Gilles Salles SallesG@mskcc.org Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/10428194.2023.2268228.

from 5.8 to 12.5 months with subsequent treatment, excluding chimeric antigen receptor (CAR) T-cell therapies, in this population [6–9]. A low survival rate among 149 patients receiving non-CAR T-cell therapies following BTKi discontinuation was also observed in the SCHOLAR-2 multi-center, retrospective, observational study (median OS of 9.7 months) [10]. CAR T-cell therapies targeting CD19 have recently emerged as effective treatments for R/R B-cell lymphomas [5]. Brexucabtagene autoleucel (brexu-cel, formally known as KTE-X19), an autologous anti-CD19 CAR T-cell therapy, was approved in July 2020 in the United States for the treatment of R/R MCL and subsequently in January 2021 in the European Union for the treatment of R/R MCL after two or more lines of systemic therapy including a BTKi based on a phase 2 study (ZUMA-2, NCT02601313) [5].

The comparative efficacy of newer therapies and SOC for MCL in the post-BTKi setting has not been evaluated in randomized controlled trials (RCTs). While RCTs are widely considered as the gold standard of evidence, utilizing real-world evidence to serve as external controls for single-arm trials has been increasingly accepted over recent years, including for health technology assessment [11]. In the current study, based on individual patient data (IPD) from both ZUMA-2 and SCHOLAR-2, we performed an indirect treatment comparison of brexu-cel versus SOC for treatment of R/R MCL post-BTKi in terms of OS using alternative statistical methods to adjust for imbalances in prognostic factors between the two non-randomized study populations.

Methods

Data sources

ZUMA-2 was a pivotal, single-arm, phase 2 trial of brexu-cel (study start date: 9 November 2015; primary analysis date: 24 July 2019) conducted at 20 sites in the United States and Europe. Study details of ZUMA-2 have been previously reported [5,12]. ZUMA-2 included patients aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and histologically-confirmed MCL that was R/R to up to five prior regimens, including an anthracycline-containing or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and BTKi therapy. For comparison to SCHOLAR-2, the base-case analysis used the modified intention-to-treat (mITT) population which consisted of the 68 patients treated with brexu-cel at a target dose of 2 x 10^6 CAR T-cells/kg. Two other ZUMA-2 analysis sets were included as scenarios to assess the sensitivity of results to different inclusion criteria: intention-to-treat (ITT, $n = 74$ enrolled/leukapheresed patients, including six patients who did not receive brexu-cel) and inferential (n = first 60 patients who were treated with brexu-cel and included in ZUMA-2 primary analysis). The data cutoff date for the current analysis was 24 July 2021.

SCHOLAR-2 was a retrospective, observational, chart review study that collected survival outcomes of patients aged ≥18 years with R/R MCL who initiated BTKi therapy between July 2012 and July 2018 and had experienced disease progression while on BTKi therapy or were intolerant to BTKi therapy. Study details of SCHOLAR-2 have been previously reported [10]. SCHOLAR-2 was conducted in multiple European centers (United Kingdom, France, Germany, Spain, Italy, Sweden, and Denmark). Similar to ZUMA-2, patients with prior CAR T-cell therapy or other genetically modified T-cell therapy and a history or presence of central nervous system disorder were excluded. Data were collected between February 2020 and December 2020 for 240 eligible patients, of whom 149 patients received active therapies in the post-BTKi setting (Figure 1). For comparison to ZUMA-2, real-world evidence on the effectiveness of SOC was based on a subset of the SCHOLAR-2 post-BTKi treated population that better resembled the patient population of ZUMA-2. This subset consisted of 60/149 patients with an ECOG performance status score of 0 or 1, who had received subsequent active therapy after a BTKi therapy, and who had a minimum of 12-month potential follow-up from initiation of a post-BTKi therapy.

As SCHOLAR-2 was retrospective in design, patients could theoretically enter the cohort at multiple time-points (i.e. have multiple baselines) if they had received more than one line of post-BTKi therapy. An appropriate definition of time zero for cohort entry (i.e. the index date) is an important aspect of the study design when patients may be eligible at multiple time-points [13]. To minimize selection bias, two SCHOLAR-2 cohorts (initial-line and period-prevalence cohorts) were included in the analysis, with each cohort assigned a pre-defined index date as depicted in Figure 1. For both cohorts, patients were allowed to enter the cohort once (i.e. one index date), which was at the initiation of a new line of therapy in the post-BTKi setting during the predefined time-period. The period-prevalence cohort (scenario analysis) was a subset of the initial-line cohort that mimicked the enrollment period of the ZUMA-2 trial to avoid potential confounding factors that could arise due to timing differences.

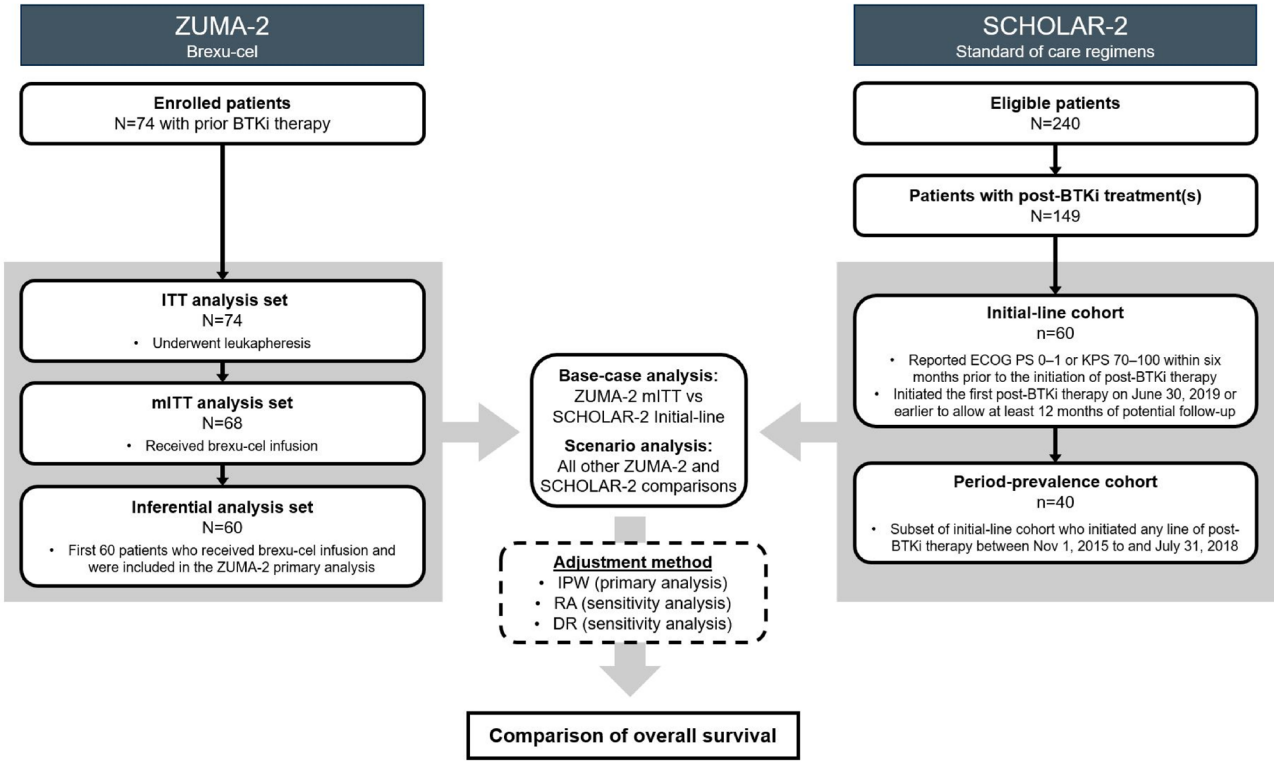

Figure 1. Creation of analysis sets for overall survival comparisons. Brexu-cel: brexucabtagene autoleucel; BTKi: Bruton tyrosine kinase inhibitor; DR: doubly-robust; IPW: inverse probability weighting; ITT: intention-to-treat; mITT: modified intention-to-treat; RA: regression adjustment; ECOG PS: Eastern Cooperative Oncology Group performance score.

Study endpoint and confounding variables

The outcome evaluated was OS, measured from the index date to the date of death due to any cause. For ZUMA-2, the index date was the date of brexu-cel infusion for the mITT and inferential sets and the date of enrollment/leukapheresis for ITT. For the SCHOLAR-2 initial-line cohort ($n = 60$), the index date was the start date of the earliest line of post-BTKi therapy, while for the SCHOLAR-2 period-prevalence cohort ($n = 40$) the index date was the start date of the earliest line of post-BTKi therapy that was initiated between 1 November 2015 (study start date of ZUMA-2) and 31 July 2018 (approximately 12 months prior to primary analysis cutoff date for ZUMA-2). In cases where reported dates had a missing day, the 15th was assigned. Patients who had not died by the data cutoff date were censored at the last date known alive.

Based on data availability (required to be reported in >75% of patients in both studies) and clinical input, four variables were identified as key prognostic factors and/or effect modifiers of highest relevance to be balanced between populations: response to prior BTKi therapy (complete/partial response versus no response), duration on prior BTKi therapy, number of prior lines of therapy, and prior autologous stem cell transplantation (SCT, yes versus no). To help achieve a better balance in these four key variables between the populations, another four variables that were also pre-specified as clinically relevant potential confounders for OS were considered for model inclusion: age, sex (male versus female), disease staging (≤3 versus 4), and ECOG performance status (0 versus 1).

Statistical methods

Three different methods were performed to adjust for differences in baseline characteristics across the two independent data sources: (1) inverse probability weighting (IPW) with ZUMA-2 as the target population, (2) regression adjustment (RA) using a multivariable regression model, and (3) doubly robust (DR) which combines IPW and RA. These methods aligned with recommendations from the National Institute for Health and Care Excellence (NICE) guidance for estimating relative treatment effects using IPD from non-RCTs [14,15].

Propensity score weighting method

Our primary analytical approach was based on the propensity score (PS) method, specifically IPW. Average treatment effect on the treated (ATT) weights, also known as standardized mortality ratio weights, were

applied to the patients in SCHOLAR-2 to create an external control arm with a similar covariate distribution as ZUMA-2 [16,17]. The objective behind constructing the PS model was to achieve balance in the distribution of all four key variables between the two study populations, rather than identifying a correctly-specified model [18]. Thus, instead of simply selecting the PS model that included these four variables, all 255 possible PS models, ranging from the simplest model with one covariate to the full model with all eight covariates, were fitted. The performance of each model was examined using model diagnostics based on the absolute standardized difference (ASD) across the four key variables [19]. The PS model with ATT weights that achieved the most balanced distribution across these key variables was selected as the IPW-main model. The extent of overlap/difference between both populations, before and after applying weights, for each variable was measured by ASD with threshold of 10%, which is less sensitive to sample size than p-values [19].

Missing data for response to prior BTKi therapy (≤5% in SCHOLAR-2), duration on BTKi therapy (≤5% in ZUMA-2), and disease stage (18% in SCHOLAR-2) were replaced with the average obtained from the non-missing covariate values (i.e. mean imputation). In the main analysis, mean imputation was used, where the mean value of covariates remains unchanged. This is a reasonable choice given that ASD, a measure of the extent of balance in covariates, compares the group mean value of each covariate. Although single imputation tends to underestimate the standard error of parameter estimates, the extent of underestimation was expected to be non-significant, given the small proportion of missing data [20].

In addition to the IPW-main model, alternative models were explored as sensitivity analyses to ensure the robustness of the IPW approach: IPW-SA MI model (using multiple imputation given the high missing rate of disease stage in SCHOLAR-2) and IPW-SA full model (balancing all eight covariates). Further details of the IPW method and multiple imputation are provided in Supplemental Sections 1 and 2.

Regression adjustment and doubly-robust methods

In addition to the more commonly-used IPW approach, alternative methods were included to explore the sensitivity of results to different means of adjustment for population differences. For the RA approach, a Cox regression model was constructed with a term for treatment and terms for all relevant covariates included. Since RA alone is sensitive to model mis-specification, the DR method was also explored to provide further adjustment for potential confounding [14,21]. The DR approach used the regression method, where each observation was weighted as in the IPW analysis; therefore, the model adjusted for the differences in populations as well as the differences in outcomes that were not attributable to treatment assignment. For these two regression-based approaches, univariate analyses were first performed to identify potential confounders using $p < 0.3$ as the cut-point. Backward elimination was then performed to obtain the most parsimonious model based on the Akaike information criterion. Additional RA and DR models were also explored as sensitivity analyses.

Survival analysis

The median follow-up time was estimated using the reverse Kaplan-Meier curve method [22]. Unweighted and weighted Cox proportional hazards (PH) models were used to estimate the treatment effect of brexu-cel relative to SOC on OS for the unadjusted (naïve) and population-adjusted indirect comparisons, expressed as hazard ratios (HR) with 95% confidence intervals (CIs). For the weighted Cox model, robust sandwich variances estimators were computed to obtain 95% CIs for the relative treatment effects since applying weights to SCHOLAR-2 patients introduced within-patient correlations [16]. The validity of proportional hazards assumption was assessed with the Grambsch and Therneau test and visual inspection of the Schoenfeld residuals and the log cumulative hazards plots. All analyses were performed in R version 4.1.2 [23].

Results

Baseline characteristics

Table 1 presents the reported baseline patient characteristics of ZUMA-2 mITT set ($N = 68$), SCHOLAR-2 all post-BTKi treated population ($N = 149$) and SCHOLAR-2 initial-line cohort ($N = 60$). The base-case analyses included the ZUMA-2 mITT set and SCHOLAR-2 initial-line cohort, which are described further below.

The comparability of reported baseline characteristics between the ZUMA-2 mITT set and SCHOLAR-2 initial-line cohort is also illustrated in Figure 2, with the extent of differences for each characteristic summarized as ASD. Both duration on prior BTKi therapy and response to prior BTKi therapy had ASD <10%, indicating good balance between both groups, while other baseline characteristics were less balanced. The proportion of patients with prior autologous SCT was slightly higher in ZUMA-2 mITT set (43%) than in SCHOLAR-2

Table 1. Reported baseline patient characteristics in ZUMA-2 and SCHOLAR-2.

Baseline characteristics	ZUMA-2, mITT (*N* = 68)	SCHOLAR-2, All post-BTKi treated (*N* = 149)	SCHOLAR-2, initial-line cohort (*N* = 60)
Response (ORR) to prior BTKi therapy, *n* (%)	26 (38.2)	46/133 (34.6)	23/58 (39.7)
Duration on prior BTKi therapy, months			
Mean (SD)	11.4 (11.2)	11.7 (12.0)	11.8 (12.2)
Number of prior lines of therapy			
Mean	3.3	3.2	3.0
Median (range)	3 (1 – 5)	3 (1–11)	3 (1 – 6)
1 prior, *n* (%)	1 (1.5)	4 (2.7)	2 (3.3)
2 prior, *n* (%)	12 (17.6)	52 (34.9)	22 (36.7)
3 prior, *n* (%)	30 (44.1)	44 (29.5)	19 (31.7)
≥4 prior, *n* (%)	25 (36.8)	49 (32.9)	17 (28.3)
Prior autologous SCT, *n* (%)	29 (42.6)	48 (32.2)	22 (36.7)
Ki-67 proliferation index[a]			
≥30%, *n* (%)	43/52 (82.7)	17/22 (77.3)	7/11 (63.6)
≥50%, *n* (%)	37/52 (71.2)	13/22 (59.1)	6/11 (54.5)
Blastoid morphology[a], *n* (%)	17 (25.0)	17/46 (37.0)	8/20 (40.0)
Age, years			
Mean (SD)	63.2 (7.9)	70.9 (9.45)	69.5 (9.5)
Male sex, *n* (%)	57 (83.8)	108 (72.5)	43 (71.7)
Disease stage			
I, *n* (%)	0 (0.0)	5/111 (4.5)	5/49 (10.2)
II, *n* (%)	2 (2.9)	8/111 (7.2)	4/49 (8.2)
III, *n* (%)	8 (11.8)	20/111 (18.0)	9/49 (18.4)
IV, *n* (%)	58 (85.3)	78/111 (70.3)	31/49 (63.3)
ECOG performance score			
0, *n* (%)	44 (64.7)	29/103 (28.2)	27 (45.0)
1, (%)	24 (35.3)	39/103 (37.9)	33 (55.0)
2, (%)	0	35/103 (34.0)	0
s-MIPI[a]			
Low risk (score 0–3)	28/66 (42.4)	3/62 (4.8)	3/28 (10.7)
Intermediate risk (score 4–5)	29/66 (43.9)	14/62 (22.6)	9/28 (32.1)
High risk (score ≥6)	9/66 (13.6)	45/62 (72.6)	16/28 (57.1)
Splenic involvement[b], *n* (%)	23 (33.8)	41/100 (41.0)	16/43 (37.2)
Extranodal disease[b], *n* (%)	38 (55.9)	29/100 (29.0)	11/43 (25.6)
Bone marrow involvement[b], *n* (%)	37/67 (55.2)	45/100 (45.0)	21/43 (48.8)
Type of prior BTKi therapy			
Any BTKi, *n* (%)	68 (100)	149 (100)	60 (100)
Ibrutinib, *n* (%)	58 (85.3)	145 (97.3)	57 (95.0)
Acalabrutinib, *n* (%)	16 (23.5)	4 (2.7)	3 (5.0)
Presence of B symptoms[b], *n* (%)	5 (7.4)	27/100 (27.0)	6/43 (14.0)
Bulky disease[b], *n* (%)	7 (10.3)	19/100 (19.0)	5/43 (11.6)

BTKi: Bruton tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; mITT: modified intention-to-treat; N: number of patients; ORR: objective response rate (complete or partial response as best response); SCT: stem cell transplantation; SD: standard deviation; s-MIPI: simplified Mantle Cell Lymphoma International Prognostic Index.
[a]Missing values in ≥50% SCHOLAR-2 patients.
[b]Missing values in ≥25% to <50% SCHOLAR-2 patients.

initial-line cohort (37%). Similarly, the proportion of patients with ≥3 prior lines of therapy was higher in ZUMA-2 (81% versus 60%). In general, ZUMA-2 had a slightly younger population and a higher proportion of patients with ECOG performance status score of 0; however, more patients in ZUMA-2 had stage IV disease. At least 50% of patients in SCHOLAR-2 had missing Ki-67 proliferation index, blastoid morphology, and simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI); among those reported, a lower proportion of patients had Ki67 ≥ 50% and a higher proportion of patients had blastoid morphology and high s-MIPI risk compared to ZUMA-2. Table 2 presents the variety of index SOC treatments received by the initial-line cohort. The most common regimens included bendamustine ± rituximab (*n* = 12) and lenalidomide ± rituximab (*n* = 11).

After applying weights from the IPW-main model, all four key variables were well-balanced between the ZUMA-2 mITT and SCHOLAR-2 initial-line cohort (Supplemental Section 3). The effective sample size of the weighted SCHOLAR-2 initial-line cohort data was 45.7. The PS distributions before and after weighting can be found in Supplemental Section 4. All details regarding the ZUMA-2 ITT/inferential sets and SCHOLAR-2 period-prevalence cohort can be found in Supplemental Sections 3 to 6. The list of covariates included across all models in the main and sensitivity analyses are provided in Supplemental Section 7.

Overall survival

Figure 3(A) presents the reported OS for the ZUMA-2 mITT set (*N* = 68), SCHOLAR-2 all post-BTKi treated

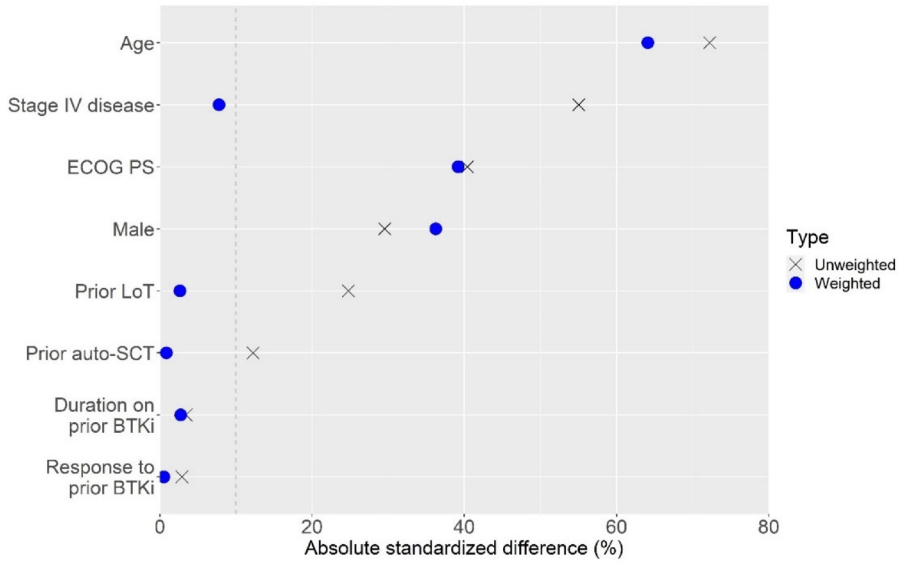

Figure 2. Absolute standard difference between ZUMA-2 mITT set and SCHOLAR-2 initial-line cohort. Absolute standardized difference before and after applying weights from the IPW-main model are shown. The variables in this figure are arranged in descending order of absolute standardized difference before applying weights (i.e. least balanced variable at the top). BTKi: Bruton tyrosine kinase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; LoT: lines of therapy; ORR: objective response rate; SCT: stem cell transplantation.

population ($N = 149$), and SCHOLAR-2 initial-line cohort ($N = 60$). As previously mentioned, the SCHOLAR-2 initial-line cohort represents a subset of the total post-BTKi treated population that had a better performance status of ECOG 0 or 1, with median survival accordingly being higher for the former as compared to the latter.

ZUMA-2 mITT set versus SCHOLAR-2 initial-line cohort

Median follow-up after index treatment was 35.8 months (95% CI: 34.0–49.8) for the ZUMA-2 mITT set and 27.6 months (95% CI: 21.9–38.7) for the SCHOLAR-2 initial-line cohort. Reported median OS was 46.6 months (12-month OS rate, 80.9%; 36-month OS rate, 57.9%) for brexu-cel and 15.4 months (12-month OS rate, 56.5%; 36-month OS rate, 25.9%) for SOC. The naïve (unadjusted) analysis showed brexu-cel was more effective compared to SOC with an HR of 0.42 (95% CI: 0.26–0.68; $p < 0.001$). After IPW adjustment, the weighted OS KM curve for SOC shifted slightly downward (Figure 3(B)**)**, with a median OS of 14.0 months (12-month OS rate, 51.2%; 36-month OS rate, 21.8%). Similar to the naïve analysis, the IPW-adjusted HR of 0.38 (95% CI: 0.23–0.61; $p < 0.001$) suggested that brexu-cel reduced the risk of death relative to SOC. HR estimates were generally consistent across the sensitivity analyses conducted with alternative IPW models (Figure 4**)**. The IPW-SA MI model produced the same HR point estimate (0.38) as the IPW-main model, although the 95% CI was slightly wider (0.21–0.68) but still significant. In the IPW-SA full model, the HR was 0.46 (95% CI: 0.25–0.83).

Consistent results were obtained from the RA and DR analyses. The estimated HR was 0.45 (95% CI: 0.28–0.74) from the RA model and 0.37 (95% CI: 0.23–0.59) from the DR model, again suggesting that brexu-cel reduced the risk of death relative to SOC. Other sensitivity analyses which adjusted for various combinations of covariates in the regression model yielded similar results (Figure 4).

Additional scenario analyses

The comparisons with ZUMA-2 mITT and SCHOLAR-2 period-prevalence cohort yielded similar findings. (Figure 4; Supplemental Section 8). Additionally, results obtained based on the ZUMA-2 ITT population and ZUMA-2 inferential population were consistent with these findings (Figure 4).

Discussion

The clinical outcomes for patients with MCL who progress post-BTKi are generally poor when treated with currently available non-CAR T-cell therapies, which are not curative but aim to palliate and prolong survival. The limited amount of data available on the effectiveness of existing treatments in the post-BTKi setting, alongside the ambiguity regarding what constitutes SOC, makes it difficult to determine the survival

Table 2. Index standard of care treatments in SCHOLAR-2 initial-line cohort.

Index treatments	SCHOLAR-2 initial-line cohort ($N=60$)
Chemotherapies (± antibodies)	25 (41.7)
Cytarabine-containing regimens	9 (15.0)
• R-BAC	5 (8.3)
• Rituximab + cytarabine	2 (3.3)
• R-DHAOx	1 (1.7)
• R-DHAP	1 (1.7)
Other chemotherapy (± antibodies)	16 (26.7)
• Bendamustine ± rituximab	12 (20.0)
• R-CHOP	2 (3.3)
• Rituximab + GMALL NHL 2002 elderly	1 (1.7)
• Tinostamustine	1 (1.7)
Targeted therapies (± antibodies)	33 (55.0)
BTKi regimens	2 (3.3)
• Ibrutinib	1 (1.7)
• Ibrutinib + rituximab	1 (1.7)
Lenalidomide-containing regimens	12 (20.0)
• Lenalidomide + rituximab	6 (10.0)
• Lenalidomide	5 (8.3)
• Lenalidomide + dexamethasone	1 (1.7)
Bortezomib-containing regimens	7 (11.7)
• RiBVD	1 (1.7)
• Rituximab + bortezomib	2 (3.3)
• Bortezomib	1 (1.7)
• BVD	1 (1.7)
• R-mini-CHOP + bortezomib	1 (1.7)
• VR-CAP	1 (1.7)
Other targeted therapies (± antibodies)	12 (20.0)
• Venetoclax	3 (5.0)
• PI3K inhibitor	2 (3.3)
• Obinutuzumab + atezolizumab	2 (3.3)
• BCL201 + idelalisib	1 (1.7)
• CD20*CD3 + R2810 (anti-PD1)	1 (1.7)
• Ofatumumab	1 (1.7)
• Rituximab + varlilumab	1 (1.7)
• Umbralisib	1 (1.7)
Other treatments	2 (3.3)
Radiotherapy	2 (3.3)

Treatments were classified into mutually exclusive sub-categories according to the following hierarchy: chemotherapies (cytarabine-containing regimen, and other chemotherapy ± antibodies), targeted therapies (BTKi regimens, lenalidomide-containing regimens, bortezomib-containing regimens, and other targeted therapies ± antibodies), and other treatments such as anti-metabolite, radioimmunotherapy, radiotherapy, or unknown. BTKi: Bruton tyrosine kinase inhibitor; BVD: bendamustine + bortezomib + dexamethasone; CHOP: cyclophosphamide + doxorubicin + vincristine + prednisone; DHAP: dexamethasone + cytarabine + cisplatin; PD-1: programmed cell death protein 1; PI3K: phosphoinositide 3-kinase; P-VEBEC: prednisone + vinblastine + epirubicin + bleomycin + etoposide + cyclophosphamide; R-BAC: rituximab + bendamustine + cytarabine; R-CHOP: rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-DHAOx: rituximab + dexamethasone + cytarabine + oxaliplatin; R-DHAP: rituximab + dexamethasone + cytarabine + cisplatin; R-GemOx: rituximab + gemcitabine + oxaliplatin; RT: radiotherapy; VR-CAP: bortezomib + rituximab + cyclophosphamide + doxorubicin + prednisone.

benefit of novel agents, such as CAR T-cell therapies, versus non-CAR T-cell SOC regimens. A recent meta-analysis reported a pooled estimate of 9.5 months in median OS with non-CAR T-cell salvage therapies in the post-BTKi setting based on the existing evidence base of small retrospective studies [24]. This suboptimal survival with non-CAR T-cell SOC was again highlighted in the SCHOLAR-2 study, underscoring the unmet clinical need in the post-BTKi setting. Promising advancements in treatment options like CAR T-cell therapies have helped improved prognosis, with other new therapies such as non-covalent BTKi and bispecifics being recently approved or undergoing evaluation in clinical trials [25,26]. Brexu-cel is the only CAR T-cell therapy approved for R/R MCL and longer-term data from ZUMA-2 confirmed its durable benefits (median OS of 46.6 months) [5,12]; in addition, data from a real-world study of brexu-cel showed similar effectiveness and safety compared to ZUMA-2 findings [27]. Results from this comparative analysis of ZUMA-2 and SCHOLAR-2 patients with similar clinical profiles receiving non-CAR T-cell SOC in routine clinical settings suggest a survival benefit with brexu-cel over SOC, which supplement the findings of the single-arm ZUMA-2 trial.

Different approaches to analyze comparative IPD from non-randomized controlled studies, such as single-arm trials and observational studies, to estimate treatment effects have been previously proposed [14,15]. Over recent years, the US Food and Drug Administration and the European Medicine Agency time have accepted single-arm trials as the basis of drug approvals, particularly for rare and aggressive forms of cancer where RCTs may be difficult to conduct [28–31]. The utilization of real-world evidence as an external control for single-arm trials has been used in drug evaluation or health technology assessment decision-making when internal controls from RCTs are not present [11,32]. In this context, several published ITCs in lymphoma have applied PS methods to account for imbalances of confounders between the single-arm trial of interest and the external control arm prior to any comparative analyses [33–35]. Similarly, in our study, PS (i.e. IPW) was the primary approach used; additionally, two other adjustment methodologies (RA and DR) were employed as sensitivity analyses. Importantly, estimates were consistent between the naïve and adjusted analyses as well as across the different adjustment methods, which provided evidence for the robustness of the study results.

Certain potential limitations may influence the findings of this study. As with any analysis of single-arm or non-comparative studies, there will always be uncertainty regarding any unknown or unmeasured prognostic factors and effect modifiers that have not been accounted for in the chosen model which may influence the outcome of interest. Several variables such as Ki67, blastoid morphology, and s-MIPI could not be considered in the model due to their high missing rates (≥50%) in SCHOLAR-2. As a conservative approach when attempting to minimize potential bias in the IPW model selection, all 255 possible PS models were fitted in search for the model that provided the best balance for the key relevant prognostic factors between

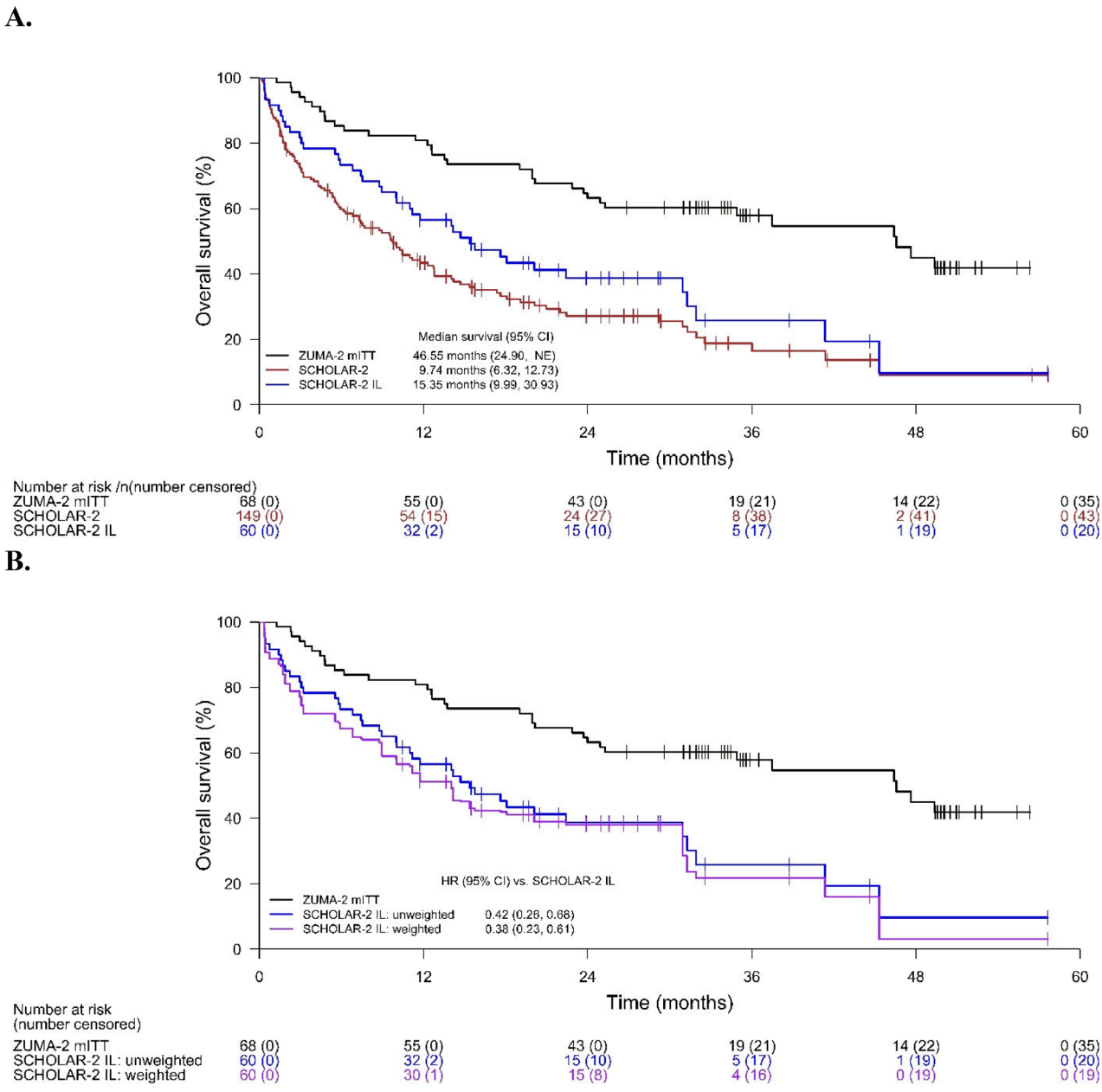

Figure 3. Overall survival. (A) Reported/unadjusted Kaplan-Meier estimates of overall survival for ZUMA-2 mITT, SCHOLAR-2 (i.e. all 149 post-BTKi treated patients), and SCHOLAR-2 IL (i.e. initial-line cohort). (B) Comparison of overall survival for ZUMA-2 mITT (unadjusted) compared to SCHOLAR-2 IL (unadjusted and IPW-adjusted). For illustrative purposes, the weights for 'SCHOLAR-2 IL: weighted' patients were standardized so that the rescaled weights are relative to the original unit weights of each SCHOLAR-2 patient; as such, the numbers at risk for both 'SCHOLAR-2 IL: unweighted' and 'SCHOLAR-2 IL: weighted' are the same at time = 0. In the actual analysis, the unscaled conventional weights were used. CI: confidence interval; HR: hazard ratio; IL, initial-line; IPW: inverse probability weighting; mITT: modified intention-to-treat; NE: not estimable.

both study populations. Additionally, the IPW-full model (balancing all eight covariates) was included as a sensitivity analysis. Similarly for the RA and DR approach, the impact of covariates in the estimation of OS HRs was assessed by comparing the adjusted OS HRs obtained from models from the main analyses (inclusion of variables identified as potential confounders based on univariate Cox models) and sensitivity analyses (restricting to the four key relevant prognostic factors of interest or balancing of all eight variables). Results suggested that OS HR was not highly sensitive to which covariates were included in the model given the small shifts in the point estimates across the models.

When comparing between methods for adjustment, it is important to highlight that the IPW provides a marginal HR, a relative treatment effect averaged over all patients in a target population, while the

Figure 4. Hazard ratios of overall survival for brexu-cel (ZUMA-2) versus standard of care (SCHOLAR-2). Across all comparisons, hazard ratio estimates were significantly meaningful at the 0.05 significance level, indicating that brexu-cel improved overall survival compared to standard of care. Brexu-cel: brexucabtagene autoleucel; CI: confidence interval; DR: doubly-robust; IL: initial-line cohort (SCHOLAR-2); INF: inferential set (ZUMA-2); IPW: inverse probability weighting; ITT: intention-to-treat set (ZUMA-2); MI: multiple imputation; mITT: modified intention-to-treat set (ZUMA-2); PP: period-prevalence cohort (SCHOLAR-2); RA: regression analysis; SA: sensitivity analysis.

regression-based analyses (RA and DR methods) provide a conditional HR given certain patient characteristics. In survival analysis, these two measures of relative treatment effects are not equivalent; therefore, it is recommended to marginalize conditional HRs for meaningful comparisons [36,37]. Although conditional HRs were not marginalized in this study, we anticipate comparable findings for both marginal and conditional HRs because the SCHOLAR-2 analysis cohorts had considerable overlap in the key prognostic factors at baseline with ZUMA-2 (two factors well-balanced with ASD <10% and other two factors with ASD ≤25%), prior to being weighted.

Our analyses were conducted using real-world data from SCHOLAR-2 in Europe which differed from ZUMA-2 in terms of study design (observational study vs clinical trial), study location (Europe vs United States/Europe), and data availability (higher rates of missing variables as anticipated in retrospective chart reviews). While SCHOLAR-2 was exclusively conducted in Europe, the majority (91%) of patients in ZUMA-2 were from the United States. Consequently, the adjusted OS in SCHOLAR-2 may not be fully representative of patients undergoing treatment in the United States or other non-European countries, attributable to the possible variations in non-CAR T-cell SOC regimens received and distinct clinical management approaches adopted across different countries and regions. Should additional real-world data become available, it would be of interest to conduct a similar comparison between ZUMA-2 and a real-world population with a similar distribution of countries and regions as ZUMA-2, considering the potential for different treatment effects stemming from differences in post-protocol therapy.

In conclusion, the naïve and adjusted indirect comparisons suggested that brexu-cel was more effective in terms of OS than non-CAR T-cell SOC for the treatment of R/R MCL post-BTKi therapy. The consistency of the results across the naive and various adjustment methods and the high concordance across the various sensitivity analyses provide compelling evidence for the validity and robustness of the study findings. The substantial improvement in OS of brexu-cel compared to SOC (adjusted HRs ranging from 0.30 to 0.52) underlines that brexu-cel is an important new advance for

R/R MCL. Given the number of assumptions and limitations around covariate adjustment and the modest SCHOLAR-2 cohort sample size, results should be interpreted with caution; nevertheless, our findings suggest that brexu-cel can help address the significant lack of effective treatments for patients with R/R MCL who have previously received a covalent BTKi therapy.

Acknowledgement

G.H., G.S., M.D., L.O., E.G., P.L.Z., K.L., A.V., M.J., A.O., S.S., C.T., J.L., V.R.Z., J.M.S., A.J.U., L.F., and T.A.E. contributed to the study concept and design, data collection, and interpretation of data. J.M.H.C., J.E.P., and S.K. contributed to the study concept and design, analysis and interpretation of data, manuscript drafting, project administration, statistical analysis, and verification of the underlying data reported in the manuscript. J.J.W., S.W.W., and A.N. contributed to the study concept and design, interpretation of data, project administration, and verification of the underlying data reported in the manuscript. J.R. contributed to the study concept and design, and interpretation of data. All authors reviewed, revised, and approved the final manuscript for submission.

Disclosure statement

G.H. has received grants or contracts from Kite, a Gilead Company, Incyte, Janssen, Morphosys, Pfizer, Roche, and Abbvie; has received consulting fees from Abbvie, ADC-Therapeutics, AstraZeneca, BMS, Genmab, Kite, a Gilead Company, Incyte, Janssen, Miltenyi, Novartis, Roche, and Lilly; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, AstraZeneca, Beigene, BMS, Genmab, Kite, a Gilead Company, Incyte, Janssen, Lilly, and Roche; has received support for attending meetings and/or travel from Kite, a Gilead Company, and Janssen; and has participated on a Data Safety Monitoring Board or Advisory Board for Miltenyi. M.D. has received institutional support for clinical trials from Abbvie, Bayer, Celgene/BMS, Kite, a Gilead Company, Janssen, and Roche; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astra Zeneca, Beigene, Kite, a Gilead Company, Janssen, Lilly, Novartis, and Roche; has received support for attending meetings and/or travel from Janssen and Roche; and has participated on a Data Safety Monitoring Board or Advisory Board for Abbvie, AstraZeneca, Beigene, Celgene/BMS, Kite, a Gilead Company; Janssen, Lilly/Loxo, Novartis, Roche. L.O. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen; has received support for attending meetings and/or travel from Roche and AstraZeneca; and has participated on a Data Safety Monitoring Board or Advisory Board for Roche and Gilead Sciences. P.L.Z. has received consulting fees from MSD, Eusapharma, and Novartis; has received payment or honoraria for speakers bureaus from Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, AstraZeneca, Takeda, Roche, Eusapharma, Kyowa Kirin, Novartis, Incyte, Beigene; and has participated on an Advisory Board for Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, AstraZeneca, Takeda, Roche, Eusapharma, Kyowa Kirin, Novartis, ADC Therapeutics, Incyte, and Beigene. K.L. has received consulting fees from Genmab, Roche, Kite, a Gilead Company, and Beigene; has received payment or honoraria for educational events from Abbvie and Celgene/BMS; has received support for attending meetings from BMS and Takeda; and has leadership or fiduciary role in NCRI, EHA LyG, WiL, and Epcoritamab Global Council. A.V. has received payment or honoraria for educational events and support for attending meetings and/or travel from AstraZeneca; and has participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca. M.J. has received honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Pierre Fabre, and Kite, a Gilead Company. S.S. has received grants or contracts; consulting fees; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; support for attending meetings and/or travel; equipment, materials, drugs, medical, writing, gifts or other services; and payments for participation on a Data Safety Monitoring Board or Advisory Board from AbbVie, Acerta, Amgen, AstraZeneca, BeiGene, BMS, Celgene, Genentech, Gilead Sciences, GSK, Hoffmann-La Roche, Incyte, Infinity, Janssen, Novartis, Pharmacyclics, Sunesis, and Verastem. J.L. has received support for attending meetings and/or travel from Novartis, Takeda, BMS, and Kite, a Gilead Company; and participated on a Data Safety Monitoring Board or Advisory Board for Blueprint pharma and Kite, a Gilead Company. V.R.Z. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gentili, Incyte, Janssen, Lilly, Novartis, and Takeda; has received support for attending meetings and/or travel from Takeda, Janssen, and Roche; and has participated on a Data Safety Monitoring Board or Advisory Board for Kite, a Gilead Company, Janssen, MSD, Roche, Servier, and Takeda. J.M.S. has received honoraria for medical educational events from Roche, Kite, a Gilead Company, Celgene/BMS, Novartis, Janssen, and Incyte; has received honoraria for consultancy from Roche and Incyte; has received support for attending meetings and/or travel from Roche and Kite, a Gilead Company; and has received honoraria for participation in Advisory Board from Roche, Kite, a Gilead Company, Celgene/BMS, Novartis, Janssen, Incyte, Beigene, and Lilly. T.A.E. has received research funding from Beigene and AstraZeneca; has received consulting fees from Loxo Oncology, Janssen, Lilly, Abbvie, AstraZeneca, Roche, Incyte, Autolus, Beigene, and Kite, a Gilead Company; has received payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Loxo Oncology, Janssen, Lilly, Abbvie, AstraZeneca, Roche, Beigene, and Kite, a Gilead Company. J.J.W. is an employee of Kite, a Gilead Company; has received honoraria from the Patient-Centered Outcomes Research Institute (PCORI), both as a member of the Rare Disease Advisory Panel, and as a grants reviewer for the Improving Methods Program; has received travel/meeting support from Kite, a Gilead Company, and Amgen; owns stock in Gilead Sciences, Amgen, Abbott, AbbVie, Pfizer, Roche, Curis, Avid Biosciences, Evofem, Lensar, VBI Vaccines,

and Viracta Therapeutics. A.N. is an employee of Gilead Sciences Europe; own stocks in Gilead Sciences and Amgen; and has received support for attending meetings and/or travel from Kite, a Gilead Company; J.R. has received support from Kite, a Gilead Company and Janssen; S.W.W. has received consulting fees from Kite, a Gilead Company, Abbvie and Johnson & Johnson. G.S. has received consulting fees from Abbvie, Celgene/BMS, Epizyme, Genmab, Incyte, Janssen, Kite, a Gilead Company, Loxo, Milteniy, Molecular Partners, Morphosys, Nordic Nanovector, Novartis, Rapt, and Takeda; has received payment or honoraria for speaking in symposium from Bayer, Epizyme, and Regeneron; has participated on a Data Safety Monitoring board or Advisory Board for Beigene; and has stock or stock options from Owkin. J.M.H.C., S.K., and J.E.P. are employees of PRECISIONheor which received funding for this study from Kite, a Gilead Company. E.G., A.O., C.T., A.J.U., and L.F. declare no competing interests.

Funding

This study was sponsored by Kite, a Gilead Company.

ORCID

Jenny M. H. Chen http://orcid.org/0000-0002-0575-3699
Sam Keeping http://orcid.org/0000-0002-4281-1536

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