Research Article

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Effectiveness of tisagenlecleucel versus real-world standard of care in relapsed/refractory follicular lymphoma

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Aim: To contextualize the effectiveness of tisagenlecleucel versus real-world standard of care (SoC) in relapsed/refractory follicular lymphoma. **Materials & methods:** A retrospective indirect matched comparison study using data from the phase II ELARA trial and the US Flatiron Health Research Database. **Results:** Complete response rate was 69.1 versus 17.7% and the overall response rate was 85.6 versus 58.1% in tisagenlecleucel versus SoC, post weighting by odds. For overall survival, an estimated reduction in the risk of death was observed in favor of tisagenlecleucel over SoC. The hazard ratio for progression-free survival was 0.45 (95% CI: 0.26, 0.88), and for time-to-next treatment was 0.34 (95% CI: 0.15, 0.78) with tisagenlecleucel versus SoC. **Conclusion:** A consistent trend toward improved efficacy end points was observed in favor of tisagenlecleucel versus SoC.

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Follicular lymphoma (FL) is an indolent B-cell lymphoproliferative disorder characterized by diffuse lymphadenopathy, splenomegaly and involvement of the bone marrow [1,2]. It is the second most common non-Hodgkin lymphoma (NHL) subtype, accounting for approximately 35% of all NHL cases (~70% of indolent lymphomas) diagnosed in the USA and Western Europe [2–4]. FL is a slow-growing form of NHL with a relapsing-remitting course of disease [4–7]. National Comprehensive Cancer Network (NCCN) guidelines recommend anti-CD20 monoclonal antibody-based chemoimmunotherapy for patients with FL at first relapse following their first line of therapy [8]. Evidence reveals that 19–26% of patients with FL develop relapsed/refractory (r/r) FL within 2 years of initial chemoimmunotherapy [9,10]. The US FDA/NCCN approved or recommended contemporary treatments for r/r FL include, radioimmunotherapy (e.g., 90Yttrium ibritumomab tiuxetan) [11], immunomodulatory drug-monoclonal antibody combinations (e.g., lenalidomide with rituximab) [12], PI3K delta and CK-1 epsilon inhibitors (e.g., umbralisib) [13], selective EZH2 inhibitors (e.g., tazemetostat) [14] and BTK inhibitors (e.g., ibrutinib) [8,15]. However, approvals for several PI3K inhibitors (e.g., duvelisib, umbralisib, ublituximab and idelalisib) have been revoked by FDA or drugs have been withdrawn by the manufacturers due to toxicity or trial completion issues [16]. A significantly low overall survival (OS), multiple early relapses and a more aggressive disease course were reported in 20% of patients with FL [17]. The analysis of the National LymphoCare study revealed poor survival in patients with POD24 (progression of disease within 2 years of treatment); the findings revealed 68% of OS at 2 years and 50% of OS at 5 years compared with 97 and 90%, respectively, in the reference group [10]. Therefore, there is an unmet need for effective and well-tolerated treatments for patients with r/r FL [5].

With the advent of immunotherapy, chimeric antigen receptor (CAR-T) cell products (axicabtagene ciloleucel and tisagenlecleucel) were recently approved by both FDA and EMA based on their promising response rates in patients with r/r FL [1,17,18]; in addition, TRANSCEND-FL trial is currently evaluating lisocabtagene maraleucel

for r/r FL (NCT04245839) [17,19]. Recently, the mosunetuzumab, an anti-CD3/CD20 bispecific antibody received approval based on high response rates in heavily pretreated patients with r/r FL (ORR [CRR]: 78.9% [57.8%]) [20–23].

Tisagenlecleucel is an autologous anti-CD19 CAR-T cell therapy for the treatment of patients aged ≤25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse, and in adult patients with r/r large B-cell lymphoma after ≥2 lines of systemic therapy including diffuse large B-cell lymphoma arising from FL [24,25]. The efficacy and safety of tisagenlecleucel in this patient population were assessed in phase II, single-arm ELARA trial in adult patients with r/r FL disease after ≥2 lines of prior therapy. In a primary analysis of the ELARA trial (n = 94; median follow-up: 16.59 months), the primary end point was met, with a complete response rate (CRR) of 69.1% (95% confidence interval [CI]: 58.8, 78.3), and an overall response rate (ORR) of 86.2% (95% CI: 77.5, 92.4) [1]. Tisagenlecleucel is an effective treatment for patients with r/r FL, including in high-risk patient subgroups [1,26]. Tisagenlecleucel demonstrated a favorable safety profile in the r/r FL patient population, evidenced by manageable rates of cytokine release syndrome (48.5%; grade ≥3, 0%), neurological events (37.1%; grade ≥3, 3%), immune effector cell–associated neurotoxicity syndrome (4.1%, grade ≥3, 1%), and absence of treatment related deaths [1]. Based on these encouraging results, tisagenlecleucel has been recently approved by both and the EMA for patients with r/r FL who have had ≥2 lines of prior systemic therapy [24,25].

However, there is a lack of comparative evidence on the efficacy of tisagenlecleucel versus that of other therapies for patients with r/r FL. In this study, a combination of the target trial and ICH E9(R1) estimand frameworks [27,28] was used to define and emulate a target randomized controlled trial when contextualizing the ELARA trial using real-world data (RWD) [29,30]. Target trial emulation is a causal inference tool originally proposed in the context of observational studies to mitigate bias through design and analysis. Investigators begin by specifying the target (randomized) trial that we would have ideally performed, and then stipulate the design and analysis of the nonrandomized study to emulate this as closely as possible. Meanwhile, the estimand framework was originally proposed in the context of clinical trials. It is described in the ICH E9 addendum on estimands and sensitivity analyses in clinical trials with the aim to align clinical trial objectives with study design, data collection and analysis through a precise definition of the scientific quantity of interest (i.e., the 'estimand'). A combination of these approaches facilitated an evaluation of whether the external control data were adequate and sufficient to address the research question of interest and enabled alignment of the analysis with the target estimand [30]. More details on their application are provided elsewhere [28].

The aim of the current study was to contextualize the effectiveness of tisagenlecleucel as observed in the ELARA clinical trial versus real-world standard of care (SoC) as derived from the US Flatiron Health Research Database (FHRD). No safety analyses were planned considering that the safety profile of tisagenlecleucel is well-established and very distinct compared with the non-CAR-T therapies.

Materials & methods

Study design

This was a retrospective, indirect comparison of tisagenlecleucel for the treatment of r/r FL, using data from the single-arm, phase II ELARA trial (NCT03568461; named thereafter ELARA cohort), versus real-world standard of care (SoC), using data from the Flatiron 3L+ FL Outcomes Spotlight Study as external control (named thereafter real-world SoC cohort). Details of the ELARA clinical trial has been published previously [1]. The ELARA data cutoff date for the ELARA cohort in the present analysis was 29 March 2021. The real-world SoC cohort was based on data from the FHRD [31], which is a nationwide, electronic health record (EHR) derived, de-identified database originated from approximately 280 cancer clinics in the US (~800 sites of care; ~80% of community oncology practices and ~20% of academic centers) and composed of de-identified patient-level structured and unstructured data, curated through technology enabled abstraction [32,33]. In the present analysis, the data cutoff date for the real-world SoC cohort was 30 June 2020.

Patients

Inclusion criteria for patients in the ELARA cohort were based on the ELARA study and have been described previously [1]. In brief, patients were aged ≥18 years with r/r FL grade I, II or IIIA and met one of the following criteria: refractory to a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second or later line of systemic therapy; relapsed during anti-CD20 antibody maintenance (following at least 2 lines of therapies as above) or within 6 months after

maintenance completion; and relapsed after autologous hematopoietic stem cell transplantation (HSCT). Patients were excluded if they had evidence (at/before the study index date) of histologic transformation, FL grade 3B, anti-CD19 therapy or allogeneic HSCT [1], gene therapy or adoptive T-cell therapy, non-FL primary malignancy and active CNS involvement by malignancy.

For the real-world SoC cohort, inclusion and exclusion criteria from the ELARA trial were used to select patients from the FHRD (Supplementary Figure 1). Patients aged ≥18 years were included if: they were diagnosed with NHL (International Classification of Diseases 9th revision or 10th revision) and had two or more visits documented in the Flatiron Health network on or after 1 January 2011; had a tumor grade of I, II or IIIA or low grade not otherwise specified at the time of initial FL diagnosis on or after 1 January 2011; had received at least 3 lines (3L+) of systemic therapy for the treatment of FL, with the initiation of the third-line therapy no later than 3 months prior to the real-world SoC cohort data cutoff date to allow for a minimum of 3 months of follow-up; ;and had exposure to anti-CD20 therapy (rituximab, obinutuzumab or ofatumumab) and alkylating agents (cyclophosphamide, carmustine, bendamustine, ifosfamide, carboplatin, oxaliplatin, cisplatin, melphalan, chlorambucil, busulfan, dacarbazine or procarbazine) after FL diagnosis. For patients who were eligible for multiple 3L+ treatment options, a single 3L+ therapy was selected (index treatment) based on the highest propensity score (PS), in other words, the highest probability of being eligible for enrolment to ELARA, conditional on observed covariates measured at the start of each eligible line of therapy (refer to 'propensity score method and weighting by odds' in the Statistical Analysis section).

Treatments

In the ELARA trial, patients received tisagenlecleucel as a single intravenous infusion of a protocol specified dose range between 0.6×10^8 and 6×10^8 CAR^+ viable T cells on day 1. If needed, patients received optional bridging therapy and lymphodepleting therapy prior to tisagenlecleucel infusion, at the investigator's discretion [1]. In the real-world SoC cohort, the choice of SoC regimen was based on the patient's treatment eligibility criteria and was administered according to local practice, at the treating clinician's discretion.

Study end points

Study end points included complete response (CR), overall response (OR), OS, progression-free survival (PFS), PFS considering new anticancer therapy as an event and time-to-new treatment (TTNT).

CR and OR were defined as the absence of detectable cancer or any response (partial response or CR), respectively. In the ELARA trial, the response was determined based on Lugano 2014 classification response criteria [34]. The real-world response development approach began with a review of clinically relevant aspects for the population or disease of interest. While the adoption and implementation of the Lugano criteria have been limited in the real-world practice, key elements of the Lugano criteria, including the type of radiographic imaging or PET/CT scans, as well as clinician interpretation of these radiographic images, are available in the EHR. The real-world response development approach for this noninterventional study did not attempt to directly use the Lugano criteria but instead focused on abstracting data to support a clinically meaningful response. Abstractors enter the radiology scan date (i.e., the assessment date) from radiology reports. Abstractors bundle scans into assessment time points that encompass imaging performed within a +14 day window. If more than one radiology scan was performed within a 14-day period, this was abstracted as a single real-world response assessment, and the assessment date was recorded as the earliest scan date among those assessments.

OS was defined as the time from enrollment (for the ELARA trial) and treatment initiation (for the real-world SoC cohort) to death due to any cause, with the death date being the event date. In the real-world SoC cohort, death was assessed by Flatiron health, based on multiple census sources (EHR, social security death index and obituary data) [35]. If death was not observed, OS was censored at the patient's last activity date in the Flatiron network (corresponding to the patient's last clinic visit). Activity date was defined as the point in time when a record was entered as structured activity abstracted in the EHR, indicating that a patient was alive at that time.

Two versions of PFS with different approaches in handling the intercurrent event of initiation of a new anticancer therapy were considered. First, PFS was defined as the time from enrollment (for the ELARA trial) or treatment initiation (for the real-world SoC cohort) to first documented disease progression or death due to any cause, with the event date being the earliest date of progression or death. Patients were censored at the time of initiating a new anticancer therapy if no progression or death was observed before the new anticancer therapy. If a new anticancer

therapy was not observed, patients in the ELARA cohort and the real-world SoC cohort were censored at the last assessment date and last clinic note date, respectively.

In the ELARA trial, progression was assessed per Lugano 2014 classification criteria. In the real-world SoC cohort, progression was abstracted from EHR and defined as a distinct episode, in which the treating clinician concludes that there has been growth or worsening in FL disease based on a variety of evidence. The last clinic note dates reflect the date of the last clinic visit note in a patient's chart at the time of abstraction. This is reflective of the last time the patient had the potential to be assessed for progression by the clinician.

The second version of PFS considered the start of a new line of anticancer therapy as an event. For this analysis, PFS was defined as the time from enrollment (for the ELARA trial) or treatment initiation (for the real-world SoC cohort) to the earliest documented disease progression, death due to any cause or the start of a new line of anticancer therapy. In this analysis, patients without disease progression, death due to any cause, or the start of a new anticancer therapy were censored at the last assessment date or last clinic note date as described above.

TTNT was defined as the time from enrollment (for the ELARA trial) or treatment initiation (for the real-world SoC cohort) to the initiation of a new line of anticancer therapy (including hematopoietic stem cell transplant) or death due to any cause. The event date was defined as the earliest date of documented death or the start of another therapy. Patients in the real-world SoC cohort without an event during follow-up were censored on the last activity date.

Statistical analysis

Propensity score method & weighting by odds

Selection of index line for the real-world SoC cohort

For the real-world patients who had received 3L+ therapy, and hence satisfied ELARA inclusion/exclusion criteria for r/r disease at multiple time points, a PS model was used to select one line of 3L+ therapy per real-world patient [28]. A generalized estimating equation approach was used to fit a logistic regression among all ELARA patients and FHRD patients satisfying the inclusion/exclusion criteria, using a robust sandwich variance estimator to account for the correlation between repeated observations on the same patient.

The fitted logistic regression was used to derive a point estimate of the PS for each patient in the FHRD at each eligible line of therapy. The PS represents the probability of a real-world patient to be enrolled in the ELARA study, conditional on the observed covariates measured at the start of each line of therapy. One line of 3L+ therapy per real-world SoC patient was selected based on the highest PS, corresponding to the line of 3L+ therapy, at which the patient's baseline covariates were most closely aligned with those of the ELARA patient population. For example, for a real-world SoC patient who had received third-line, fourth-line, and fifth-line treatments, with the corresponding PS for each treatment line being 0.3, 0.6 and 0.2 respectively, the fourth-line treatment was selected for this patient. The key baseline prognostic covariates included in the PS model were age, race, gender, number of prior treatment lines, group stage at initial FL diagnosis, number of months between initial FL diagnosis and an indication of index treatment, double refractory status and disease progression within 24 months from the first anti-CD20 containing therapy prior to index treatment, sites of nodal involvement at the initial diagnosis and history of autologous stem cell transplant. These variables were selected prior to any study analyses following input from clinical collaborators and health authorities. All listed variables were anticipated to be strongly prognostic for the clinical outcomes of interest.

Balancing between ELARA & the real-world SoC cohort

After the selection of one line of 3L+ therapy for each real-world SoC patient, weighting by odds was performed. Patients in the ELARA cohort were assigned a weight of 1, and patients in the real-world SoC cohort were weighted by their estimated odds of being in the ELARA cohort, which is (PS)/(1-PS). Patients in the real-world SoC cohort whose propensity score did not fall within the range of propensity score from the ELARA cohort were excluded from the weighting process. Following the weighting-by-odds approach, real-world patients with a fitted PS greater than 0.5 were upweighted (i.e., assigned a weight greater than 1), while real-world patients with a fitted PS less than 0.5 were downweighted (assigned a weight less than 1). The final sample size of the real-world cohort after weighting could therefore be greater or less than the original (unweighted) sample size depending on the number of patients excluded and the original sample size with respective to the target (ELARA) population. A weighting-by-odds approach was adopted to reduce the systematic differences in baseline characteristics between the ELARA cohort and real-world SoC cohort and to estimate the average causal effect of prescribing tisagenlecleucel versus SoC as

measured by CRR, ORR, OS, PFS and TTNT among patients treated with tisagenlecleucel (i.e., average treatment effect on the treated patients). After weighting, cohorts were considered balanced if the absolute standardized mean difference (SMD) between cohorts for all prognostic variables included in the model were <0.25 [36].

Two prespecified key prognostic variables, history of autologous HSCT and sites of nodal involvement at initial diagnosis, were omitted from the weighting by odds model due to extreme imbalance and to achieve a better balance for all other prognostic variables. Given that ELARA patients had worse prognoses with respect to these prognostic variables, not adjusting for these prognostic variables represented a more conservative scenario where the outcomes favor the control group.

Evaluation of clinical outcomes

CR and OR were reported in proportions as CRR and ORR, and the average treatment effect on the treated was summarized using rate differences with 95% CI. Only real-world SoC patients with at least one known evaluation for response or documented death during treatment at the selected index line were considered for response analyses. PFS, OS, PFS considering new anticancer therapy as an event and TTNT were analyzed using Kaplan–Meier methods, with the average treatment effect on the treated summarized by the hazard ratio (HR) from a univariate Cox proportional hazards regression and 95% CIs. All 95% CIs were estimated using a bootstrap estimator with 10,000 samples [37]. The 2.5th and 97.5th percentiles of the empirical distribution for the treatment effect estimator were taken as the 95% CI. For the time-to-event end points, only data from the first 24 months after enrollment in the ELARA trial or 24 months after the start of the index treatment in the real-world SoC cohort were used, as few patients in the ELARA trials had >24 months of follow-up.

Sensitivity analyses

Primary analyses were not adjusted for missing or remaining imbalanced baseline prognostic variables. Two sensitivity analyses were carried out to assess the impact of prognostic variables that remained imbalanced (i.e., absolute SMD ≥0.25) after weighting: a subgroup analysis of patients without prior HSCT; and a regression adjustment that included all the remaining imbalanced prognostic variables in a regression model. In addition, three sensitivity analyses were carried out to assess the impact of missing key prognostic baseline variables: a complete-case analysis of patients with complete data on key prognostic variables; a worst-case analysis of patients with imputed values via single imputation for key prognostic variables to generate a conservative worst-case scenario (i.e., covariates imputed to the worst possible value for Flatiron, imputed to the least severe value for ELARA); and an analysis that compared patient characteristics by missing ECOG performance status.

Results

Patient attrition

For this indirect comparison, all 97 infused patients from the ELARA primary analysis were included in the ELARA cohort [1]. One patient was excluded from ELARA due to the missing value in the disease stage at the initial diagnosis. This patient was excluded to achieve model convergence for the generalized estimating equation approach in selecting the index line. For the real-world SoC cohort, records from overall 168,178 patients diagnosed with NHL with visits on or after 1 January 2011 were available in the FHRD. Of these, 519 patients had received at least 3 lines of systemic therapy for the treatment of FL, 419 patients had received anti-CD20 therapy and an alkylating agent and 391 patients had initiated at least one line of 3L+ therapy on or before 31 March 2020. After applying additional inclusion and exclusion criteria, 98 patients were included in the real-world SoC cohort (Supplementary Figure 1).

Baseline demographics & clinical characteristics

The baseline characteristics of the study cohorts evaluating time-to-event end points are presented in Table 1. Baseline characteristics of patient subgroups included in the CRR/ORR analyses (patients in the ELARA cohort and patients in the real-world SoC cohort with at least one known evaluation for response or documented death) are presented in Supplementary Table 1.

In the real-world cohort, SoC regimens in the selected line of therapy included anti-CD20 antibody plus alkylating agent (42 of 98; 42.9%), anti-CD20 antibody without an alkylating agent (36 of 98; 36.7%), an alkylating agent without anti-CD20 antibody (3 of 98; 3.1%) and regimens other than anti-CD20 antibody and an alkylating agent such as phosphoinositide 3-kinase inhibitor (17 of 98; 17.3%). The absolute SMD between the

Table 1. Baseline characteristics of the population used to evaluate time-to-event end points.

Baseline characteristics	ELARA cohort‡	Real-world SoC (before weighting)§		Real-world SoC (after weighting)§	
	(n = 97)	(n = 88)†	Absolute SMD (before weighting)¶	(n = 88)†	Absolute SMD (after weighting)¶
Prognostic factors included in PS modeling					
Age at index date# in years, median (range)	58 (29, 73)	63.5 (30, 85)	-0.54	55 (30, 85)	0.17
Male, %	66.0	54.1	0.24	71.5	-0.11
White, %	75.3	72.5	0.06	66.6	0.20
>4 lines of therapy received prior to index date#, %	28.9	6.1	0.62	27.0	0.05
Stage III-IV at initial diagnosis, %	80.4	80.6	-0.01	86.3	0.15
Months between initial diagnosis and index date#, median (range)	66.2 (6.4, 355.4)	41.07 (2.83, 100.30)	0.79	67.48 (2.83, 100.3)	0.37
Double refractory, %	68.0	63.3	0.10	76.4	-0.17
POD24, %	62.9	79.6	-0.37	68.9	-0.13
Prognostic factors not included in PS modeling					
Prior autologous HSCT, %	37.1	2.0	0.98	4.2	0.92
>4 sites of nodal involvement at initial diagnosis, %	44.3	14.3	0.70	7.2	0.86
Follow-up period (months), median (range)	15.1 (0.7, 26.1)	12.2 (0.03, 70. 7)	-0.08	13.6 (0.07, 70.7)	0.01

†Baseline characteristics represent the main population used for evaluating all time-to-event end points.
‡One patient from ELARA with missing for stage at initial diagnosis was excluded.
§The index line was selected from a GEE model including all the prespecified prognostic variables in the suggested format/categorization.
¶An absolute SMD value of <25% (or <0.25) for a particular prognostic variable was considered balanced.
#Index date is defined as the start date of standard of care in FHRD and date of enrollment in ELARA.
CRR: Complete response rate; FHRD: Flatiron Health Research Database; HSCT: Hematopoietic stem cell transplantation; ORR: Overall response rate; POD24: Progression of disease within 24 months; PS: Propensity scoring; SMD: Standardized mean differences; SoC: Standard of care.

two cohorts was assessed before and after weighting. Weighting by odds was used to address imbalances between the ELARA cohort and the preweighted real-world SoC cohort dataset, with the most baseline covariates showing absolute SMDs of less than 0.25 between groups, except for duration from the initial diagnosis to index date and two covariates excluded from the model in the overall study population. The median follow-up time for the ELARA cohort and the overall real-world SoC (postweighted) cohort were 15 and 14 months, respectively.

Clinical outcomes

ORR with tisagenlecleucel versus real-world SoC was 85.6 versus 62.5% of preweighting, and 85.6 versus 58.1% of postweighting (Table 2). Thus, differences in ORR for the ELARA cohort versus the real-world SoC cohort increased from 23.1% (95% CI: 9.9, 35.9) to 27.4% (95% CI: -3.0, 65.0) after weighting. For CRR, outcomes with tisagenlecleucel versus real-world SoC were 69.1 versus 27.8% of preweighting and 69.1 versus 17.7% of postweighting; thus, the differences in CRR increased after weighting from 41.3% (95% CI: 27.1, 55.1) to 51.4% (95% CI: 21.2, 68.8).

In the Kaplan–Meier analysis of OS, the median OS (after weighting) was not reached for both the ELARA cohort and the real-world SoC cohort in the first 24 month period (Figure 1). After weighting, Kaplan–Meier estimates of OS rates at 12 and 24 months were 96.6 and 87.8%, respectively, in the ELARA cohort, versus 84.5 and 79.1%, respectively, in the real-world SoC cohort. In Cox proportional hazards regression, an estimated reduction in the risk of death (by 59%) was in favor of tisagenlecleucel over SoC (HR: 0.41 [95% CI: 0.11, 1.47]).

The median PFS (postweighting) was not reached in the ELARA cohort and 9.9 months in the real-world SoC cohort (Figure 2). The estimated probability of PFS at 12 and 24 months was 73.2 and 56.1%, respectively, with tisagenlecleucel, versus 41.8 and 26.2%, respectively, with real-world SoC. The corresponding HR for PFS was 0.45 (95% CI: 0.26, 0.88), which indicates an estimated 55% of reduction in risk of progression or death with the ELARA cohort versus the real-world SoC cohort.

The median PFS considering the start of a new anticancer therapy as an event was not reached in the ELARA cohort and was 9.9 months in the real-world SoC cohort (postweighting analysis). The estimated probability of being progression free at 12 and 24 months was 70.5 and 54.1%, respectively, with tisagenlecleucel and 39.4 and 24.6%, respectively, with real-world SoC. The corresponding HR was 0.45 (95% CI: 0.27, 0.83), which indicates

Table 2. Efficacy comparison between ELARA cohort (primary analysis) and real-world standard of care cohort.

Variables	ELARA cohort‡	Real-world SoC (before weighting)†	Real-world SoC (after weighting)†
Response rate§	**n = 97**	**n = 72**	**n = 89**
Overall response rate, % (95% CI)	85.6 (78.4, 91.8)	62.5 (51.4, 73.6)	58.1 (21.3, 88.2)
Difference, % (95% CI)		23.1 (9.9, 35.9)	27.4 (-3, 65)
Complete response rate, % (95% CI)	69.1 (59.8, 78.4)	27.8 (18.1, 37.5)	17.7 (3.8, 46.9)
Difference, % (95% CI)		41.3 (27.1, 55.1)	51.4 (21.2, 68.8)
Progression-free survival	**n = 97**	**n = 98**	**n = 88**
Median, % (95% CI)	NR	9.9 (6.8, 19.3)	9.9 (8.0, 19.3)
12 months, % (95% CI)	73.2 (64.1, 82.1)	45.2 (34.1, 56.5)	41.8 (20.0, -67.2)
24 months, % (95% CI)	56.1 (41.8, 68.9)	32.6 (20.9, 44.4)	26.2 (8.1, 52.0)
HR (95% CI)		0.45 (0.29, 0.69)	0.45 (0.26, 0.88)
Overall survival	**n = 97**	**n = 98**	**n = 88**
Median, % (95% CI)	NR	NR	NR
12 months, % (95% CI)	96.6 (92.3, 100)	77.0 (67.5, 86)	84.5 (64.9, 95.9)
24 months, % (95% CI)	87.8 (77.3, 96.2)	67.7 (56.5, 78.5)	79.1 (58.8, 92.5)
HR (95% CI)		0.24 (0.08, 0.51)	0.41 (0.11, 1.47)
PFS considering new anticancer therapy as event	**n = 97**	**n = 98**	**n = 88**
Median, % (95% CI)	NR	9.6 (5.8, 15.9)	9.9 (8.0, 17.3)
12 months, % (95% CI)	70.5 (61.1, 79.8)	42.3 (31.7, 53.2)	39.4 (18.7, 63.4)
24 months, % (95% CI)	54.1 (40.2, 66.7)	29.2 (18.5, 40.3)	24.6 (7.6, 48.4)
HR (95% CI)		0.44 (0.29, 0.67)	0.45 (0.27, 0.83)
Time-to-new therapy or death	**n = 97**	**n = 98**	**n = 88**
Median, % (95% CI)	NR	11.6 (8.0, 19.0)	19 (8.3, 22.1)
12 months, % (95% CI)	85.9 (78.2, 92.5)	47.6 (36.5, 58.7)	54.2 (29.2, 75.5)
24 months, % (95% CI)	68.4 (47.0, 84.1)	34.5 (23.0, 46.2)	45.5 (18.9, 68.1)
HR (95% CI)		0.25 (0.15, 0.41)	0.34 (0.15, 0.78)

†The effective sample sizes were 18 and 29 in the population used for evaluating response and TTE endpoints, respectively.
‡One patient from ELARA with missing for stage at initial diagnosis was excluded.
§Only patients with at least one evaluation for response or a documented death during treatment were considered for this analysis (N = 72; 25 patients were excluded). Because propensity score models are different for the response and TTE outcomes, a different subset of real-world patients was excluded due to nonoverlapping propensity score. As the model would up-weigh/down-weigh each individual patient differently depending on the propensity score, the final sample size after weighting (ie, sum of weights) may be greater or less than the original (unweighted) sample size. Kaplan–Meier and Cox regression results are based on survival data within the first 24 months (patients with survival data beyond 24 months were censored at Month 24). Ten thousand bootstrap samples were randomly drawn to calculate the percentile-based 95% CI.
CI: Confidence interval; FHRD: Flatiron Health Research Database; HR: Hazard ratio; NR: Not reached; SoC: Standard of care; TTE: Time-to-event.

an estimated 55% of reduction in risk of progression, death or start of new anticancer therapy with tisagenlecleucel versus real-world SoC.

The median duration to TTNT or death was not reached in the ELARA cohort and was 19.0 months in the real-world SoC cohort (postweighting analysis). The corresponding HR of death was 0.34 (95% CI: 0.15, 0.78) in the ELARA cohort versus the real-world SoC cohort (Table 2).

In sensitivity analyses to adjust for imbalanced or missing key prognostic variables, results were largely consistent with the findings from the primary analysis. For instance, the CRR was in favor of the ELARA cohort with at least a difference of 39% among all the sensitivity analyses (Supplementary Table 2). The difference in ORR for the ELARA cohort versus the real-world SoC cohort was at least 28.6% among all the sensitivity analyses. Overall survival was in favor of the ELARA cohort with HRs all smaller than 0.46 among all the sensitivity analyses (Supplementary Table 2).

Discussion

This indirect comparison in patients with r/r FL assessed the effectiveness of tisagenlecleucel, as reported in the ELARA clinical trial, versus real-world SoC, as recorded in the FHRD. When a randomized controlled study design is not feasible due to practical or ethical reasons, the use of an external control derived from RWD can be a valid option to generate contextual information on treatment effectiveness and can help interpret the results of an investigational single-arm trial such as the ELARA trial [38]. The present analyses were performed to contextualize

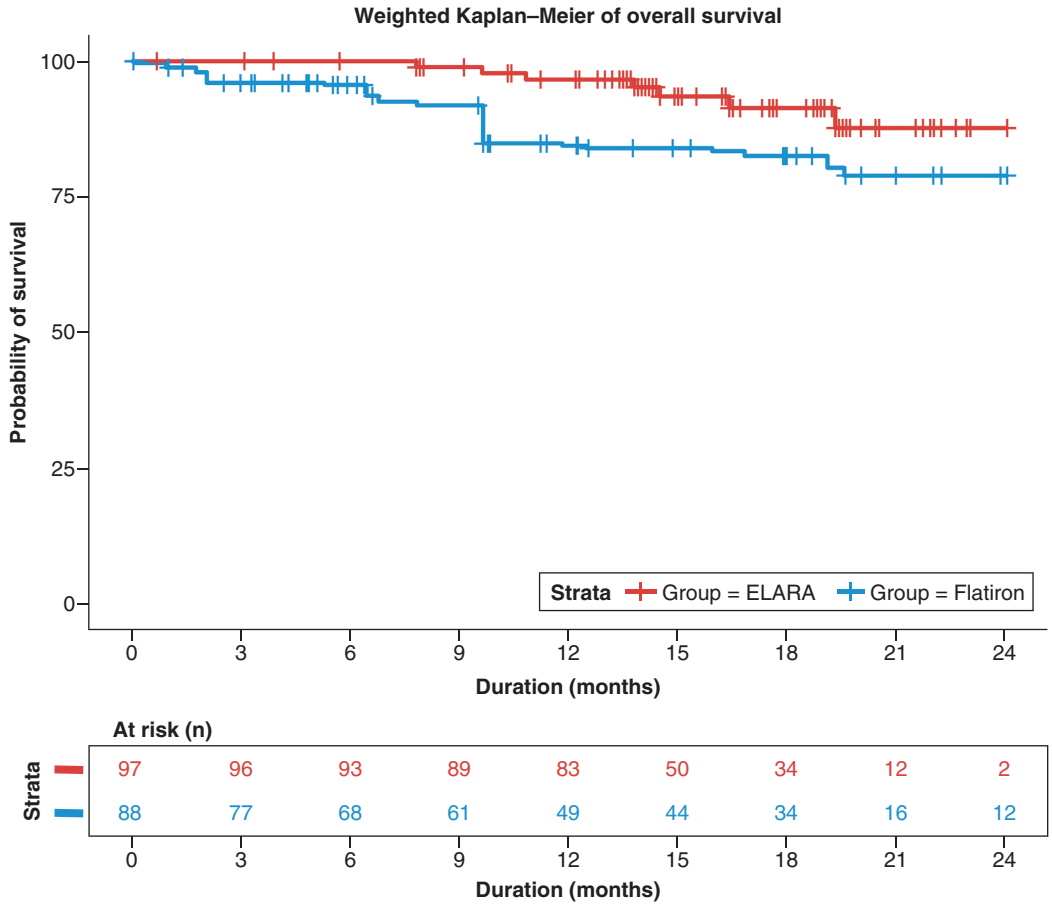

Figure 1. Kaplan–Meier curve of overall survival after weighting adjustment. For Kaplan–Meier curve, Hall–Wellner confidence bands were not provided, as we have used bootstrap to estimate the confidence intervals.

efficacy results of tisagenlecleucel in the ELARA trial in a similar group of patients with r/r FL treated with SoC in the real-world setting.

In the present study, a combination of the target trial and the ICH E9 (R1) estimand frameworks was applied to design and analyze a real-world-based external control arm for the ELARA trial. The aim was to emulate an active controlled randomized trial comparing the tisagenlecleucel treatment strategy evaluated in ELARA with the SoC per physician's choice [28]. Use of the frameworks facilitated a precise definition of the question of scientific interest as well as discussions between interdisciplinary team members regarding similarities and differences between the target randomized trial and the planned indirect comparison and whether differences impacted on the feasibility of the proposed comparison. More recently, the FDA draft guidance on Considerations for the Design and Conduct of Externally Controlled Trials recommends use of the estimand framework to inform the design of an externally controlled trial [39].

The present indirect comparison indicates a consistent trend in the PFS, OS and TTNT HRs in favor of tisagenlecleucel versus real-world SoC. However, the median OS was not reached for both the ELARA cohort and the real-world SoC cohort in the first 24 month period, and an analysis based on the Cox regression model favored tisagenlecleucel over SoC, given there was an estimated 59% of reduction in the risk of death. These results suggest a potential clinical benefit for patients in the ELARA cohort versus those in the real-world SoC cohort, as indicated by the improvement in response rates and survival. Findings from the current study can be compared with other studies, which were conducted with the similar aim of constructing an external control cohort to provide comparative evidence on tisagenlecleucel in r/r patients with FL. A study by Salles *et al.* [40] performed an indirect treatment comparison for patients from the ELARA trial and from ReCORD-FL (a real-world cohort study that met similar eligibility criteria to ELARA). The CRR was 69.1% for tisagenlecleucel versus 37.3% for usual care; the

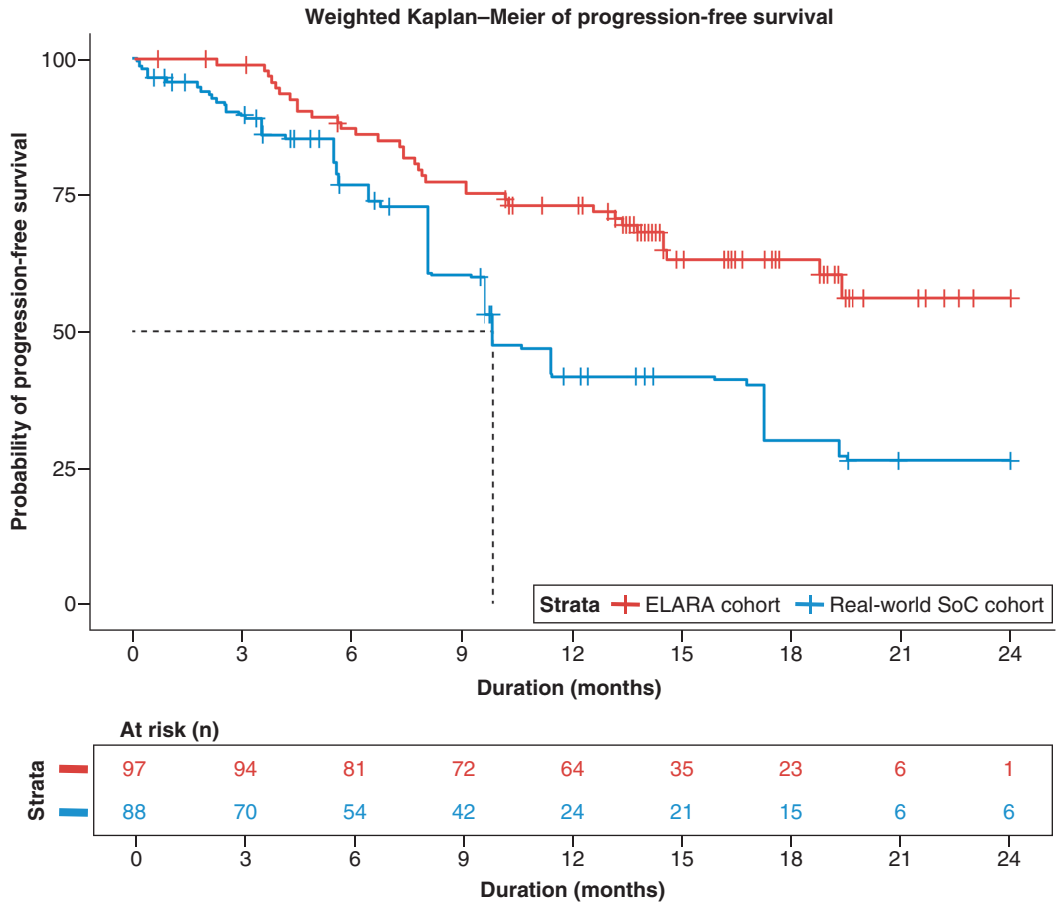

Figure 2. Kaplan–Meier curve of progression-free survival after weighting adjustment. For Kaplan—Meier curve, Hall-Wellner confidence bands were not provided, as we have used bootstrap to estimate the confidence intervals.

ORR was 85.6% for tisagenlecleucel versus 63.6% for usual care [40], which are comparable with the results from the current study. A retrospective, observational study was conducted by Ghione *et al.* to contextualize the clinical benefit associated with axicabtagene ciloleucel in patients with r/r FL by comparing the results from a single-arm phase II trial (ZUMA-5) with an external control real-world cohort (SCHOLAR-5). The ORR and CR rates were 94.2% and 79.1% in ZUMA-5 and 49.9 and 29.9% in SCHOLAR-5 [41]. In a retrospective study by McGouch *et al.*, clinical outcomes were compared between a RWD; Flatiron external control cohort and a mosunetuzumab single-arm phase II trial (M SAT) cohort in patients with r/r FL. ORR was 80 versus 75% and CRR was 60 versus 33%, respectively, in the M SAT cohort versus the RWD cohort [42].

In the current study, 25% of cutoff for SMD was aligned with recommendations from the literature [36,43]. A larger threshold was chosen in consideration of smaller sample size as change in proportion of a covariate could be driven by a difference of a few patients. For matched samples, or regression adjustment to be trustworthy, the absolute standardized differences of means should be less than 0.25 and the variance ratios should be between 0.5 and 2 [36,43].

The current study has some limitations. Although RWD may provide a wide range of available data, its application in externally controlled trials may be challenging [38]. There are notable differences between prospectively collected trial data and data collected from FHRD, which comprises observational data collected retrospectively. There may be inconsistency in the collection and availability of relevant variables captured between FHRD and ELARA. Although the target population can be emulated based on key ELARA eligibility criteria, not all criteria can be captured in the RWD (e.g., ECOG status or laboratory results may not be recorded or incomplete). CR and progression in the RWD were also assessed differently and not per the Lugano 2014 classification criteria [28,34] as used in ELARA. Another limitation is missing data for key prognostic variables, which was addressed in this study by conducting sensitivity analyses. Additionally, there may be inherent, unmeasured differences between patients

in the FHRD receiving SoC and patients who chose to enroll in ELARA and were seeking cell therapy. It should be acknowledged that despite best attempts, the potential for selection bias, as well as unmeasured and residual confounding, cannot be fully ruled out.

The real-world external control data extracted from the FHRD provide an opportunity to explore outcomes for patients with r/r FL who have received at least 3 lines of therapy with a poor prognosis and a high unmet need.

Conclusion

In the analyses with adjustment for baseline prognostic factors, there was a consistent trend toward greater CRR, ORR, OS, PFS and TTNT in favor of tisagenlecleucel versus SoC in patients with r/r FL. The improved efficacy benefits associated with tisagenlecleucel are consistent for both primary and sensitivity analyses. This indirect comparison provides supportive evidence of the clinically meaningful benefit associated with tisagenlecleucel observed in the ELARA trial in a patient population with a high unmet need.

Summary points

- This retrospective study contextualized the effectiveness of tisagenlecleucel as observed in the ELARA clinical trial among real-world standard of care as derived from the US Flatiron Health Research Database in patients with relapsed/refractory follicular lymphoma.
- The indirect comparison highlights a consistent trend toward greater complete response rate, overall response rate, overall survival, progression-free survival and time-to-new treatment in favor of tisagenlecleucel compared with standard of care in the relapsed/refractory follicular lymphoma setting.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0173

Financial & competing interests disclosure

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Ethical conduct of research

The ELARA study was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. Approvals were obtained from the institutional review board/independent ethics committee for the trial protocol, written informed consent form, and patient recruitment procedures [1]. Before enrollment in the ELARA study, written informed consent was obtained from each participant. Institutional review board approval of the study protocol for FHRD was obtained prior to the study conduct and included a waiver of informed consent.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with the applicable laws and regulations. The availability of trial data is according to the criteria and process described on www.clinicalstudydatarequest.com. This report contains data originating from US Flatiron Health Research Database.

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