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Poster: HPR125

Real-World External Control Arm to Support Indication for Tisagenlecleucel in Relapsed/Refractory Follicular Lymphoma in the European Union: A Use Case

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KEY FINDINGS & CONCLUSIONS

- Real-world evidence (RWE) of the clinically meaningful benefit associated with tisagenlecleucel, as demonstrated in a patient population with high unmet need in the ELARA trial, was generated using a rigorous methodological approach implemented by a cross-functional project team.[5]
- Health Authority opinions and recommendations can be leveraged to develop fit-for-purpose RWE to supplement clinical trial data and meet regulatory stakeholder requirements.
- Tisagenlecleucel became the first CAR-T cell therapy approved in the EU for adults with relapsed/refractory (r/r) follicular lymphoma (FL).

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BACKGROUND AND PROBLEM STATEMENT

- In the single-arm Phase 2 ELARA trial (NCT03568461), tisagenlecleucel demonstrated efficacy and a favorable safety profile in patients with relapsed/refractory (r/r) follicular lymphoma (FL) after ≥ 2 lines of prior therapy.[1]
- During the clinical trial application Health Authority review, it was acknowledged there was a lack of standardized treatment in the ELARA r/r FL patient population, and patients typically received heterogeneous treatment to manage their disease.
- The European Medicines Agency (EMA) emphasized the importance of having an external control arm (ECA) with patient-level data as part of an evidence package to support a submission for a tisagenlecleucel indication in r/r FL

KEY CHALLENGES

- Uncharted territory
  - No templates to follow for documentation (e.g., briefing book creation) and associated processes.
- Missingness in real-world data (RWD)
  - Methodological challenges of missing data and prognostic covariates from RWD, such as data on Eastern Cooperative Oncology Group (ECOG) status.
- Endpoint assessment
  - Designing and defining the RWE and trial endpoints was challenging due to difficulties aligning endpoint definitions and inclusion/exclusion criteria.

APPROACH

- As part of the strategy to address this need, a cross-functional, multi-stakeholder team developed a plan to generate RWE from two data sources: Flatiron Health Research Database (FHRD, presented here) and ReCORD-FL,[2] via a target trial to estimate the efficacy of tisagenlecleucel compared with real-world standard of care (SoC).[3,4]
- ELARA primary and secondary clinical endpoints were used to identify suitable real-world databases for inclusion in the target trial.
- FHRD is a de-identified longitudinal database derived from electronic health records (EHR) from over 280 cancer clinics (~800 sites of care), comprising ~80% community oncology practices and ~20% academic centers in the US.
- Real-world endpoints including response and progression were assessed for abstraction reliability and data completeness as part of the feasibility assessment by FHRD. Sufficient evidence was found to support the use of these real-world endpoints.
- Key ELARA eligibility criteria were applied to the FHRD to select a cohort of patients with >3 lines of systemic FL therapy.
- Anonymized patient-level ELARA clinical trial data was evaluated to characterize key patient demographic and baseline clinical characteristics to ensure comparability of tisagenlecleucel and FHRD cohorts and to facilitate statistical analysis.

TARGET TRIAL METHODS AND COHORT CREATION

Methods

Study Design

A non-interventional, retrospective cohort study utilizing the FHRD and anonymized patient-level data from the single-arm Phase 2 ELARA trial.

Construction of Flatiron real-world SoC cohort

- Key eligibility criteria from ELARA were applied to FHRD.
- One line of therapy from FHRD was selected accounting for important prognostic variables/confounders using a generalized estimating equation (GEE) model.
- Propensity score methods were used to control for key prognostic variables/confounders and estimate average treatment effect on the treated (ATT).
- Efficacy of tisagenlecleucel was examined by complete response rate (CRR), overall response rate (ORR), overall survival (OS), progression-free survival (PFS) and time to next treatment (TTNT).

Propensity Score Methods

- Weighting by odds was utilized to reduce systematic differences in key prognostic variables (determined by expert input/literature review) between ELARA and FHRD.
- Patients in ELARA were assigned a weight of 1 and patients in FHRD were weighted by their odds of being in ELARA based on propensity score (PS): (PS) / (1-PS).
- PS is the probability to be in ELARA conditional on key prognostic factors measured at the start of each line of therapy:
  - Key prognostic factors 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 indication of index treatment, double refractoriness, and disease progression within 24 months.
- An absolute standardized mean difference (SMD) < 0.25 between ELARA and FHRD was considered to be balanced.[5]

Figure 1: Real-World Cohort Patient Selection

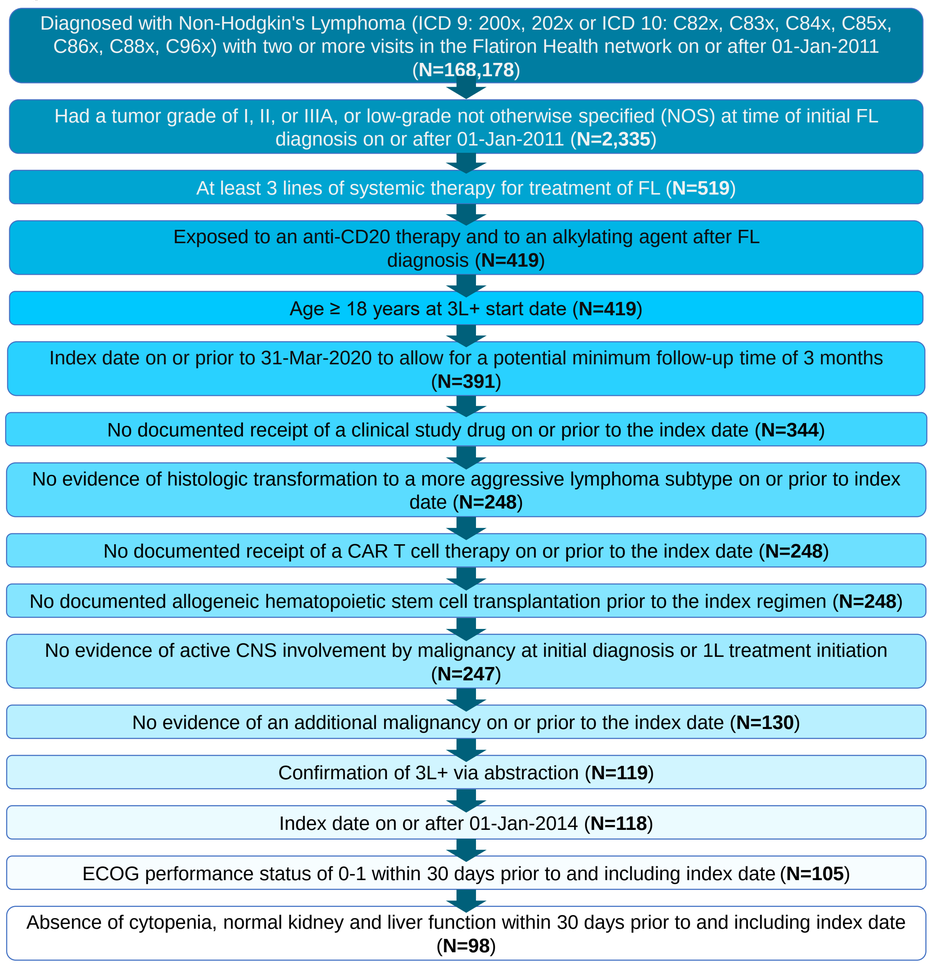


Table 1: A balanced SoC cohort was created using the Flatiron data for most key prognostic variables

Baseline characteristics	ELARA (N = 97)	FHRD (after weighting) (N = 88)*	Absolute SMD (after weighting)
Prognostic factors included in PS modeling			
Age at index date* in years, median (range)	58 (29-73)	55 (30-85)	0.17
Male	66.0%	71.5%	0.11
White	75.3%	66.6%	0.20
>4 lines of therapy received prior to index	28.9%	27.0%	0.05
Stage III, IV at initial diagnosis	80.4%	86.3%	0.15
Months between initial diagnosis and index, median (range)	66.2 (6.4-355.4)	67.5 (2.8-100.3)	0.37
Double refractory	68.0%	76.4%	0.17
Progression of disease within 24 months	62.9%	68.9%	0.13
Prognostic factors not included in PS modeling			
Prior Auto-HSCT	37.1%	4.2%	0.92
>4 sites of nodal involvement at initial diagnosis	44.3%	7.2%	0.86

*Key prognostic factors other than prior autologous HSCT and nodal involvement were also considered balanced in the sub-population for evaluating CRR/ORR. Index date was defined as the start date of standard of care in FHRD and date of enrollment in ELARA. **Abbreviations: FHRD**, Flatiron health research database; **HSCT**, hematopoietic stem cell transplantation; **PS**, propensity score; **SMD**, standardized mean difference; **CRR**, complete response rate; **ORR**, overall response rate.

Sensitivity Analysis Methods

- Two sensitivity analyses assessed the impact of remaining imbalanced variables:
  - Subgroup analysis of patients without prior hematopoietic stem cell transplantation (HSCT)
  - A regression adjustment that included all the remaining imbalanced variables in a regression model
- Three sensitivity analyses assessed the impact of missing data in key prognostic 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 scenario
  - Comparison of patient characteristics by missingness of ECOG status

FINDINGS

Primary Analysis

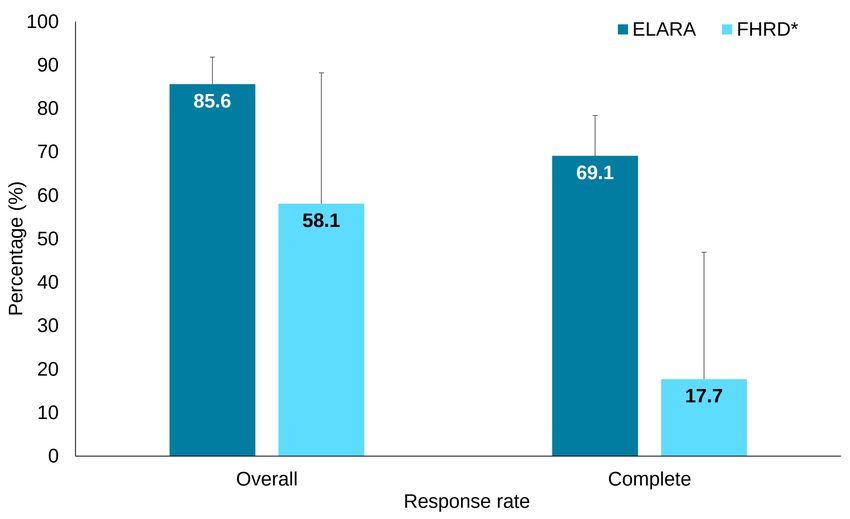
- After weighting by propensity score, overall response rate and complete response rate were compared for the ELARA trial cohort and the FHRD real-world SoC cohort. **Figure 2** illustrates that**,** post weighting, patients treated with tisagenlecleucel in the ELARA trial demonstrated a favorable efficacy profile – the complete response rate was 69.1% (95% CI, 59.8-78.4) in ELARA versus 17.7% (95% CI, 3.8-46.9) in FHRD, which translated to a difference of 51.4% (95% CI, 21.2-68.8). The overall response rate was 85.6% (95% CI, 78.4-91.8) in ELARA as compared to 58.1% (95% CI, 21.3-88.2) in FHRD; this difference equated to 27.4% (95% CI, -3 to 65).
- Other clinical endpoints from the ELARA trial were also evaluated for the PS matched ELARA and FHRD SoC cohorts. **Table 2** shows that, post-weighting, the hazard ratio was 0.45 for PFS, 0.41 for OS and 0.34 for TTNT, indicating a reduced risk of progression, death, or time to next treatment for patients treated with tisagenlecleucel in the ELARA cohort compared to patients treated with SoC in the FHRD cohort. This was consistent with the findings of ELARA vs ReCORD-FL SoC.[2]

Table 2: Primary analysis- PFS, OS, and TTNT

Variables	ELARA	FHRD (after weighting)*
Progression-free survival (PFS)	N = 97	N = 88
Median % (95% CI)	NR	9.9 (8-19.3)
12 months, % (95% CI)	73.2 (64.1-82.1)	41.8 (20-67.2)
Hazard ratio (HR) (95% CI, ELARA vs FHRD)		0.45 (0.26-0.88)
Overall survival	N = 97	N = 88
Median % (95% CI)	NR	NR
12 months, % (95% CI)	96.6 (92.3-100)	84.5 (64.9-95.9)
HR (95% CI, ELARA vs FHRD)		0.41 (0.11-1.47)
Time to new therapy or death	N = 97	N = 88
Median % (95% CI)	NR	19 (8.3-22.1)
12 months, % (95% CI)	85.9 (78.2-92.5)	54.2 (29.2-75.5)
HR (95% CI, ELARA vs FHRD)		0.34 (0.15-0.78)

*The effective sample size was 29 in the population used for evaluating time-to-event variables.
Abbreviations: CI, confidence interval; **FHRD**, Flatiron health research database; **HR**, hazard ratio; **NR**, not reached.

Figure 2: Overall response rate and complete response rate*, ELARA vs FHRD



*Only patients with at least one evaluation for response or a documented death during treatment were considered for this analysis. The effective sample size was 18 in the population used for evaluating response variables

Sensitivity Analyses

- The first sensitivity analysis examined the impact of missing data for key prognostic variables in the FHRD SoC cohort.
- This sensitivity analysis demonstrated a similar favorable treatment effect as the primary analysis. Tisagenlecleucel was associated with a higher response rate and a lower risk for death, progression, and TTNT compared to treatment with standard of care.
- The second sensitivity analysis examined the impact of remaining imbalanced variables in the PS weighted ELARA and FHRD cohorts.
- Consistent results were observed with the primary analysis. Patients treated with tisagenlecleucel had a higher response rate and a hazard ratio smaller than 1 for OS, PFS, and TTNT.

OUTCOME

- The inclusion of RWE in the evidence package led to a positive opinion from EMA without a post approval commitment of conducting a confirmatory study
- Following a positive EMA opinion on the submitted evidence package, tisagenlecleucel became the first CAR-T cell therapy approved in the EU for adults with r/r FL.
- Health Authority opinions and recommendations can be leveraged to develop fit-for-purpose RWE to supplement clinical trial data and meet regulatory stakeholder needs.
- The regulatory body stated that quality of evidence from the trial could potentially compensate for the shortcomings of the RWD.

LESSONS LEARNED

- Identification and use of RWD to enable a comparison to a single-arm trial involves a deep understanding of key methodological challenges, appropriate identification of these challenges, and employing a multi-disciplinary study team to develop a rigorous approach to adequately address such challenges.
- Active, early engagement with health authorities on assessing the sufficiency of RWD and statistical methodologies to make causal inference is critical to the acceptance of evidence packages.
- The biggest disappointment of the process was the inability to include the RWE on the EU product information (SmPC). The path/requirement for SmPC inclusion remains unclear.

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Disclosures

YH, ED and AM are employees of Novartis with stock options. HO is an employee of Novartis. WCH, CSP and JW hold consulting agreements with Novartis.