Use of external control data to adjust for treatment switching in cost-effectiveness analyses: lisocabtagene maraleucel versus standard of care in second-line relapsed or refractory large B-cell lymphoma

MSR78

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Introduction

- Reimbursement decision-making for new cancer therapies largely depends on evidence from randomized clinical trials (RCT)[1]
- In RCTs, patients sometimes switch from the control arm to investigational therapy if certain criteria are met and permitted by study design (or for other reasons)[1]
- Treatment switching may lead to challenges in health technology assessment where the decision problem is to compare treatments with current clinical practice, which often requires an estimate of long-term overall survival (OS) in the absence of switching[2]
- Traditionally, rank-preserving structural failure time (RPSFT), 2-stage estimation (TSE), and/or inverse probability of censoring weight (IPCW) are used to adjust for switching using only data from the trial under consideration[2]
- However, with the burgeoning availability of external information (eg, trials and real-world evidence), alternative methods can be considered, including observation-based methods historically used for indirect treatment comparisons
  - Possible improvements of sample sizes and data maturity from alternative methods are important for fitting more complex models for long-term extrapolation of OS, such as mixture cure models (MCM)

Objective

- This case study analyzed an external control arm (ECA) versus lisocabtagene maraleucel (liso-cel) in the absence of switching to estimate long-term OS and compared this approach with conventional statistical methods used in adjusting for crossover

Methods

Data sources

- Patient-level data from the following 2 multinational, randomized, phase 3 trials were analyzed: TRANSFORM (NCT03575351; liso-cel, n = 92) and CORAL (NCT00137995; standard of care [SOC], n = 216)
  - TRANSFORM compared the efficacy and safety of liso-cel versus SOC as a second-line treatment for patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who were intended for transplant[3]
    - The study design permitted treatment switching, and thus statistical adjustment was required to estimate the relative effect of liso-cel versus SOC in the absence of third-line chimeric antigen receptor (CAR) T cell therapy
  - The ECA was sourced from CORAL, which compared rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE) versus rituximab plus dexamethasone, cytarabine, and cisplatin (R-DHAP) in patients with previously treated diffuse LBCL followed by autologous stem cell transplantation with or without rituximab maintenance therapy[4]
- OS from CORAL reflects SOC in the absence of CAR T cell therapies, which were not available at the time CORAL was conducted
  - As there was no significant difference in survival outcomes, data for R-ICE and R-DHAP were pooled

Comparison of statistical methods

- Current guidance describes 3 commonly used statistical methods that use data solely from the focal RCT to correct for crossover as follows: RPSFT (a randomized-based method) and TSE and IPCW (2 observational-based methods)[2]
- Inverse probability of treatment weighting (IPTW) is another observational-based method that relies on the no unmeasured confounders assumption[5]

Table 1. Strengths and limitations of statistical analysis methods

	Description	Strengths	Limitations
RPSFT	• Uses counterfactual framework to estimate causal effects of treatments • Treatment effect is estimated using counterfactual events across treatment groups, where these events represent what would have been observed if no treatment was given	• Leverages TRANSFORM data • Preserves randomization	• Assumes survival time follows AFT distribution • Effect of treatment before and after EFS event is assumed to be the same and, in the case of TRANSFORM, it requires an additional assumption that the effect of liso-cel is similar before and after failing HSCT • Shrinking censoring times for switchers may introduce bias
TSE	• Recognizes that the clinical trial is randomized until disease progression, at which point the study becomes an observational trial • Treatment effect specific to patients switching treatment is estimated, and the survival times of these patients are adjusted	• Leverages TRANSFORM data • Preserves randomization until treatment switch • Relaxes the assumption of a common treatment effect	• Requires sufficient data on confounders at the time of crossover • Requires survival data for patients who were eligible to cross over but did not • Assumes that post-EFS survival follows AFT distribution • Shrinking censoring times for switchers may introduce bias
IPCW	• Involves adjusting treatment effect estimates in the presence of informative censoring • Assumes no unmeasured confounders	• Leverages TRANSFORM data • Preserves randomization • Relaxes the assumption of a common treatment effect	• Requires sufficient data on confounders during the entire follow-up, not just at the time of crossover • Requires sufficient survival data for patients who were eligible to cross over but did not
IPTW	• Weights patients in the external study to match baseline characteristics of the investigational arm	• Relaxes the assumption of a common treatment effect • Relaxes the assumption of AFT distribution	• Does not leverage TRANSFORM data for the SOC arm • Does not preserve randomization, and requires sufficient data on confounders at baseline • As with any indirect treatment comparison, assumes that the trials have sufficient overlap in target populations, study designs, and outcome measures

AFT, accelerated failure time; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation.

Comparison of statistical methods

- Strengths and limitations of each statistical method are compared in **Table 1**

IPTW

- After aligning inclusion/exclusion criteria between TRANSFORM and CORAL (definition of R/R, Eastern Cooperative Oncology Group performance status [ECOG PS], and exclusion of patients in CORAL with prior rituximab use), 216 patients from CORAL were retained and comprised the ECA

Table 2. Adjustment variables

Variable	Statistic
Age	Mean Median
ECOG PS	Percent: 0, 1, 2
Sex	Percent: male, female
Ann Arbor stage	Percent: 1, 2, 3, 4
sAAIPI	Percent: 0, 1, 2, 3
B symptoms	Percent: no, yes, unknown/missing
Bone marrow involvement	Percent: no, yes, unknown/missing
Best response to 1L treatment	Percent: responder, nonresponder
Extranodal involvement	Percent: 0, 1, 2, 3+

1L, first line; sAAIPI, secondary age-adjusted International Prognostic Index.

- An ECA was created using the IPTW method, where the SOC cohort from CORAL was weighted to match the baseline characteristics of the liso-cel population in TRANSFORM (**Table 2**)
  - To control for confounding, all available prognostic factors and effect modifiers were considered for population adjustment
- Average treatment effect in the treated estimand was used to estimate the relative efficacy of liso-cel versus SOC in the TRANSFORM population
- MCMs were used for long-term extrapolation of OS

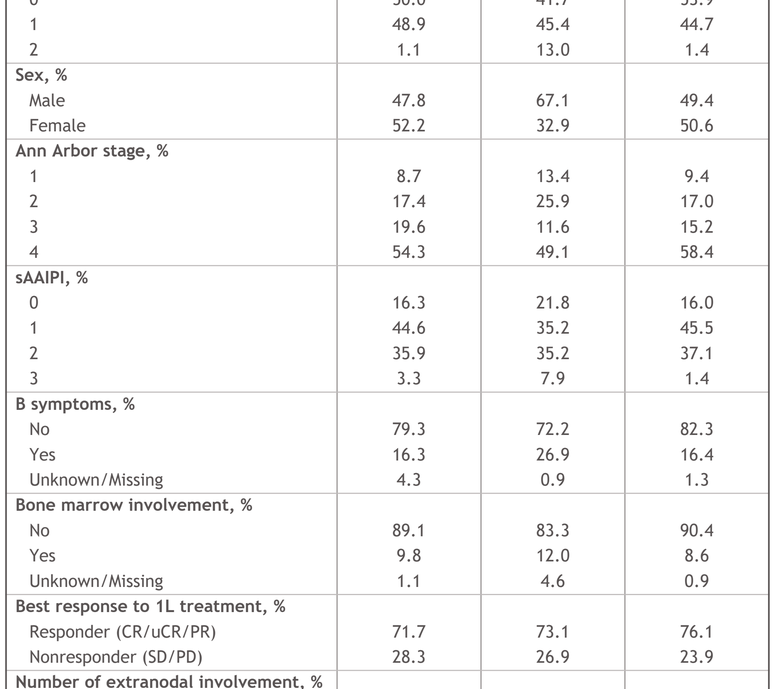
Results

Table 3. Patient characteristics in the liso-cel arm in TRANSFORM and SOC cohort in CORAL before and after adjustment

Characteristic	Liso-cel arm in TRANSFORM (n = 92)	CORAL cohort: matched and unadjusted (n = 216)	CORAL cohort: matched and adjusted (ESS = 92.5)
Age, y			
Median	60	53	59
Mean (std dev)	58.3 (12.6)	50.4 (11.4)	56.4 (8.0)
ECOG PS, %			
0	50.0	41.7	53.9
1	48.9	45.4	44.7
2	1.1	13.0	1.4
Sex, %			
Male	47.8	67.1	49.4
Female	52.2	32.9	50.6
Ann Arbor stage, %			
1	8.7	13.4	9.4
2	17.4	25.9	17.0
3	19.6	11.6	15.2
4	54.3	49.1	58.4
sAAIPI, %			
0	16.3	21.8	16.0
1	44.6	35.2	45.5
2	35.9	35.2	37.1
3	3.3	7.9	1.4
B symptoms, %			
No	79.3	72.2	82.3
Yes	16.3	26.9	16.4
Unknown/Missing	4.3	0.9	1.3
Bone marrow involvement, %			
No	89.1	83.3	90.4
Yes	9.8	12.0	8.6
Unknown/Missing	1.1	4.6	0.9
Best response to 1L treatment, %			
Responder (CR/uCR/PR)	71.7	73.1	76.1
Nonresponder (SD/PD)	28.3	26.9	23.9
Number of extranodal involvement, %			
0	37.0	35.6	35.3
1	33.7	32.4	36.3
2	12.0	17.1	11.5
3+	17.4	14.8	16.9

CR, complete response; ESS, effective sample size; PD, progressive disease; PR, partial response; SD, stable disease; std dev, standard deviation; uCR, unconfirmed complete response.

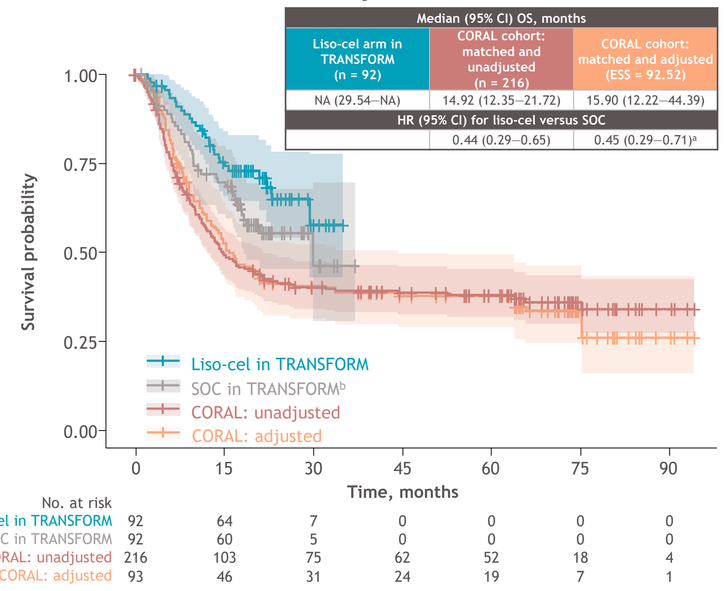
Figure 1. Covariate balance before and after adjustment



Points to the left of the dashed line indicate that the baseline distribution for a given covariate is similar between the 2 cohorts.
Inv, involvement.

- The IPTW approach reduced imbalances between liso-cel and SOC in the baseline characteristics (**Table 3**)
- The ESS for the SOC cohort was 42.8% of the unadjusted sample size
- Covariate balance improved after adjustment, evident by the reduction in absolute SMDs achieved for most variables (**Figure 1**)

Figure 2. OS before and after IPTW adjustment



[a]HRs and 95% CIs for RPSFT and TSE methods were reported as 0.279 (0.145—0.537) and 0.415 (0.251—0.686), respectively.[3]
[b]Anticipated OS due to cross over.
CI, confidence interval; HR, hazard ratio; NA, not available; | denotes a censoring event.

- Based on the IPTW analysis, the HR (95% CI) for liso-cel versus SOC was 0.45 (0.29—0.71), indicating that liso-cel was associated with a survival benefit compared with SOC in the absence of treatment switching (**Figure 2**)

Table 4. Cure fractions based on stratified MCMs

	Cure proportion (95% CI)		
	Liso-cel arm in TRANSFORM, % (n = 92)	CORAL cohort: matched and unadjusted, % (n = 216)	CORAL cohort: matched and adjusted, % (ESS = 92.5)
Exponential	Nonconvergent	38 (31—45)	35 (25—47)
Weibull	61 (38—80)	40 (34—47)	Nonconvergent
Log-normal	47 (9—89)	38 (31—45)	Nonconvergent
Log-logistic	56 (27—81)	37 (31—45)	36 (25—47)
Gompertz	61 (39—79)	40 (34—47)	33 (22—48)
Generalized gamma	Nonconvergent	39 (32—46)	Nonconvergent
Gamma	60 (35—80)	40 (33—47)	40 (29—51)

- Estimated cure fractions were higher for liso-cel in TRANSFORM alone and had higher uncertainty versus ECA (**Table 4**)

Discussion

- The IPTW analysis was conducted to supplement the RPSFT and TSE analyses performed in TRANSFORM[3] by leveraging external data from CORAL to provide additional insight on OS
- This analysis reduced imbalances between patient characteristics in the liso-cel arm (TRANSFORM) and the ECA (CORAL), indicating that liso-cel was associated with a survival benefit compared with SOC in the absence of treatment switching
- In the IPTW analysis, there is a potential for residual confounding bias as data on certain prognostic factors and effect modifiers were not collected or reported in CORAL and/or TRANSFORM
  - To retain all patients in TRANSFORM, this analysis did not fully adjust inclusion criterion for age; additional sensitivity analyses have been conducted to align the age range[6]

Conclusions

- The results of the IPTW analysis on OS (HR, 0.45 [95% CI, 0.29—0.71]) were similar to the TSE method previously conducted (HR, 0.415 [95% CI, 0.251—0.686]),[3] providing further evidence that liso-cel is associated with prolonged OS in comparison with SOC
- Using the ECA from CORAL allows for more precise estimation of a cure fraction given the relatively longer follow-up data available compared with TRANSFORM, which is the main driver of cost-effectiveness in the associated economic model comparing liso-cel versus SOC
- This case study demonstrated that adjusting for treatment switching using an ECA may be useful to supplement results from conventional analyses to demonstrate the range of estimates associated with the methodology used

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