Lifileucel versus Nivolumab plus Relatlimab (NIVO+RELA) in anti–PD-(L)1-resistant advanced melanoma: A matching-adjusted indirect comparison (MAIC) of efficacy outcomes

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Background

- Patients with anti–PD-1-resistant advanced melanoma have limited treatment options providing durable response and survival benefits. Lifileucel—a one-time, autologous, tumor-infiltrating lymphocyte (TIL) therapy—demonstrated durable responses in the single-arm, phase 2 C-144-01 trial (NCT02360579)[1-4]
- Lifileucel remains the only cellular or systemic therapy specifically approved for the post–PD-1 setting in the United States, Canada, and Australia[5]. Although NIVO+RELA is primarily approved for the treatment of first-line advanced melanoma[6-7], NCCN and ESMO guidelines also recognize its potential use in later-line settings[8-9].
- In patients with anti–PD-1-resistant advanced melanoma, NIVO+RELA has demonstrated clinical activity in the single-arm, phase 1/2 RELATIVITY-020 (RELA-020 hereafter) study[10]; however, comparative evidence evaluating survival and response outcomes between lifileucel and NIVO+RELA has not yet been characterized.

Objective

To estimate the comparative efficacy of lifileucel versus NIVO+RELA using a matching-adjusted indirect comparison (MAIC) based on published aggregate-level data from RELA-020 Part D and assess the robustness of results to cohort eligibility criteria in RELA-020 and baseline covariate adjustments.

Data Sources & Methods

- MAIC is a population-adjustment method used when IPD are available for one study but only aggregate data for the comparator, aiming to reduce confounding from observed cross-study population differences[11,12].
- Analyses used individual patient-level data (IPD) from lifileucel-infused patients in the C-144-01 full analysis set (FAS; n=153; median follow-up: 57.9 months; dose range: 1.2–99.5 × 10^9 viable TIL cells).
- RELA-020 comprised two mutually exclusive cohorts as D1 and D2 differing in prior treatment history, primarily anti–PD-(L)1 therapy exposure and was therefore analyzed separately by cohort.
- Cohort D1 had more restrictive prior-treatment criteria, requiring exactly one prior metastatic anti–PD-1 regimen, one prior BRAF ± MEK inhibitor therapy for BRAF-mutant patients, and no prior (neo)adjuvant anti–PD-1 therapy; whereas D2 included patients not meeting these criteria, including those with qualifying prior (neo)adjuvant anti–PD-1 therapy exposure.
- Published aggregate-level baseline characteristics and efficacy outcomes were obtained separately for RELA-020 Cohort D1 (n = 354, minimum follow-up: 19.4 months) and Cohort D2 (n = 164, minimum follow-up: 26.9 months). Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) for each cohort were digitized to reconstruct underlying time-to-event data[13]
- MAIC optimized patient-level weights in C-144-01 to match the weighted means and/or proportions of selected baseline characteristics reported for the RELA-020 D1 and D2 cohorts. Before weighting, RELA-020 D1 and D2 eligibility criteria were applied to C-144-01 to identify comparable lifileucel populations (D1-eligible, n=46; D2-eligible, n=101). Attrition of D1- and D2-eligible lifileucel cohorts is summarized in **Figure 1**.
- Covariates for MAIC were selected based on data availability and consistency of definitions across trials, prognostic relevance, cross-trial imbalances, population overlap, and sample size. Covariates were a priori categorized as "primary" or "secondary" based on prognostic strength and feasibility of cohort-specific adjustment (**Table 1**).
- Both cohort-specific analyses adjusted for the primary covariates. The relatively larger D2-eligible lifileucel cohort also enabled adjustment for secondary covariates versus RELA-020 D2.

Figure 1. Patient selection flowchart for derivation of MAIC-eligible cohorts from C-144-01. A) D1-eligible cohort, B) D2-eligible cohort.

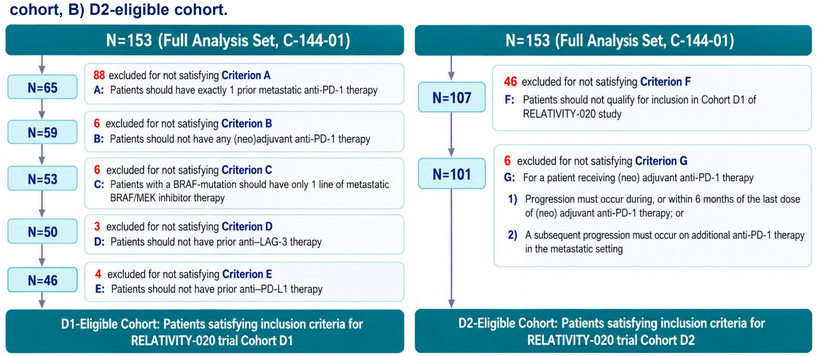


Table 1. Baseline characteristics of C-144-01 and RELA-020 cohorts before & after adjustment

Characteristic	C-144-01 FAS (n = 153)	C-144-01 D1 eligible, before matching (n = 46)	C-144-01 D1 after matching	RELA-020 D1 (n = 354)	C-144-01 D2 eligible, before matching (n = 101)	C-144-01 D2 after matching	RELA-020 D2 (n = 164)
Primary covariates							
Mean age, years*	55	55	63	63	54	62	62
Sex							
Male	54.2%	58.7%	61.6%	61.6%	51.5%	51.8%	51.8%
Female	45.8%	41.3%	38.4%	38.4%	48.5%	48.2%	48.2%
ECOG performance status							
0	54.9%	65.3%	68.9%	68.9%	49.5%	67.7%	67.7%
≥1	45.1%	34.7%	31.1%	31.1%	50.5%	32.3%	32.3%
LDH level							
≤2× ULN	81.0%	93.5%	86.7%	86.7%	76.2%	85.4%	85.4%
>2× ULN**	19.0%	6.5%	13.3%	13.3%	23.8%	14.6%	14.6%
Liver metastasis							
Yes	38.6%	34.8%	34.2%	34.2%	40.5%	29.9%	29.9%
No	61.4%	65.2%	65.8%	65.8%	59.5%	70.1%	70.1%
BRAF status							
Mutation	26.8%	26.1%	19.2%	19.2%	28.7%	37.8%	37.8%
No mutation**	73.2%	73.9%	80.8%	80.8%	71.3%	62.2%	62.2%
Prior anti-CTLA-4 systemic therapy							
Yes	81.7%	76.1%	39.3%	39.3%	86.1%	59.8%	59.8%
No	18.3%	23.9%	60.7%	60.7%	13.9%	40.2%	40.2%
Number of prior systemic regimens							
1	11.1%	28.3%	46.3%	46.3%	3.0%	17.1%	17.1%
>1	88.9%	71.7%	53.7%	53.7%	97.0%	82.9%	82.9%
Secondary covariates							
PD-L1 expression status							
≥1%***	49.7%	52.2%	Not adjusted	37.9%	50.5%	34.8%	34.8%
<1%	20.9%	17.3%	Not adjusted	41.5%	21.8%	45.1%	45.1%
Mean time from initial diagnosis to treatment (in years)*	5.7	5.9	Not adjusted	3.2	5.7	4.3	4.3
Melanoma subtype							
Mucosal	6.5%	4.3%	Not adjusted	9.9%	7.9%	6.7%	6.7%
Non-mucosal**	93.5%	95.7%	Not adjusted	90.1%	92.1%	93.3%	93.3%
Disease stage at entry							
Stage IV	93.5%	91.3%	Not adjusted	93.8%	94.1%	90.9%	90.9%
Stage III	6.5%	8.7%	Not adjusted	6.2%	5.9%	9.1%	9.1%

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; LDH, lactate dehydrogenase; PD-L1, programmed cell death 1/programmed cell death-ligand 1; RELA-020, RELATIVITY-020; ULN, upper limit of normal.
Notes. *Mean age and mean time from initial diagnosis to treatment were not reported in RELA-020 and therefore assumed to be equivalent to their respective reported median values.
** Unknown/missing RELA-020 covariate values were assigned to this category
*** PD-L1 expression categories may not sum to 100% due to unknown/indeterminate status; therefore, the proportions with PD-L1 ≥1% and <1% were matched separately in the MAIC.

- Comparative outcomes included the odds ratio (OR) for objective response rate (ORR), hazard ratios (HRs) for PFS and OS estimated using Cox proportional hazards models, and the 3-year OS rate difference between treatments.
- Effective sample size (ESS), a diagnostic measure of population overlap, quantified the loss of statistical information due to unequal weighting of patients in MAIC.
- Leave-one-covariate-out analyses were conducted separately for D1 and D2 to assess the marginal influence of individual covariates on outcomes.

Table 2. Summary of results

Reference Cohort in RELA-020	Efficacy Measure (Lifileucel vs NIVO+RELA)			3-year OS rate differential, (Lifileucel vs NIVO+RELA)	Eligible C-144-01 patients for MAIC (n)	Effective Sample Size, n (% of eligible population)*
	PFS HR	OS HR	ORR OR			
D1	0.58	0.68	8.7	+8.1	46	14 (30.4%)
D2	0.66	0.75	6.2	+13.1	101	26 (25.7%)

* Relative to number of patients in C-144-01 eligible for MAIC

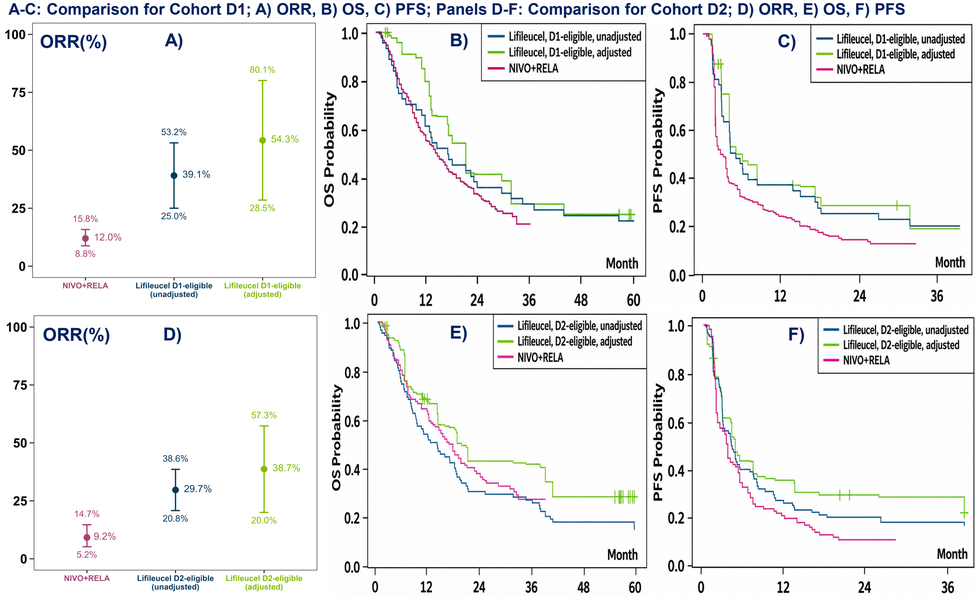
Conclusions

- Eligibility criteria for RELA-020 D1 and D2 represent distinct treatment pathways regarding prior and repeated anti–PD-1 therapy exposure. Therefore, numerical improvements with lifileucel over NIVO+RELA across all efficacy outcomes in both comparisons support its potential role across these pathways and provide insights to inform treatment selection.
- In this high-unmet-need setting, findings address an important comparative evidence gap but should be interpreted cautiously due to limited ESS and unanchored comparison of two single-arm trials where potential residual confounding from unmeasured characteristics may remain.

Results

- Before adjustment, notable baseline differences existed between lifileucel and NIVO+RELA cohorts. D1-eligible lifileucel patients were younger and more heavily pretreated than RELA-020 D1; D2-eligible patients were younger and more often had ECOG PS ≥1, elevated LDH, liver metastases, prior anti–CTLA-4, and multiple prior regimens than RELA-020 D2 (**Table 1**)
- After population adjustment, point estimates across all efficacy outcomes numerically favored lifileucel over NIVO+RELA in both D1 and D2 comparisons, reflected in improvements of at least 8.1 percentage points in 3-year survival rates (**Table 2, Figure 2**).
- Given the limited follow-up in RELA-020, 2-year PFS rates were also compared. After adjustment, lifileucel was estimated to improve 2-year PFS by 14.4 and 19.0 percentage points versus NIVO+RELA in D1 and D2, respectively (**Figure 2**).
- While PFS and OS improvements were not statistically significant in either D1 or D2, with 95% CIs for HRs crossing 1, ORR improvements were more pronounced, with non-overlapping 95% CIs between treatments in both comparisons.
- Across all leave-one-covariate-out analyses, treatment-effect estimates consistently favored lifileucel over NIVO+RELA across endpoints, although the most influential covariates varied by cohort and endpoint.

Figure 2. Comparison of unadjusted and adjusted efficacy outcomes between C-144-01 and RELA-020 Cohorts. Panels A-C: Comparison for Cohort D1; A) ORR, B) OS, C) PFS; Panels D-F: Comparison for Cohort D2; D) ORR, E) OS, F) PFS



Discussion

- Estimated improvements in lifileucel's PFS and OS trends and ORR after adjustment—particularly greater PFS separation from NIVO+RELA and reversal of the comparative effect in D2—highlight the sensitivity of naïve cross-trial comparisons to baseline differences.
- Limited ESS values in both comparisons reflect substantial reweighting to align baseline characteristics and modest overlap between trial populations, potentially reducing precision and increasing uncertainty in estimated treatment effects.
- This analysis was limited to efficacy outcomes in the C-144-01 FAS. Safety, quality of life, and resource use were outside the scope. Feasibility of an MAIC for the subgroup receiving lifileucel within the FDA-approved dose range and manufactured at commercially approved sites (7.5 × 10^9–72 × 10^9 viable TIL cells; n=106)[14] was constrained by limited sample size.

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