Therapeutic Architecture Rather Than Population Differences Drives Front-Line Outcomes in T-Cell/Histiocyte-Rich Large B-Cell Lymphoma: A Comparison-Specific Pooled Analysis of Rituximab-Era Cohorts

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Background

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a rare variant of diffuse large B-cell lymphoma with limited evidence guiding frontline therapy. While R-CHOP remains standard, intensified strategies such as dose-adjusted R-EPOCH and alternating R-CHOP followed by R-ICE are variably employed. Whether observed differences in outcomes are driven by treatment strategy itself or by baseline population heterogeneity has not been systematically assessed.

Methods

- We conducted a study-level pooled comparative effectiveness analysis of rituximab-era THRLBCL cohorts (MSKCC, MD Anderson, Emory; n≈220), including only studies with direct within-cohort regimen comparisons. Complete response (CR) outcomes were derived using regimen-level 2×2 tables and pooled as odds ratios with random-effects models.
- Non-comparative cohorts were used descriptively. Survival outcomes were summarized but not pooled due to reporting heterogeneity.
- Exploratory meta-regression assessed the impact of baseline differences (e.g., stage, IPI), and Bayesian hierarchical modeling was performed as a sensitivity analysis to estimate uncertainty and generate probabilistic regimen rankings (SUCRA).

Results

- **Across 4 cohorts**, baseline characteristics were broadly comparable, with a predominance of advanced-stage disease; descriptive baseline metrics and treatment distributions are summarized separately.
- In comparative pooled analysis, **alternating R-CHOP→R-ICE was associated with substantially higher CR compared with R-CHOP (95% vs 70%), yielding a pooled odds ratio of 3.7 (95% CI 1.0–13.7). DA-R-EPOCH did not demonstrate improved CR or survival relative to R-CHOP.**
- Landmark survival comparisons showed superior long-term outcomes with R-CHOP→R-ICE (5-year EFS 80% vs 50%; 5-year OS 100% vs 72%), whereas DA-R-EPOCH showed no progression-free or overall survival advantage.
- **Bayesian sensitivity analysis yielded a posterior mean OR ≈3.4 with a 94% posterior probability of benefit for intensified therapy**.
- Bayesian ranking demonstrated a clear hierarchy**: R-CHOP→R-ICE (SUCRA ≈0.90; P[rank = 1] ≈0.82), R-CHOP (SUCRA ≈0.52; P[rank = 1] ≈0.15), and DA-R-EPOCH (SUCRA ≈0.08; P[rank = 1] ≈0.03)**.
- **Meta-regression did not identify stage or IPI distribution as modifiers of treatment effect.**

Regimen	Cohort Role	Complete Response (CR)	Relative Effect vs R-CHOP	Survival Outcomes (Landmark)
R-CHOP → R-ICE	Intensified (non–cross-resistant)	~95%	OR 3.7 (95% CI 1.0–13.7)	5-year EFS ~80%; OS ~100%
R-CHOP	Standard comparator	~70%	Reference	5-year EFS ~50%; OS ~72%
DA-R-EPOCH	Intensified (dose-adjusted)	No improvement vs R-CHOP	No significant difference	No PFS or OS advantage

Conclusion

- In this comparison-specific analytical pooled analysis, **non–cross-resistant regimen architecture emerged as the dominant determinant of frontline outcomes in THRLBCL.**
- **Alternating R-CHOP→R-ICE demonstrated the highest estimated treatment effect, greatest posterior probability of benefit, and highest SUCRA ranking, independent of baseline disease risk.**
- DA-R-EPOCH did not confer additional benefit over R-CHOP. These findings support R-CHOP→R-ICE as the most effective frontline strategy for fit patients with THRLBCL and warrant prospective validation in registry-based studies.