# Long-Term Outcomes of Salvage Radiation Therapy in Relapsed/Refractory Large B-Cell Lymphoma Patients After CAR T-Cell Therapy Failure

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## INTRODUCTION

- While chimeric antigen receptor (CAR) T-cell therapy can lead to durable remission in many patients with relapsed/refractory (rel/ref) large B cell lymphoma (LBCL), the majority will develop progressive disease, necessitating effective salvage strategies.
- We sought to assess the long-term outcomes of salvage radiation therapy (RT) compared to other salvage regimens for patients with rel/ref LBCL after CD19-targeted CAR T-cell therapy failure.

## AIM

- Estimate long-term local control following RT in patients with rel/ref LBCL after failure of CD19 CAR T-cell therapy.
- Compare outcomes between RT alone, systemic therapy (ST) alone, and combined modality therapy (CMT).
- Evaluate the impact of radiation field size on survival.

## METHOD

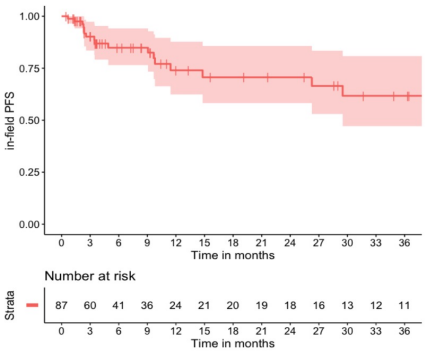
- A multi-institutional retrospective study was conducted in a database of 352 consecutive LBCL patients who received axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between 2017 and 2021.
- Patients who relapsed following CAR T-cell therapy following ≥2 prior therapies and then received salvage therapies were analyzed. All three categories were defined at the time of the first salvage therapy following CAR T-cell therapy failure.
- The CMT cohort included only patients who had been planned for both RT and systemic therapy as a first salvage regimen, regardless of the response to either.
- A separate analysis was then conducted for patients who were treated with comprehensive versus focal RT; only the first RT course was included in this analysis for patients receiving >1 salvage RT course.
- Comprehensive RT was defined as RT to all sites of disease, while focal RT was defined as RT to a subset of disease sites.

## RESULTS

- A total of 128 patients with post-CAR T relapsed LBCL received salvage therapies (RT alone, 24 patients; CMT, 16 patients; ST, 88 patients).
- **Median follow-up after CAR T**: 14.2 mo (IQR: 6.3-41.0 months)
- **Median follow-up after salvage:** 7.1 mo (IQR: 3.0-24.0 months)
- **Median PFS post-CAR T:** 3.0 mo (95% CI: 3.0-3.8 mo)
- Sites of failure
  - 75% failed in previous sites of disease (n=96)
    - 26% in these sites alone
    - 49% concurrent with de novo sites
- Patients progressing within 6 months of CAR T infusion (n=93) showed inferior OS compared to those progressing later (n=35) (median OS of 10.7 vs. 42.0 months; $p = 0.0008$)
- The median OS was significantly higher in patients relapsing post-complete remission (n=61) than in those with refractory disease post-CAR T (n=67) (24.4 vs. 12.3 months; $p = 0.03$)
- There was no significant difference in OS or PFS post-salvage therapy start date based on the class of salvage therapy
- 55 patients received any RT to total of 101 sites
  - Median dose: 30 Gy (range, 4-50.4 Gy)
  - Median fx: 10 (range, 1-28 fx)
- 3 y-local control (in-field PFS) was > 60%
  - 17 sites experienced local recurrence with a median time to in-field progression of 3.5 months (IQR: 2.4-9.8 months)
- Median out-of-field PFS was 2.6 months (95% CI: 1.7 months – 7.5 months)

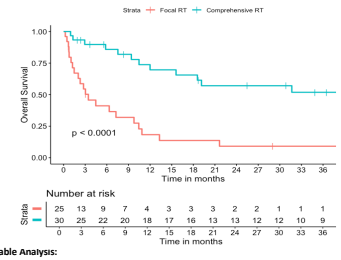
### Patient Characteristics

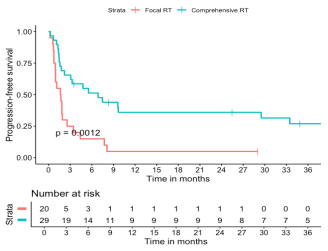
| | Overall (n=128) | RT (n=24) | CMT (n=16) | ST (n=88) |
|---|---|---|---|---|
| Median age (range) | 62 (15-81) | 63 (43-81) | 62 (40-78) | 62 (15-79) |
| Bridging therapy | 59 (46.1%) | 12 (50.0%) | 9 (56.2%) | 38 (43.2%) |
| Axi-cel (vs. tisa-cel) | 90 (70.3%) | 14 (58.3%) | 10 (62.5%) | 66 (75.0%) |
| CR post-CAR T | 61 (47.7%) | 12 (50.0%) | 6 (37.5%) | 43 (48.9%) |
| ORR (CR+PR) | 97 (75.8%) | 21 (87.5%) | 12 (75.0%) | 64 (72.7%) |
| ECOG 0-1 | 110 (85.9%) | 22 (91.7%) | 12 (75.0%) | 76 (86.4%) |
| Stage I-II | 55 (43.0%) | 17 (70.8%) | 7 (43.8%) | 31 (35.2%) |
| Extranodal disease | 93 (72.7%) | 16 (66.7%) | 13 (81.3%) | 64 (72.7%) |
| CNS disease | 19 (14.8%) | 4 (16.7%) | 2 (12.5%) | 13 (14.8%) |
| Bulky (>5 cm, non-CNS) | 32 (29.4%) | 5 (25.0%) | 5 (35.7%) | 22 (29.3%) |
| Elevated LDH | 76 (59.8%) | 9 (37.5%) | 11 (68.8%) | 56 (64.4%) |




## RESULTS

- Trend towards improved in-field PFS with high-dose RT
  - High-Dose RT (BED$_{10}$ ≥ 39 Gy): Median PFS Not Reached
  - Low-Dose RT (BED$_{10}$ < 39 Gy): Median PFS 11.4 Months
- 55 patients received RT:
  - Comprehensive: 30 patients
    - 2-yr OS: 55%
    - 2-yr PFS: 36%
  - Focal: 25 patients
    - 2-yr OS: 10%
    - 2-yr PFS: 5%
- Factors Affecting OS After Salvage Therapy in Multivariable Analysis:
  - Associated with Inferior OS:
    - Advanced-stage disease
    - Elevated LDH
    - Shorter interval from CAR T infusion to salvage therapy
  - Associated with Superior OS:
    - Response to last line of therapy (Complete or Partial Response)
- Factors Associated with Shorter PFS After Salvage Therapy in Multivariable Analysis:
  - Advanced-stage disease
  - Elevated LDH




## CONCLUSIONS

- Our findings suggest that RT is a viable therapeutic strategy that can provide excellent long-term local control for LBCL patients post-CAR T-cell therapy failure
- Patients suitable for comprehensive RT exhibit superior survival outcomes compared to those receiving focal RT
- High tumor burden at the time of salvage therapy is associated with worse outcomes
- Analysis of the dose-response relationship may be limited by the number of local failures and selection bias; therefore, larger cohorts are needed to confirm our findings