



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALY AVAILABLE THERAPIES

**Impact of "Cell-of-Origin" on Outcome after Axicabtagene-Ciloleucel CAR-T Cell Therapy in Relapsed/Refractory Aggressive Non-Hodgkin B-Cell Lymphomas**

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**Introduction:** Despite significant advances in characterizing aggressive B-cell non-Hodgkin lymphomas (aNHL) based on molecular and genetic signatures, the Hans algorithm, determined by immunohistochemistry, remains the most commonly used approach to differentiate aNHLs based on the cell-of-origin (COO) into germinal center B-cell (GCB) and non-GCB types. Although the Hans algorithm has demonstrated reliability as a predictor of better outcomes in newly diagnosed GCB cases, conflicting evidence has emerged, particularly in the relapsed/refractory (R/R) setting, and there are no definitive data about the impact of COO in patients (pts) receiving CAR-T cells. Thus, we conducted a retrospective analysis to evaluate the impact of COO extended to R/R aNHLs who underwent treatment with axicabtagene-ciloleucel (axi-cel).

**Methods:** We retrospectively collected data from pts with R/R aNHLs treated with axi-cel at Fred Hutchinson Cancer Center between February 2018 and August 2022. The Hans algorithm, using CD10, BCL6 and MUM1 markers, was employed to stratify the pts into two cohorts: GCB and non-GCB. Paired biopsies of diagnosis and relapse before CAR-T eligibility were reviewed at our institution. Response to CAR-T was assessed at one month per Lugano PET/CT criteria.

Univariate cox proportional hazard regression was used to estimate associations between baseline factors and outcomes. Statistically significant factors ( $p < .05$ ) in univariate analysis were further evaluated by multivariate analysis. Continuous variables were compared by Mann-Whitney U test and categorical variables by Fischer's exact test. Progression-free survival (PFS) was calculated from the date of CAR-T cell infusion to the date of death from any cause, disease progression or relapse. Overall survival (OS) was calculated from the date of CAR-T cell infusion to the date of death from any cause.

**Results:** Sixty-four pts were included in this analysis, with an equal distribution of pts in the two cohorts: 32 with GCB subtype and 32 with non-GCB subtype. Baseline pts' characteristics and histology subtypes are listed in Table 1. Transformed follicular lymphoma and primary mediastinal B-cell lymphoma were not included in this analysis. The presence of bulky disease (defined as  $>5\text{cm}$  diameter) was higher in the GCB subtype (56% vs 22%,  $p < .001$ ). Although primary refractory cases were more frequent in the GCB cohort (87.5 vs 66%), statistical significance was not reached (NR) ( $p = .07$ ). The same proportion of pts received bridging therapy in the two groups (53% vs 53%,  $p = .99$ ). Pts evaluable for response assessment were 62. Median time to best response was 29 days (range, 21-186) for GCB pts and 31 days (range, 22-182) for non-GCB pts ( $p = .91$ ). The overall response rate was 70% for GCBs (34.5% complete response [CR], 34.5% partial response [PR]) and 75% for non-GCBs (44% CR, 31% PR). After a median follow-up of 24.5 months (range, 9-121), comparable outcomes were observed for both the COO groups: despite the estimated median OS of 14 months (95% CI, 4.73-NR) for GCB vs 40 months (95% CI, 12.55-67.46) for non-GCB, we did not find any significant differences ( $p = .73$ ) (Figure 1A). Estimated median PFS was 10 months (95% confidence interval [CI], 3.5-16) for GCB and 11 months (95% CI, 0-24) for non-GCB ( $p = .57$ ) (Figure 1B). The 2-year OS and PFS were: GCB, 45% (95% CI, 30-69) and 44% (95% CI, 29-67) respectively; non-GCB, 55% (95% CI, 38-79) and 29% (95% CI, 16-55), respectively.

Treatment-related toxicities did not differ between GCB and non-GCB, with cytokine-release syndrome rates of 97% vs 94% ( $p=.99$ ) and neurotoxicity rates of 53% vs 62.5% ( $p=.61$ ), respectively. The incidence of infectious complications was 25% vs 19% ( $p=.76$ ).

On univariate analysis, the impact of COO on OS (HR=0.82, 95% CI 0.39-1.73,  $p=.60$ ) and PFS (HR=1.18, 95% CI 0.61-2.28,  $p=.62$ ) was undetermined. After adjusting for bulky disease, elevated LDH, absolute lymphocyte count  $\leq 1000/\mu\text{L}$ , performance status  $\geq 2$ ,  $>2$  lines of therapy and response status before axi-cel infusion, the impact of COO on OS (adjusted HR [aHR]=1.73, 95% CI 0.71-4.22,  $p=.23$ ) and PFS (aHR=2.01, 95% CI 0.93-4.35,  $p=.08$ ), remained undetermined.

Conclusion: We could not confirm an association between COO, as determined by Hans algorithm, and outcomes in R/R aNHLs who received axi-cel at our center. Prospective analyses on larger datasets and other types of CAR-T products are needed.

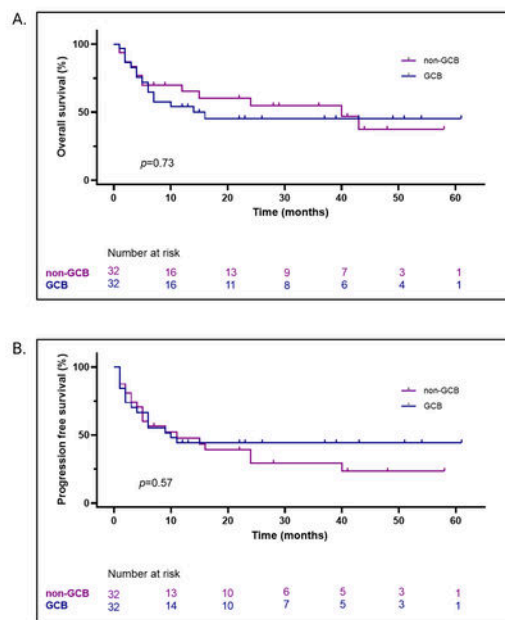
**Disclosures Gauthier:** Kite Pharma: Consultancy, Honoraria; Century Therapeutics: Other: Independent data review committee; Angiocrine Bioscience: Research Funding; MorphoSys: Consultancy, Research Funding; Legend Biotech: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; Celgene (a Bristol Myers Squibb company): Research Funding; Juno Therapeutics (a Bristol Myers Squibb company): Research Funding; Sobi: Consultancy, Honoraria, Research Funding. **Lynch:** TG Therapeutics: Research Funding; Incyte: Research Funding; Bayer: Research Funding; Cyteir: Research Funding; Genentech: Research Funding; Seagen Inc.: Research Funding; Rapt: Research Funding; Cancer Study Group: Consultancy; SeaGen: Consultancy; Foresight Diagnostics: Consultancy; Abbvie: Consultancy; Merck: Research Funding. **Gopal:** Compliment Corporation: Current holder of stock options in a privately-held company; Incyte, Kite, Morphosys/Incyte, ADCT, Acrotech, Merck, Karyopharm, Servier, Beigene, Cellectar, Janssen, SeaGen, Epizyme, I-Mab bio, Gilead, Genentech, Lilly, Caribou, Fresenius-Kabi: Consultancy; 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**Table 1.** Patients' baseline characteristics, overall and by subtype

| Characteristic                   | Overall patients, n = 64 | GCB n = 32 | Non-GCB n = 32 | p-value <sup>1</sup> |
|----------------------------------|--------------------------|------------|----------------|----------------------|
| Age (years), Median (Range)      | 61 (29-74)               | 62 (29-74) | 60 (34-74)     | 0.73                 |
| Age > 60 years, n (%)            | 42 (66%)                 | 19 (59%)   | 16 (50%)       | 0.62                 |
| Male sex, n (%)                  | 25 (58%)                 | 22 (69%)   | 20 (63%)       | 0.79                 |
| Disease subtype, n (%)           |                          |            |                | 0.32                 |
| DLBCL, NOS                       | 47 (73%)                 | 21 (66%)   | 26 (81%)       |                      |
| DLBCL/HGBCL                      | 6 (9%)                   | 5 (15.5%)  | 1 (3%)         |                      |
| HGBCL                            | 8 (13%)                  | 5 (15.5%)  | 3 (10%)        |                      |
| EBV DLBCL                        | 1 (2%)                   | 0          | 1 (3%)         |                      |
| FL3B                             | 2 (3%)                   | 1 (3%)     | 1 (3%)         |                      |
| ECOG PS>2, n (%)                 | 8 (12.5%)                | 5 (15.5%)  | 3 (10%)        | 0.71                 |
| Stage                            |                          |            |                | 0.34                 |
| Localized (I-II)                 | 12 (19%)                 | 8 (25%)    | 4 (12.5%)      |                      |
| Advanced (III-IV)                | 52 (81%)                 | 24 (75%)   | 28 (87.5%)     |                      |
| Elevated LDH (≥210 U/L), n (%)   | 31 (48%)                 | 15 (47%)   | 16 (50%)       | 0.99                 |
| Bulky (≥5 cm), n (%)             | 25 (39%)                 | 18 (56%)   | 7 (22%)        | <0.001               |
| Extranodal, n (%)                | 36 (56%)                 | 16 (50%)   | 20 (62.5%)     | 0.45s                |
| ≥2 extranodal sites              | 24 (37.5%)               | 10 (31%)   | 14 (44%)       | 0.44                 |
| B-Symptoms                       | 30 (47%)                 | 16 (50%)   | 14 (44%)       | 0.8                  |
| IPI                              |                          |            |                | 0.8                  |
| 0-2                              | 32 (50%)                 | 17 (53%)   | 15 (47%)       |                      |
| 3-5                              | 32 (50%)                 | 15 (47%)   | 17 (53%)       |                      |
| >2 lines of therapy before CAR-T | 25 (39%)                 | 12 (37.5%) | 13 (41%)       | 0.99                 |
| Any CRS, n (%)                   | 61 (95%)                 | 31 (97%)   | 30 (94%)       | 0.99                 |
| Any ICANS, n (%)                 | 37 (58%)                 | 17 (53%)   | 20 (62.5%)     | 0.61                 |
| Infections, n (%)                | 14 (22%)                 | 8 (25%)    | 6 (19%)        | 0.76                 |
| Bridging therapy                 | 34 (53%)                 | 17 (53%)   | 17 (53%)       | 0.99                 |

<sup>1</sup>Mann-Whitney U-test, Fischer's exact test. Abbreviations: CRS, cytokine release syndrome; DLBCL, NOS, diffuse large B-cell lymphoma; DLBCL/HGBCL, diffuse large B-cell lymphoma/high grade B-cell lymphoma; EBV DLBCL, Epstein-Barr virus-positive diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL3B, follicular lymphoma grade 3B; GCB, germinal B center; HGBCL, high grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IPI, International Prognostic Index; LDH, lactate dehydrogenase; non-GCB, non-germinal B center.

**Figure 1.** Kaplan-Meier Curves stratified by Cell-of-Origin. A) Overall survival; B) Progression-free survival.



**Figure 1**

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