2024 ASCO® ANNUAL MEETING

# A Pilot Study of Axicabtagene Ciloleucel in Relapsed/Refractory Primary and Secondary Central Nervous System Lymphomas (PCNSL & SCNSL)

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# Conclusions / Key Takeaways

- Axi-cel was found to be safe in primary and secondary CNS (central nervous system) lymphomas in this study
  - The risk of ICANS was similar to that noted in systemic DLBCL

- Axi-cel has promising efficacy in CNS Lymphoma.
  - CR/uCR rate : 67% (ORR 94%)
  - Median progression-free survival : 14.3 months (95% CI, 6.3- NR)

# Background

- Treatment of primary(P-) & secondary(S-) CNS lymphomas
  - Induction with HD-MTX based chemotherapy
  - Consolidation with thiotepa-based ASCT in eligible patients

- Relapse rates are high:
  - 50-60% in the 1st 2 years
    - Within 6-9 mo in SCNSL
  - Primary refractory: 15-23% in PCNSL, ~40% in SCNSL

- Optimal salvage treatment for R/R CNS lymphomas is not established
  - Median OS (PCNSL) after relapse ~ 7 months (1y OS 38%)

# Background

- Axicabtagene ciloleucel (Axi-cel) is a CD28 based anti-CD19 2nd generation autologous CAR T-cell FDA-approved for:
  - Large B-cell Lymphoma (3rd line) ZUMA-1
  - Primary refractory/early relapse large B-cell lymphoma (2nd line) ZUMA-7
  - Follicular Lymphoma (3rd line) ZUMA-5

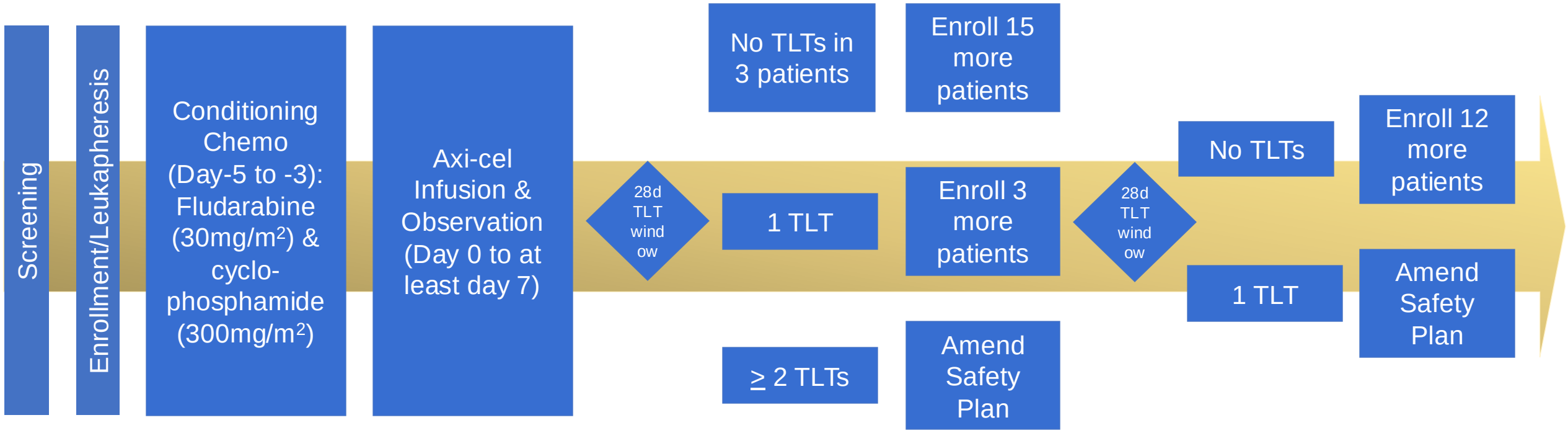
- Trials in systemic lymphoma have excluded patients with a history of, or active CNS involvement
  - PCNSL is an absolute exception

- There is retrospective evidence of efficacy with axi-cel in CNSL

# Background

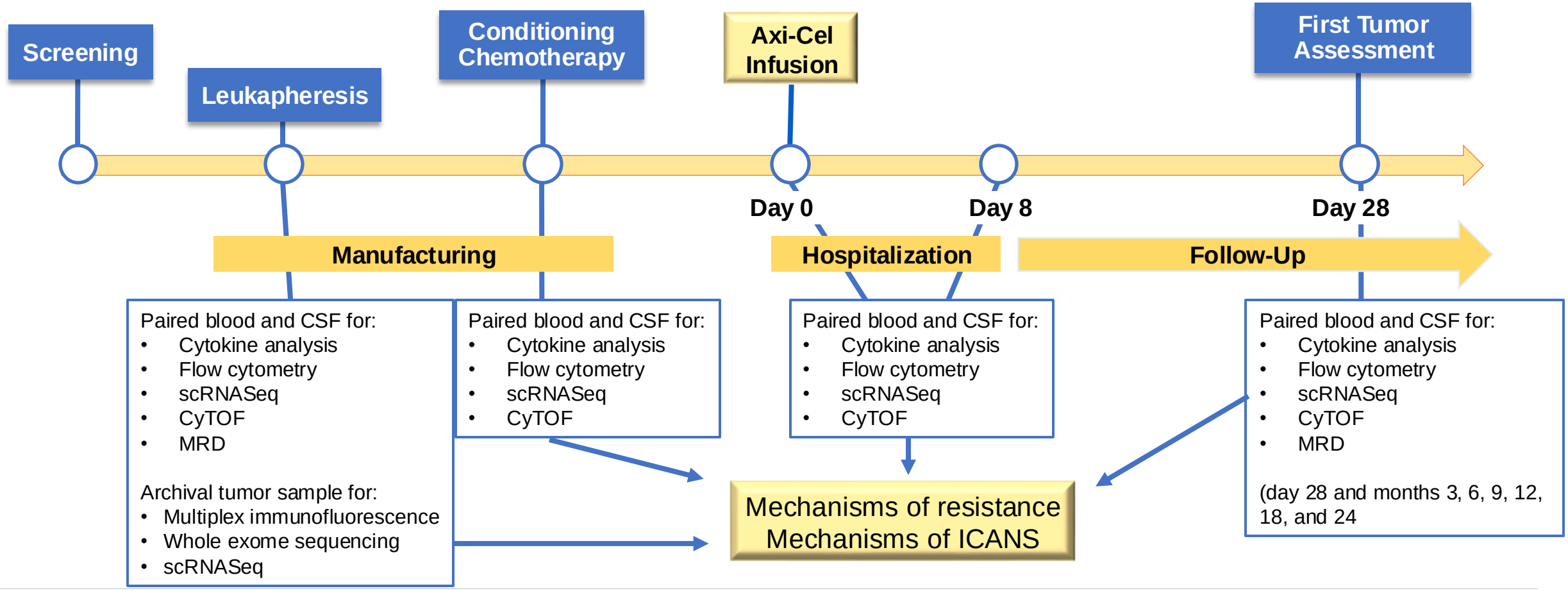
- We conducted a prospective clinical trial to evaluate the safety & efficacy of axi-cel in CNSL (NCT04608487).
  - We report on the complete cohort of 18 patients with longer follow up.

# Study Design




Total Cohort (n=18):
Patients with CNS disease including PCNSL and SCNSL w/wo systemic involvement relapsing after at least 1 prior CNS directed systemic therapy

# Study Design



# Endpoints

- **Safety**
  - Rate of TLTs and rate of grade 3+ adverse events regardless of attribution
- **Efficacy**
  - Objective response rate (ORR by IPCG for CNSL),
  - Complete response (CR/uCR) rate (uCR = persistent minimal enhancement from biopsy/hemorrhage and/or use of corticosteroids)
  - Duration of response (DOR),
  - Progression-free survival (PFS),
  - Overall survival (OS)
- **Exploratory correlatives**
  - Serum & CSF levels of axi-cel and cytokines
  - PB & CSF immune subsets by CyTOF, flow cytometry & scRNAseq
  - PB & CSF ctDNA

# Patient Characteristics

| Patient Characteristics | | N=18 (%) |
|---|---|---|
| Gender | Men<br>Women | 10 (56)<br>8 (44) |
| Age (years) | Median (range) | 62 (33-81) |
| PCNSL *v* SCNSL | PCNSL<br>SCNSL<br>Systemic & VRL | 13 (72)<br>4 (22)<br>1 (6) |
| Tumor Location | Parenchymal<br>CSF cytology +ve<br>CSF atypical/suspicious<br>Eye<br>Systemic | 17 (94)<br>0 (0)<br>3 (17)<br>2 (11)<br>1 (6) |
| Number of prior treatments<br>• Prior ASCT | Median (range) | 3 (1-7)<br>6 (33%) |
| Time from diagnosis to enrollment | Days (range) | 489 (150-8665) |
| Time from last tx to enrollment | Days (range) | 72 (4-1273) |

- 24 patients screened
  - 6 screen fails-
    - organ function (n=2),
    - infection (n=2),
    - progression (n=1),
    - pt preference (n=1)
- Axi-cel was successfully manufactured in **18/18** patients underwent leukapheresis
- **5/18** patients received palliative **targeted RT** immediately prior to screening for the trial
- **No bridging therapy after consenting**
- Stable/lower doses of dexamethasone allowed & tapered to 2mg qd by axi-cel infusion (except in 1 patient)
  - 5 patients continued steroids from screening to treatment

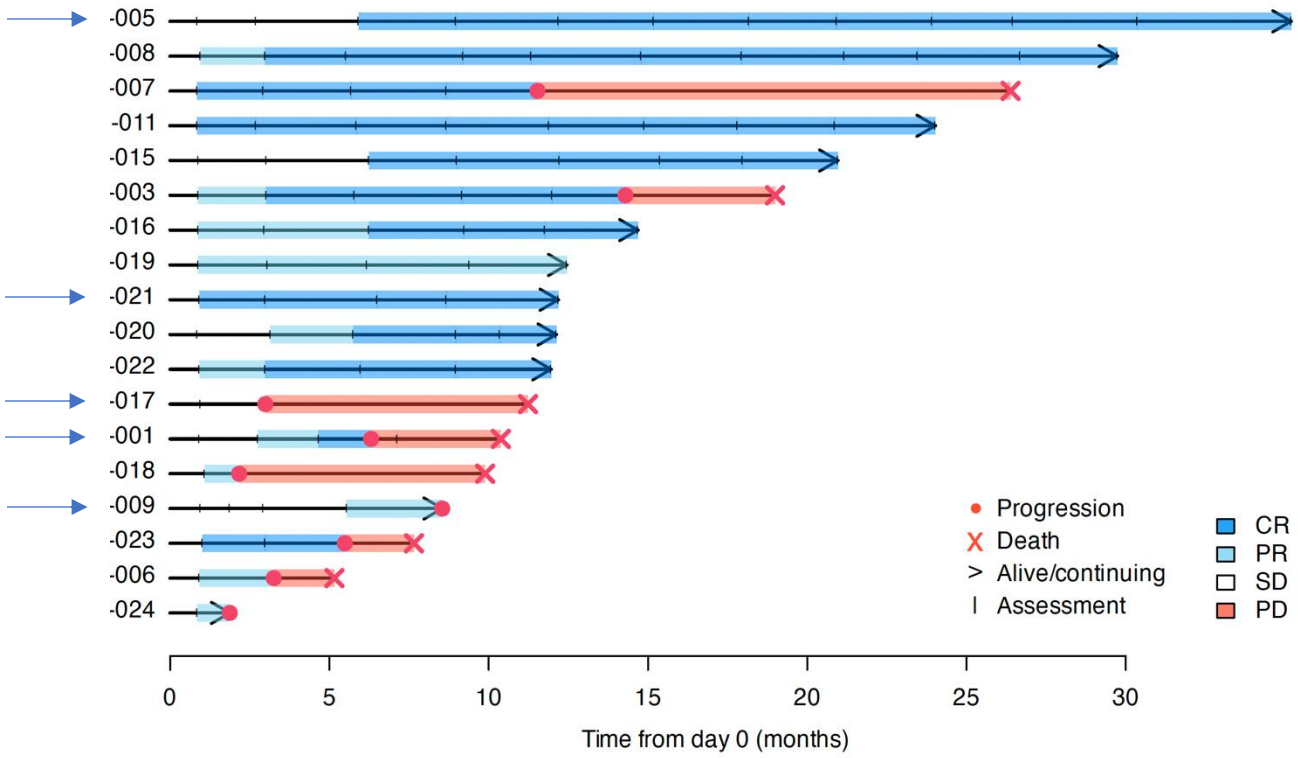
# Adverse Events of Interest

| | CRS | ICANS |
|---|---|---|
| Any grade, n (%) | 16 (89%) | 8 (44%) |
| Grade 3, n (%) | 0 (0) | 5 (28%) |
| Median time to onset (range) | 2 days (1-6) | 6 days (3-9) |
| Median duration (range) | 5.5 days (1-9) | 4 days (1-56) |
| Toci administered, n (%) | 14 (78%) | N/A |
| Median number of doses (range) | 1 (1-2) | N/A |
| Dex administered, n (%) | 13 (72%) | 5 (29%) |
| Median number of doses (range) | 1 (1-7) | 2 (1-9) |

| | 1m | 3m |
|---|---|---|
| Prolonged grade 3+ cytopenias | 10/18 (56%) | 0/18 (0%) |
| Neutropenia | 7/18 (39%) | 0/18 (0%) |
| Thrombocytopenia | 1/18 (6%) | 0/18 (0%) |
| Anemia | 5/18 (28%) | 0/18 (0%) |

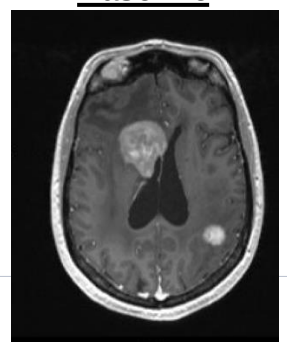
- No TLTs
- No Grade 4/5 ICANS
- Grade 3 Ommaya infection req removal : 2 patients
- Grade 3 electrographic focal status epilepticus : 1 patient
- Grade 2 low grade renal cell carcinoma : 1 patient
- Grade 4 low-risk myelodysplastic syndrome (at 12 mo): 1 patient
- Death due to PD : 7 patients

# Efficacy

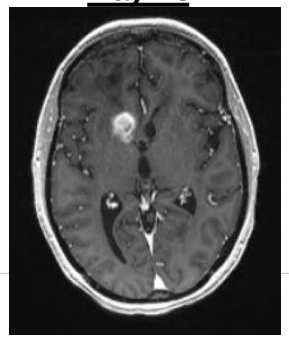



- Median f/u: 24 mo
- ORR: 17/18 (94%)
  - uCR/CR: 12/18 (67%)
  - PR: 5/18 (28%)
- Median time to best response : 3 mo (1-6)

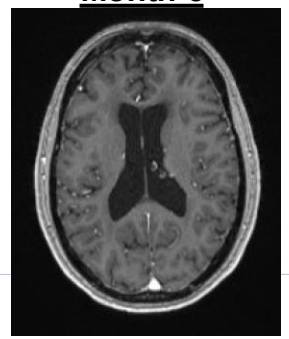
**Baseline**



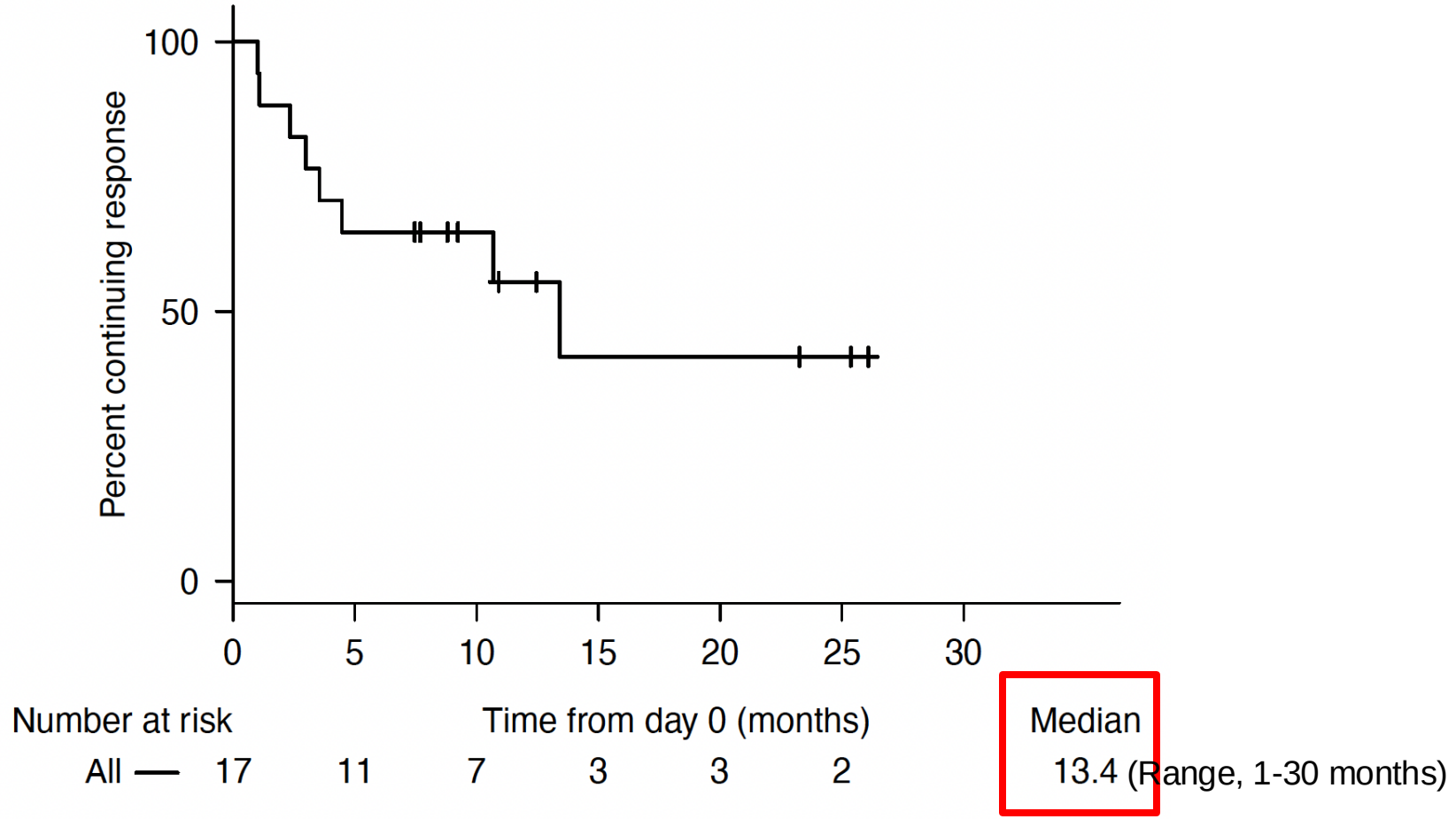
**Day 28**



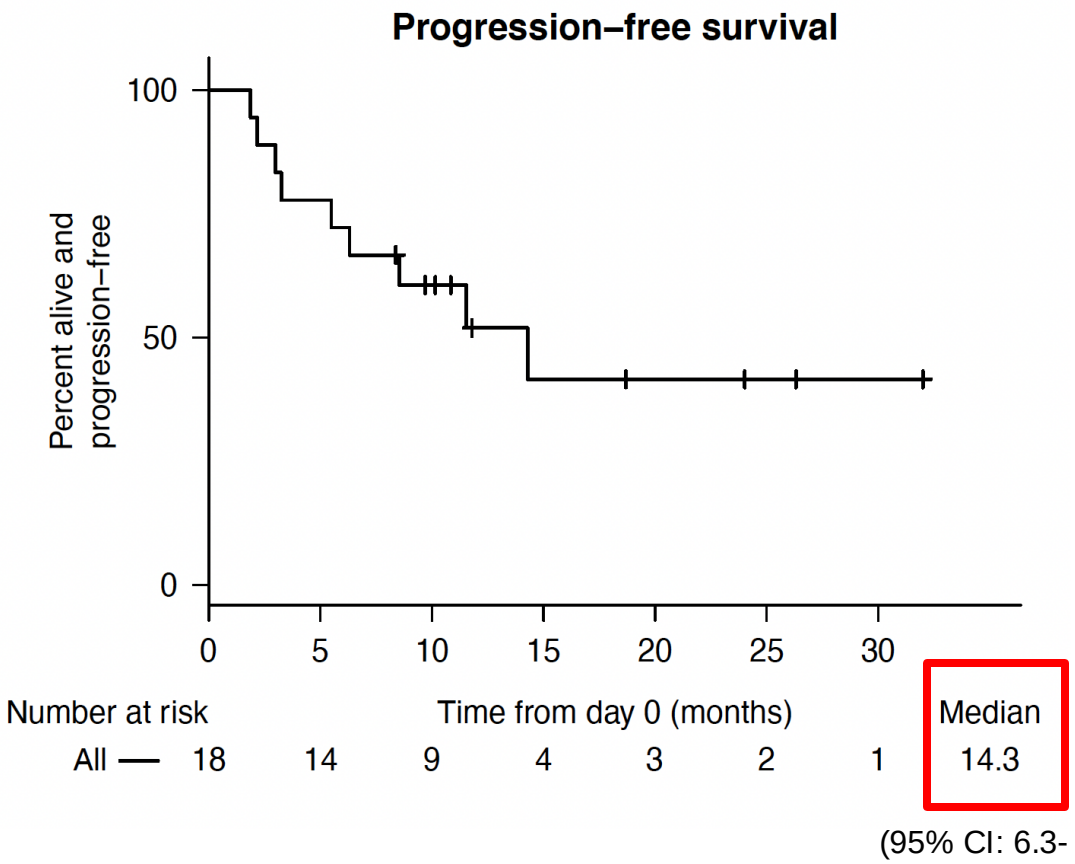
**Month 6**



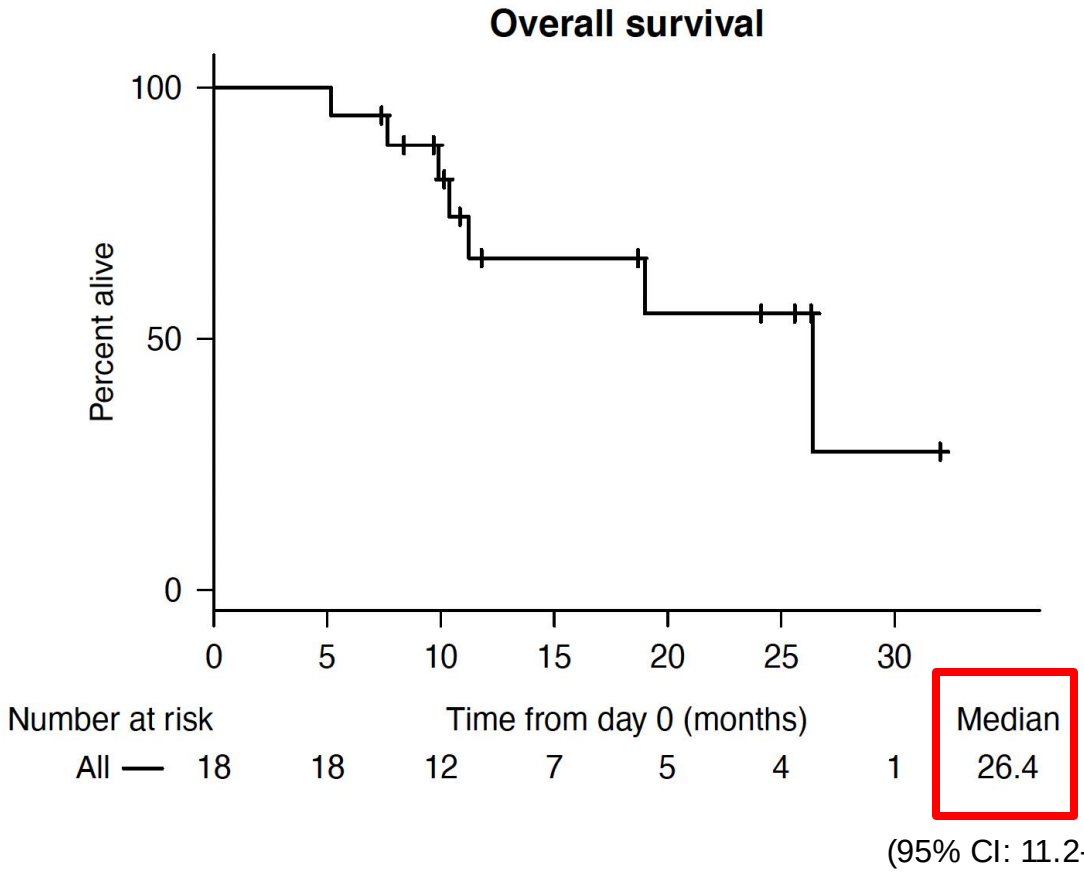
# Duration of Response



# Survival

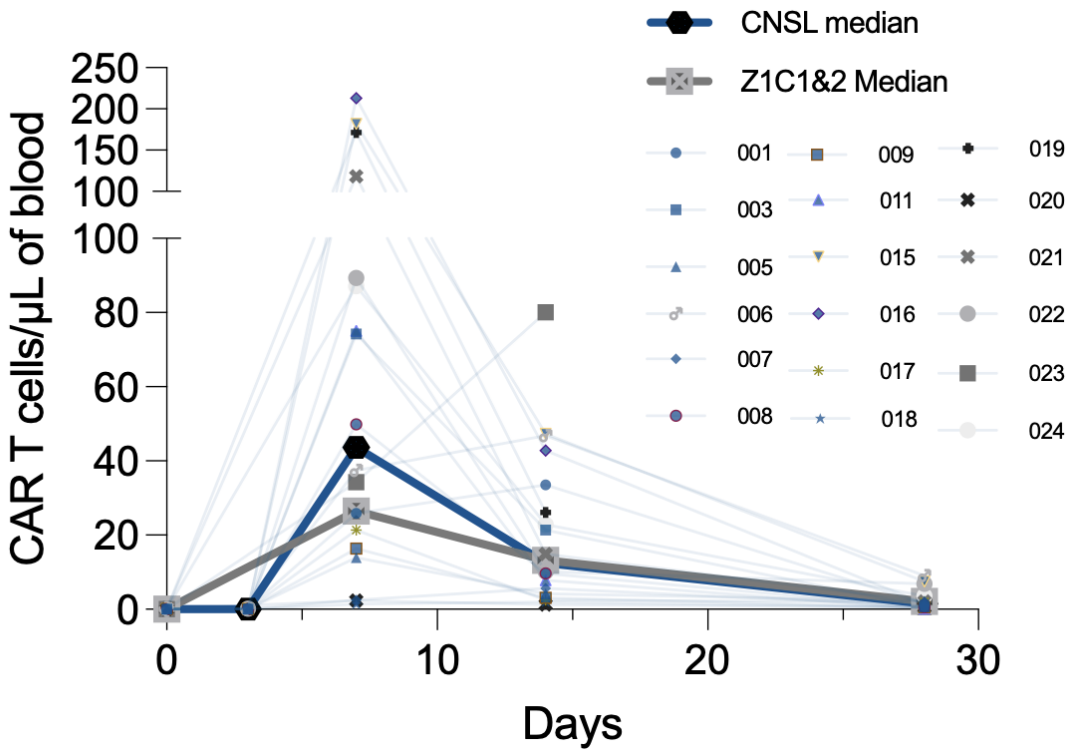


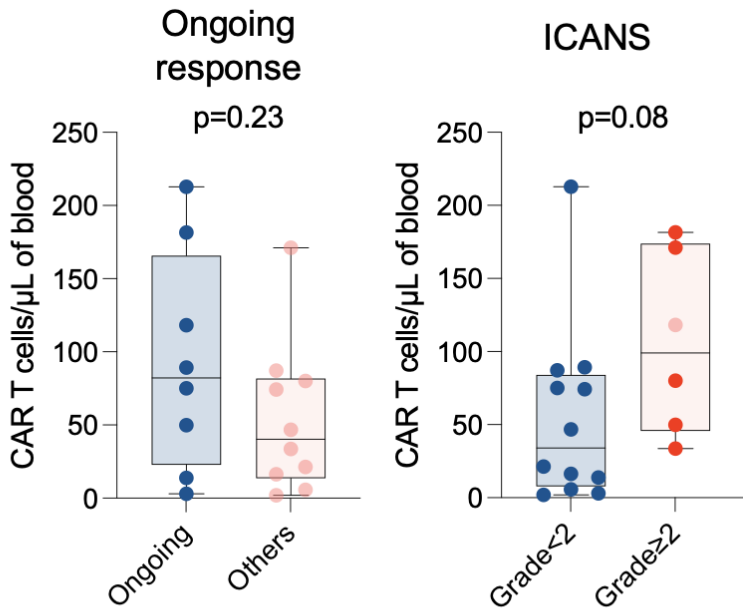

(95% CI: 6.3- NR)




(95% CI: 11.2- NR)

# CAR T cells expansion in CNSL patients (n=18) is comparable to ZUMA-1

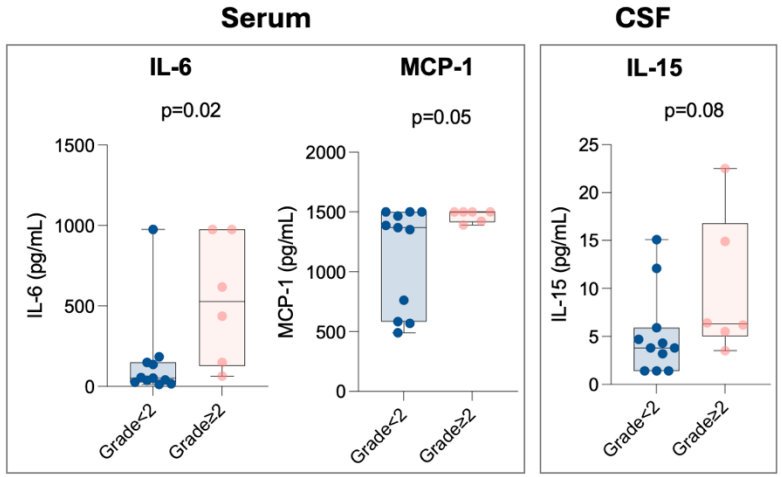



- Patients with ongoing response have higher CAR T cell expansion
- Patients with grade≥2 ICANS (dark red indicates patients who experienced grade 3 ICANS) have higher CAR T cell expansion

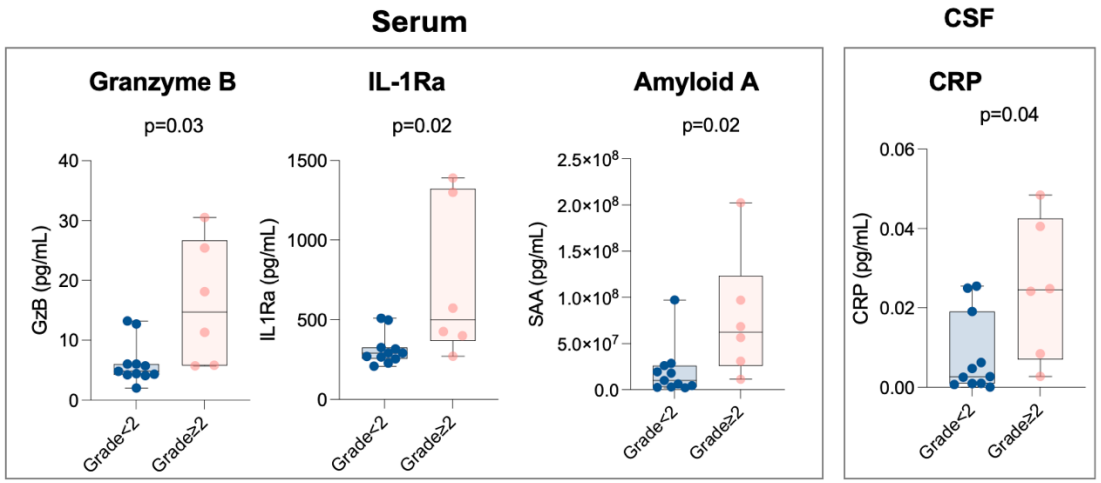
# High-grade ICANS associate with baseline and peak levels of biomarkers in serum and CSF

**Peak analytes**




- As observed in LBCL, peak levels of inflammatory IL-6, myeloid related MCP1 associate with high-grade (grade≥2) ICANS.
- Peak IL-15 is also higher in patients with grade≥2 ICANS, similar to 3L LBCL

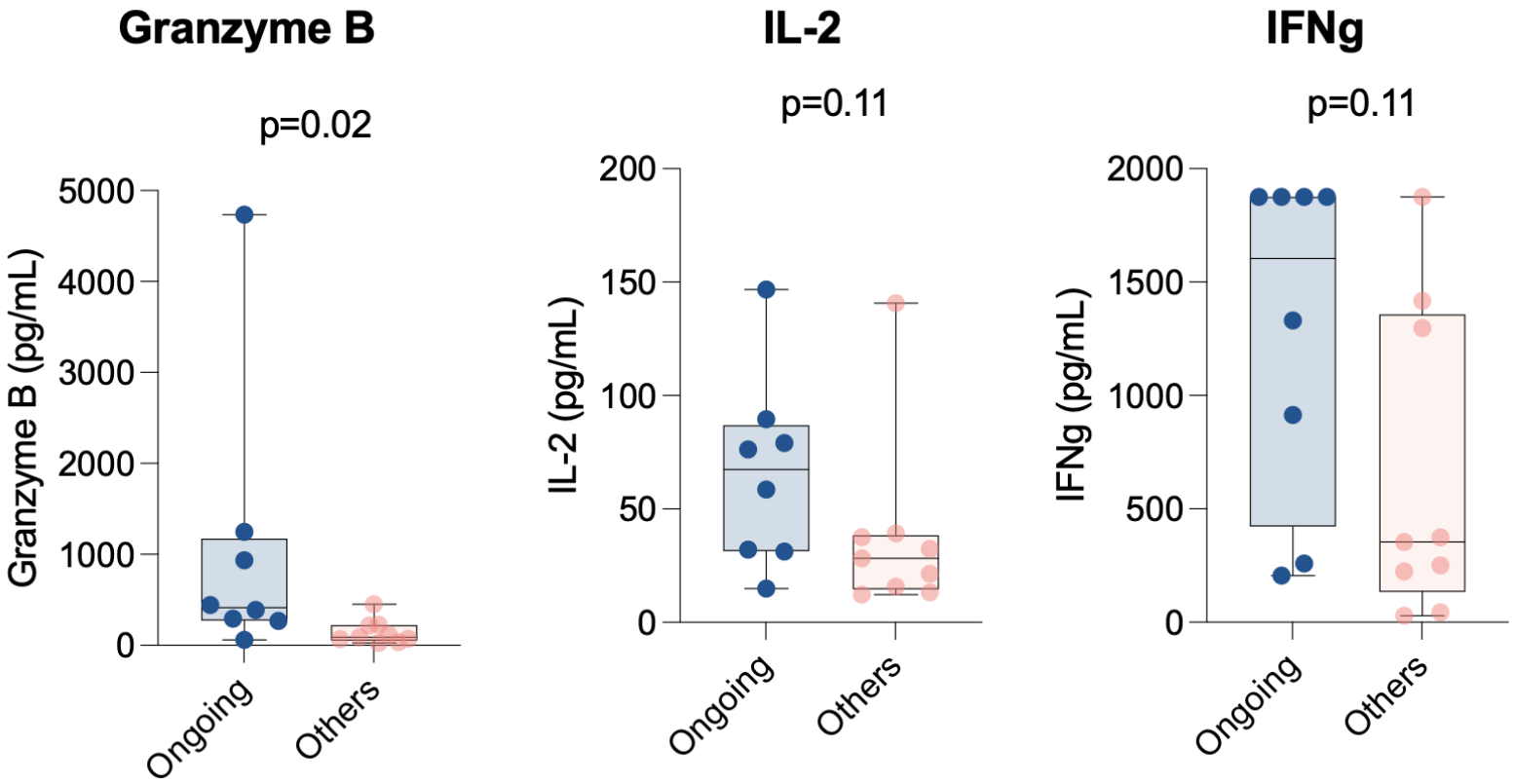
**Baseline analytes**




- Unlike LBCL, baseline inflammatory cytokines (GzB, Amyloid A in serum and CRP in CSF) and IL-1Ra in serum associated with high-grade ICANS

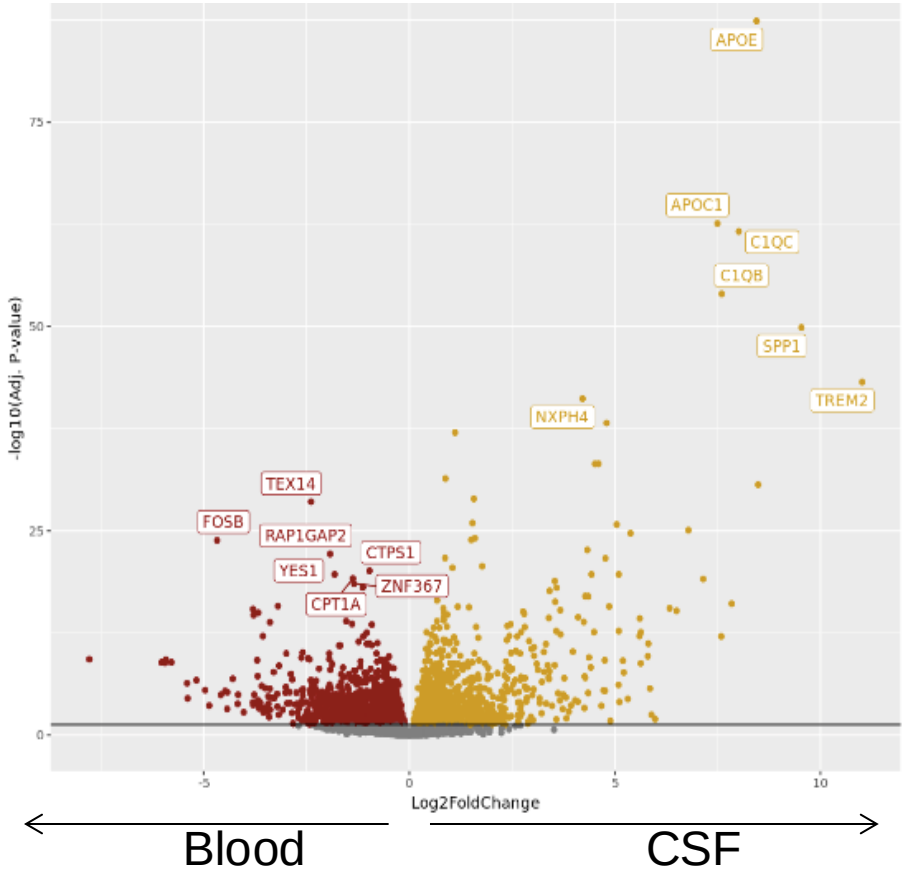
N.B. 5/6 patients in grade≥2 ICANS are grade 3 ICANS

# Ongoing responders have higher peak levels of serum inflammatory cytokines



# CD8 CSF CAR T cells show an enrichment for exhaustion associated genes

Differential Expression Blood vs CSF CAR-T cells at maximum expansion




Top 20 DE genes in CSF CAR-T cells include the T cell inhibitory genes:

- PD-1
- TIM-3
- BLIMP-1

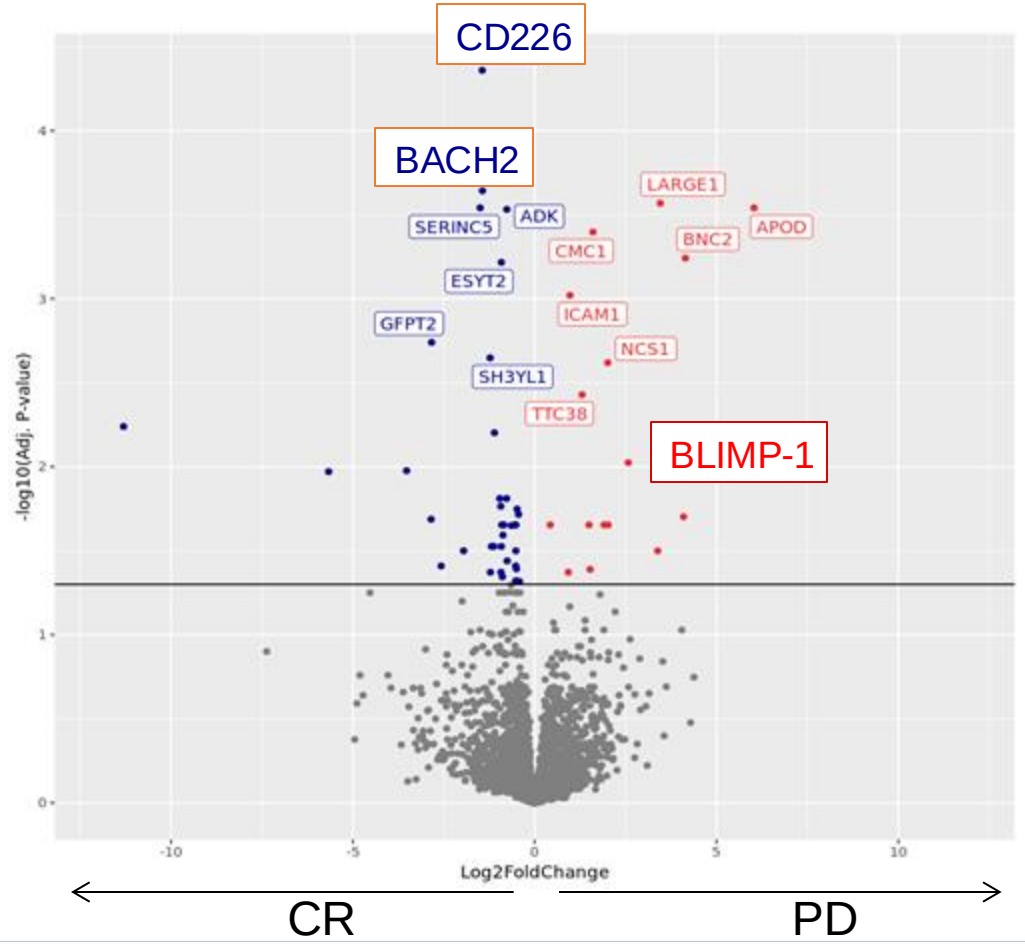
DE analysis suggest a higher risk of CAR-T cell inhibition in the CSF

# Upregulation of genes that counteract T cell inhibition in patients with CR

Differential Expression CSF CD8-CAR T cells
Complete Responders (CR) vs. Progressive Disease (PD)
at maximum expansion

**Upregulated in durable CR:**

- CD226
- BACH2




**Upregulated in early PD:**

- BLIMP-1

# Conclusions

- Axi-cel is safe for treatment of primary & secondary CNS lymphomas
  - No increased risk of high-grade ICANS or cerebral edema
- Axi-cel has promising efficacy in heavily pre-treated R/R CNS lymphomas with durable responses
  - 1-year PFS > 50%
- Patients with ongoing CR demonstrate increased levels of serum pro-inflammatory cytokines, IFNg, IL2 and GzB.
- Analysis of CSF CAR T cells from patients with durable CR show an increase in expression of exhaustion-reversing genes, CD226 and BACH2.

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# Patients & Families