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► To cite this version:

Benoît Tessoulin, Audrey Grain, Jocelyn Ollier, Thomas Gastinne, Viviane Dubruille, et al.. Biological differences between two commercial anti-CD19 CAR T cells products and impact on outcomes in lymphoma patients.. The 64th American Society of Hematology Annual Meeting and Exposition ASH 2022, Dec 2022, New Orleans, Louisiana, United States. inserm-03956740

HAL Id: inserm-03956740

<https://inserm.hal.science/inserm-03956740>

Submitted on 25 Jan 2023

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BIOLOGICAL DIFFERENCES BETWEEN TWO COMMERCIAL ANTI-CD19 CAR T CELLS PRODUCTS AND IMPACT ON OUTCOMES IN LYMPHOMA PATIENTS.

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INTRODUCTION

Axicabtagene ciloleucel (axi-cel, Yescarta® [Axi]) and tisagenlecleucel (tisa-cel, Kymriah® [Tisa]) have been approved and commercialized in Europe for Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) after 2 or more previous lines of therapy. A recent LYSA Study from a matched analysis of the Descar-T registry has reported that Axi may yield a higher disease control rate compared to Tisa but at the expense of a higher toxicity rate (Bachy E et al., Nat Med. 2022 Oct;28(10):2145-2154). Several biological reports have shed light on the importance of both the expansion and the persistence of CAR T-cells for enhancing disease control. In addition, in a mouse model, it was previously reported that viability levels of CAR T cells both immediately after thawing and after 1 days of *in vitro* culture were an important indicator of the CAR-T cells antitumor activity (Zah E et al Cancer Immunol Res. 2016).

AIM

In this single-center prospective study, we prospectively analyzed the biological characteristics of both Axi and Tisa anti-CD19 CAR T-cells infused in 48 patients and assessed their correlation with patients' outcomes.

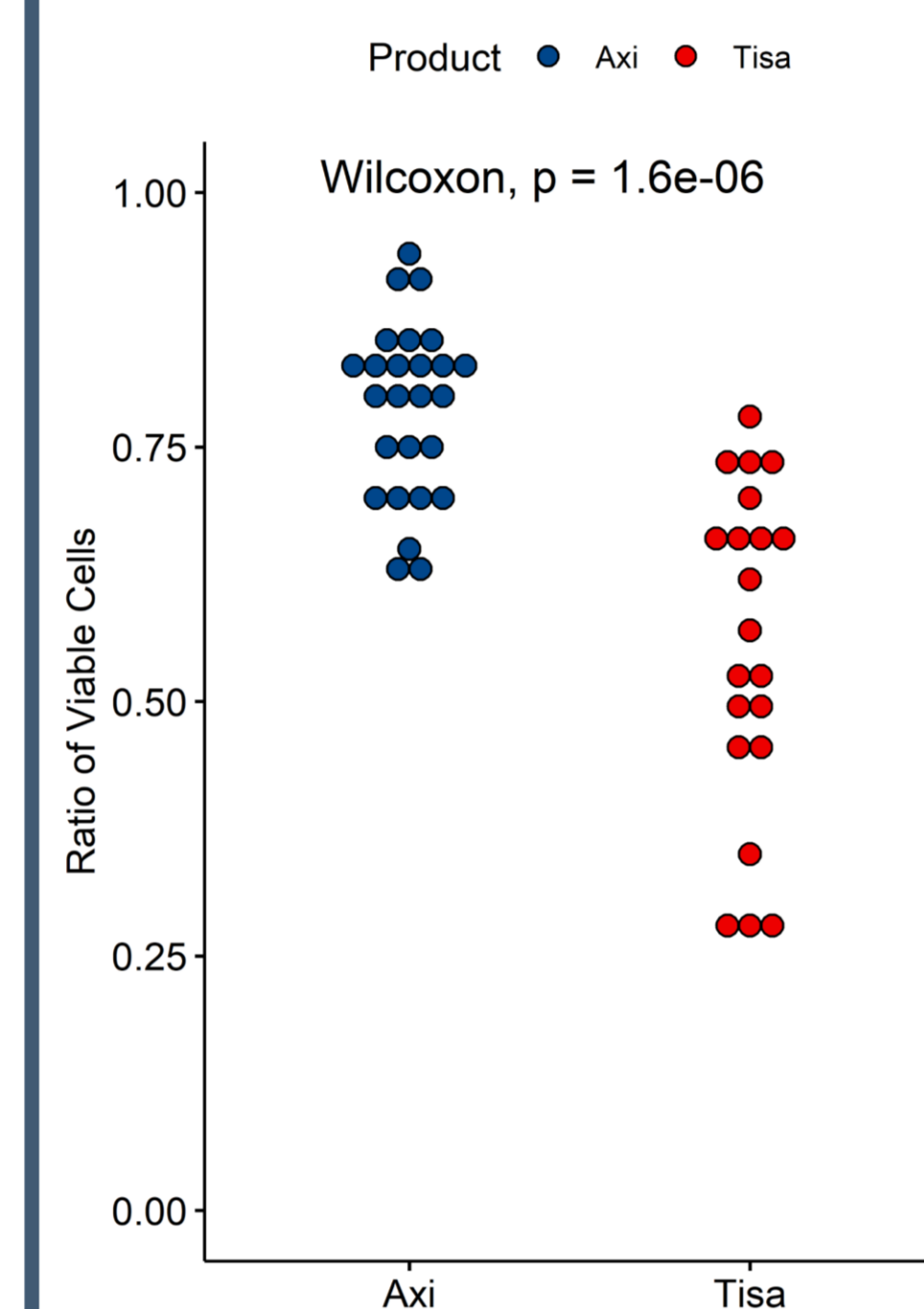
METHOD

Between March 2019 and June 2022, residual cells were obtained after washing 48 infusion product bags, including 27 Axi and 21 Tisa products.

- Cells' viability were analyzed immediately after the end of infusion and percentage of CAR positive T-cells (CAR+) were determined by flow cytometry with CD19 CAR detection reagent (Miltenyi Biotec)
- Afterwards, cells were put in complete medium (RPMI, glutamax, 8% of human serum and 300 UI of IL-2/ml) at 37°C and cell viability was assessed after 1 days of *in vitro* culture and doubling population number were monitored for 1 to 4 weeks
- Regarding the total number of infused cells:
 - Data were retrieved from Tisa certificate
 - For Axi, a virtual patient of 70kgs was simulated with a maximum amount of infused CAR+ cells of 200.10⁶

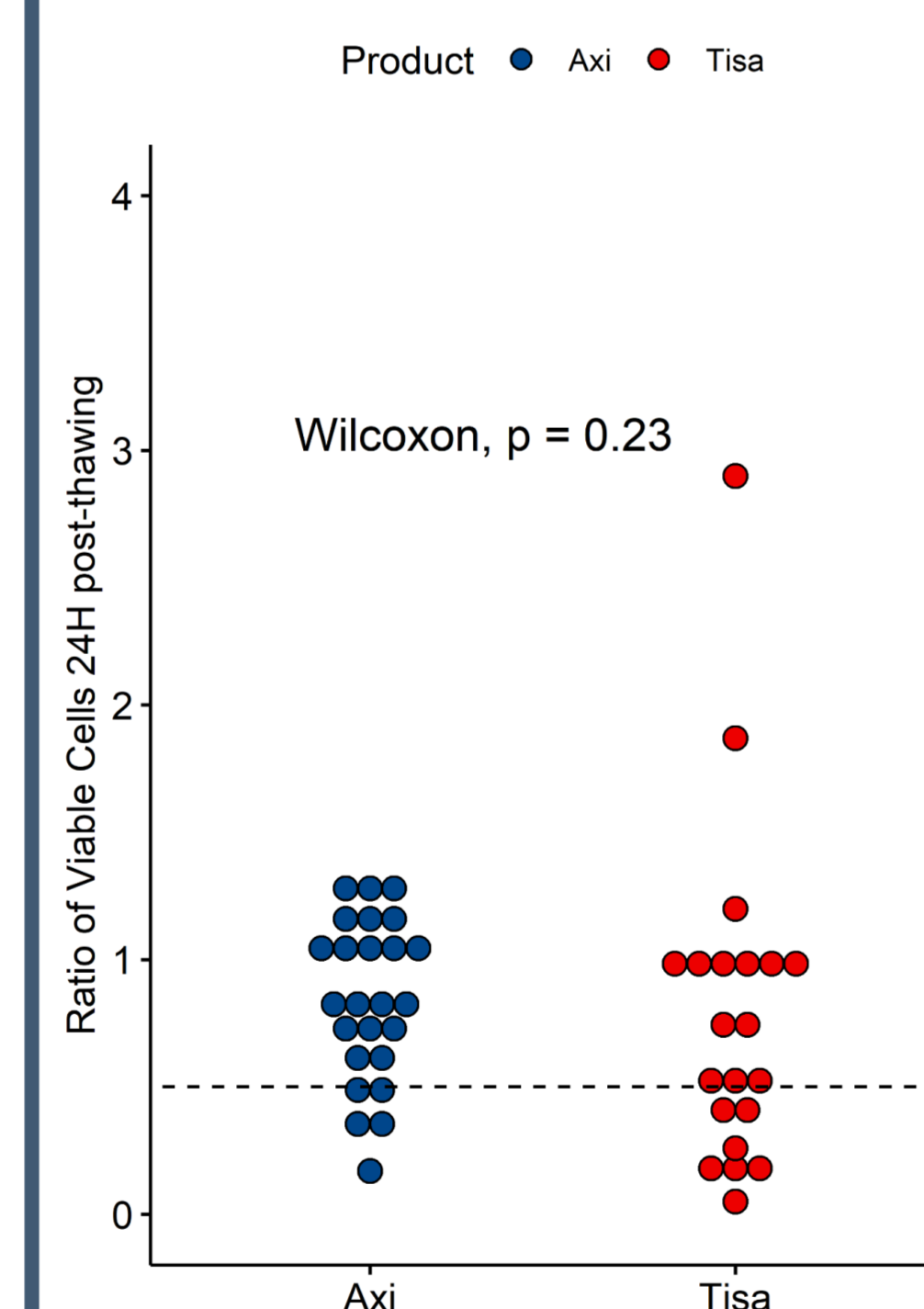
RESULTS

A. Cell Viability after the end of infusion



→ A higher rate of viable cells was noted for Axi products, at the end of infusion

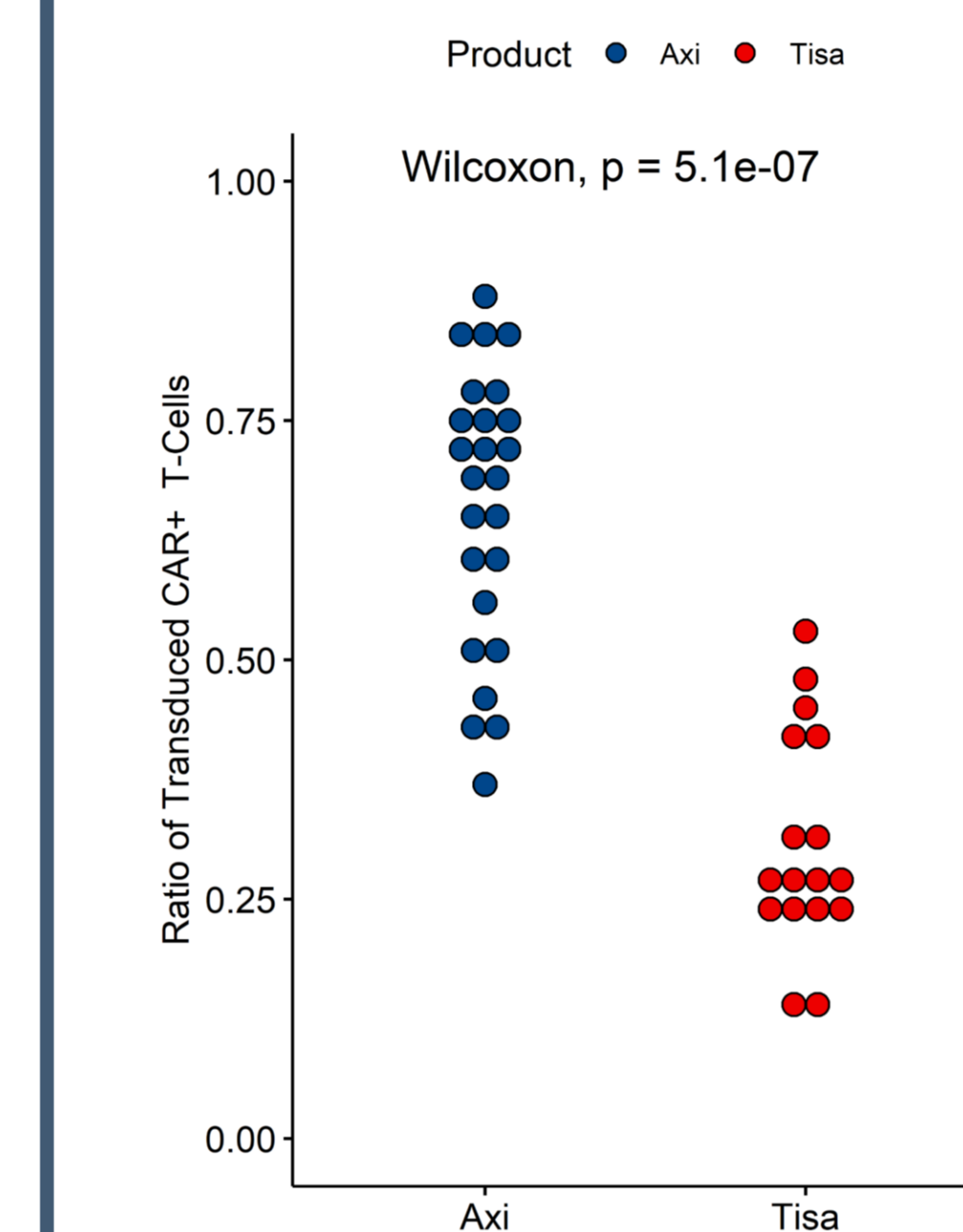
B. Viable cells recovery - 24h post-culture



→ The % of viable cells after 24H of *in vitro* culture without stimulation didn't show any absolute difference between the two products

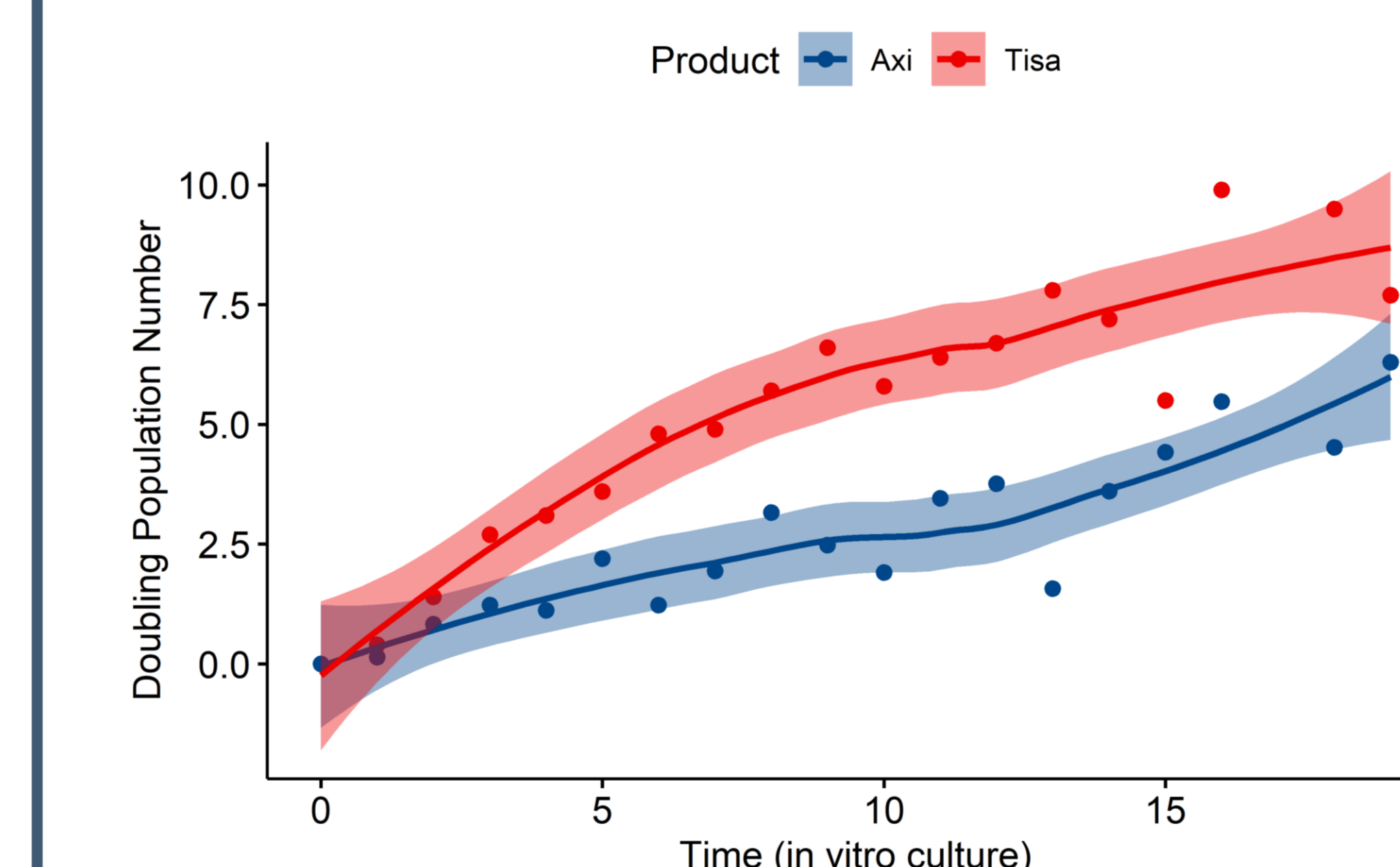
→ But, it was noted that 43% of tisa products had less than 50% of viable cells after 24H, compared to 20% for axi product.

C. Transduced CAR + T-Cells



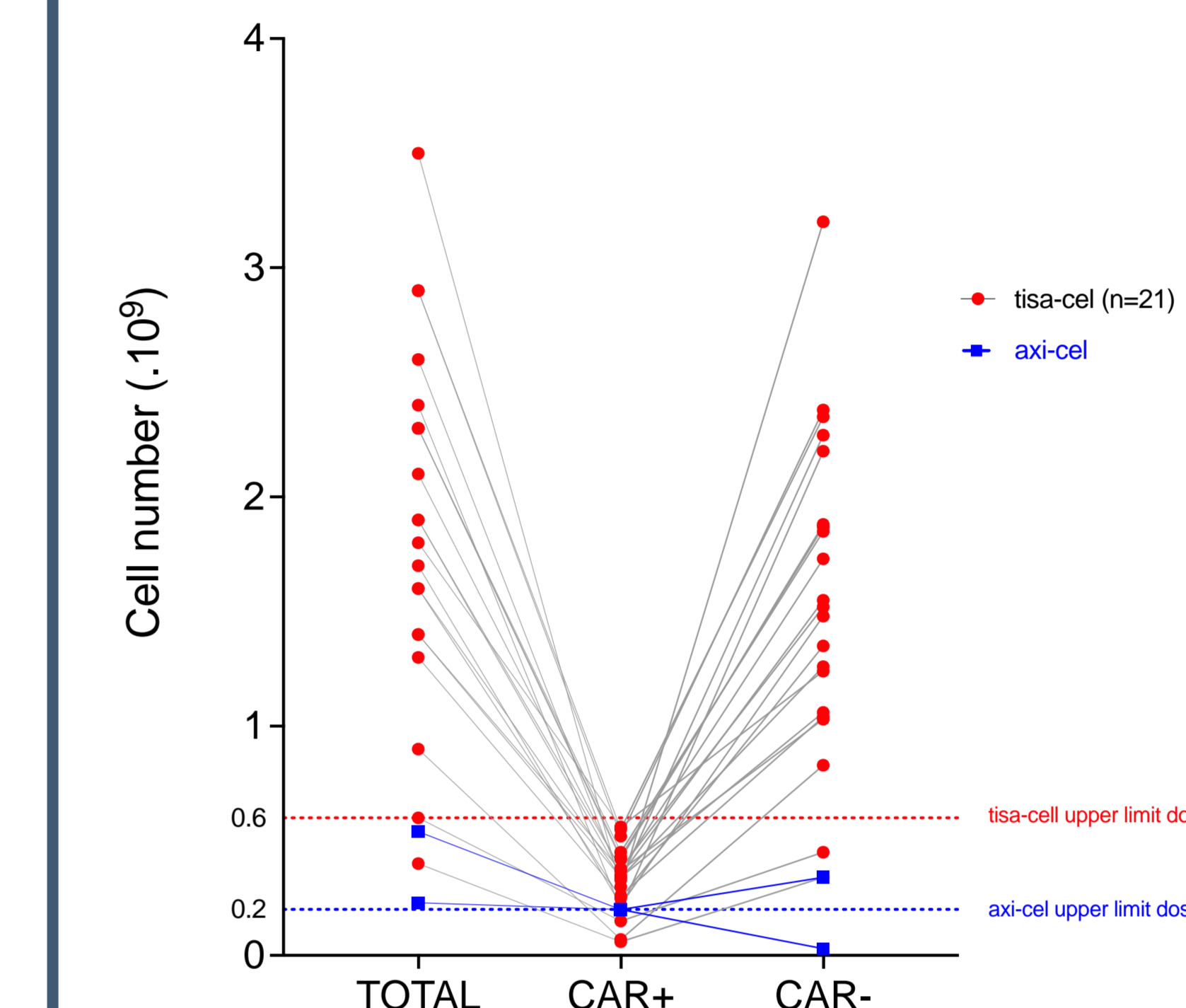
→ tisa products were characterized by a significantly lower fraction of CD3+ CAR+ T-cells as compared to Axi products

D. In-vitro proliferation



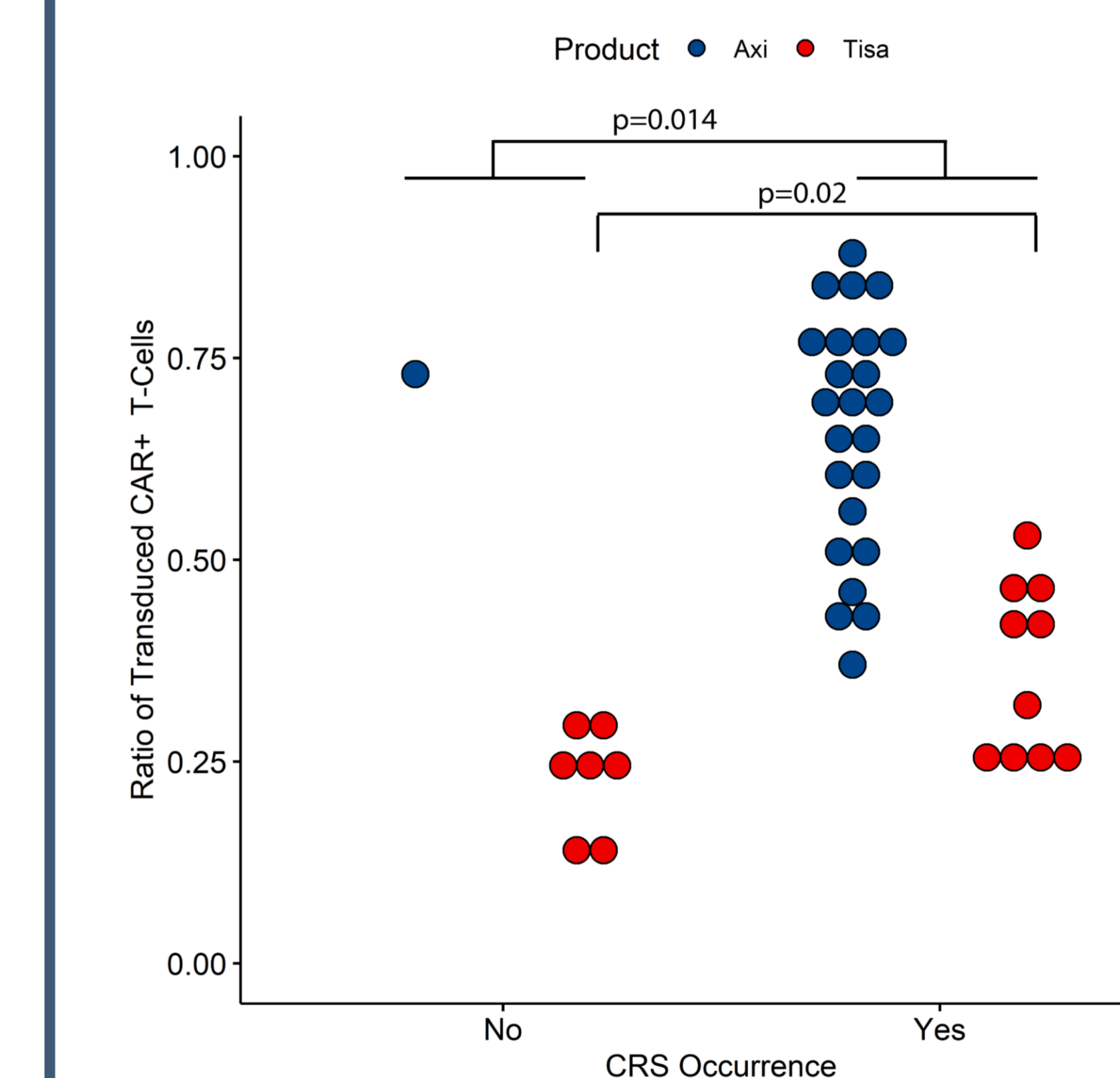
→ *In vitro* and in the absence of antigen stimulation, total T-cells were able to proliferate and tisa-Cel had a higher amplification capacity.

E. CAR negative T-cell dose



→ For tisa-cel, the proportion of CAR negative T-cells injected was highly variable between patients and ranged from 0.34 x 10⁹ to 3.5 x 10⁹.
→ For axi-cell product, the proportion of CAR negative T-cells was more homogeneous between patients and lower compared to tisa-cel

F. Correlation between CRS and % of CAR positive T-cells



→ A significant higher median % of CD3+ CAR+ T-cells was found in patients developing all grade CRS
→ This was also true when considering only patients receiving Tisa
→ No biological association with ICANs nor hematological toxicity could be reliably reported in this cohort.

CONCLUSIONS

1. Higher cell viability at the end of infusion and higher percentage of CAR+ T-cells were noted for axi-cel preparations
2. *In vitro* and without stimulation, Tisa-cel had a higher amplification capacity that may be related to a distinct activation status between tisa and axi-cel
2. For tisa-cel, a very heterogeneous total number of cells were injected
3. CAR-negative T-cell doses for tisa-cel were 3 to 400 times higher than for axi-cell
4. The correlation between rate of CRS and the percentage of CAR+ T-cells should be interpreted with caution, as a high imbalance between axi and tisa-cell occurrence of CRS existed. Although, it is to be noted that among tisa-infused patients, a higher count of CAR+ T-cells was also associated with a higher rate of CRS.
5. Because of tumor/patient heterogeneity, no analysis on the efficacy have been conducted

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