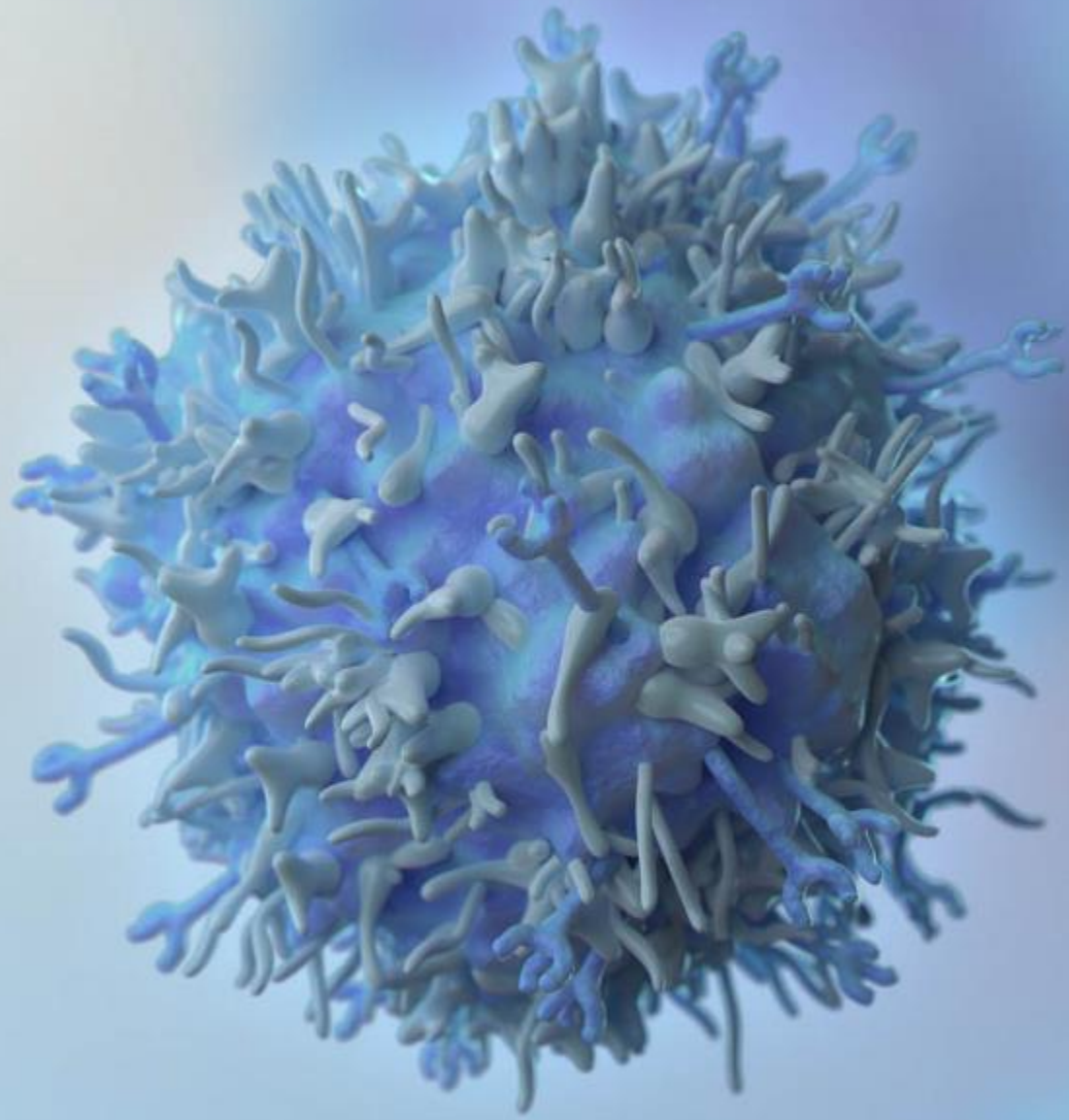

Pre- and post-treatment immune contexture correlates with long term response in large B cell lymphoma patients treated with Axicabtagene ciloleucel (axi-cel)

Mike Mattie, Ph.D.

Director of Translational Sciences and External Collaborations

ASH 2023

Abstract #226

Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma

Sattva S. Neelapu,[1,*] Caron A. Jacobson,[2] Armin Ghobadi,[3] David B. Miklos,[4] Lazaros J. Lekakis,[5] Olalekan O. Oluwole,[6] Yi Lin,[7] Ira Braunschweig,[8] Brian T. Hill,[9] John M. Timmerman,[10] Abhinav Deol,[11] Patrick M. Reagan,[12] Patrick Stiff,[13] Ian W. Flinn,[14] Umar Farooq,[15] Andre H. Goy,[16] Peter A. McSweeney,[17] Javier Munoz,[18] Tanya Siddiqi,[19] Julio C. Chavez,[20] Alex F. Herrera,[19] Nancy L. Bartlett,[21] Adrian A. Bot,[22] Rhine R. Shen,[22] Jinghui Dong,[22] Kanwarjit Singh,[22] Harry Miao,[22] Jenny J. Kim,[22] Yan Zheng,[22] and Frederick L. Locke[20,*]

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01916-x

Check for updates

OPEN

Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma

Nathalie Scholler[1,2], Regis Perbost[3], Frederick L. Locke[4], Michael D. Jain[4], Sarah Turcan[3], Corinne Danan[3], Edmund C. Chang[1], Sattva S. Neelapu[5], David B. Miklos[6], Caron A. Jacobson[7], Lazaros J. Lekakis[8], Yi Lin[9], Armin Ghobadi[10], Jenny J. Kim[1], Justin Chou[1], Vicki Plaks[1], Zixing Wang[1], Allen Xue[1], Mike Mattie[1], John M. Rossi[1], Adrian Bot[1,11] and Jérôme Galon[3,12]

Clinical response

Objective response rate was 83%

58% complete response rate
(Locke et al. Lancet Oncol. 2019)

- at 5 years follow up an OS rate of 42.6%
- 5 years durable response
  & 5 years disease specific survival at 51%
  (Neelapu *et al.* Blood 2023)

Previous pharmacodynamic results

- T cell-related biology (Immunosign 21; Immunoscore®IC) measured pretreatment in the tumor microenvironment was associated with response to axi-cel
  (Scholler *et al*. Nature Medicine 2022).
- Increased density of activated PD-1+LAG-3+/−TIM-3−CD8+ T cells, measurable pretreatment (multiplex IHC), facilitates clinical response in pts post–axi-cel.

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Tumor immune contexture analysis

The association between immune cell subset density and probability to **relapse** was evaluated in a subset of ZUMA-1 patients.

SAMPLING

26 patients treated
- 11 relapsed (6 CR/5 PR)
- 15 durable response (15 CR)

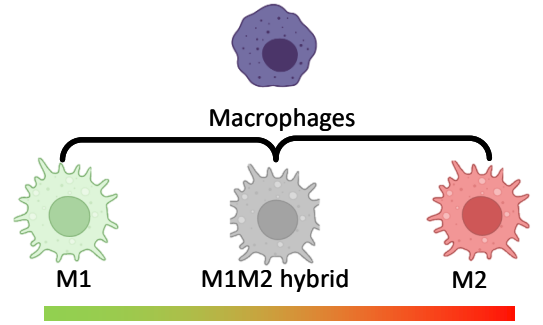
32 tumor biopsies
- 15 at baseline (13 CR/2 PR)
- 17 post-infusion (13 CR/4 PR)

MULTIOMICS ANALYSIS

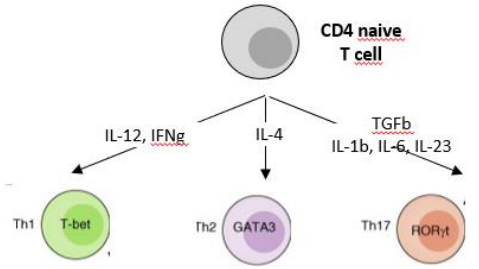
- Brightplex® T cell infiltration
  CD3 CD8 FOXP3 TIM3 PD1 LAG3 TOX
- Brightplex® regulatory T cell subtyping
  CD3 CD8 GATA3 TBET RORg BCL6 FOXP3
- Brightplex® T cell activation/exhaustion
  CD3 CD8 TIM3 LAG3 PD1 GZMB KI67
- Brightplex® Macrophage
  CD68 CD64 CD163 CD204 CD206 PDL1
- Brightplex® MDSC
  CD3 CD11B CD68 CD14 CD15 LOX1 S100A9

\+ Transcriptomic analysis, nCounter® PanCancer panel

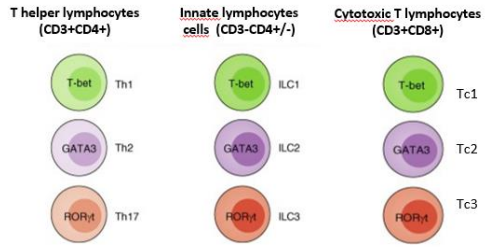
Macrophage plasticity



T helper Lineage



T cell subset



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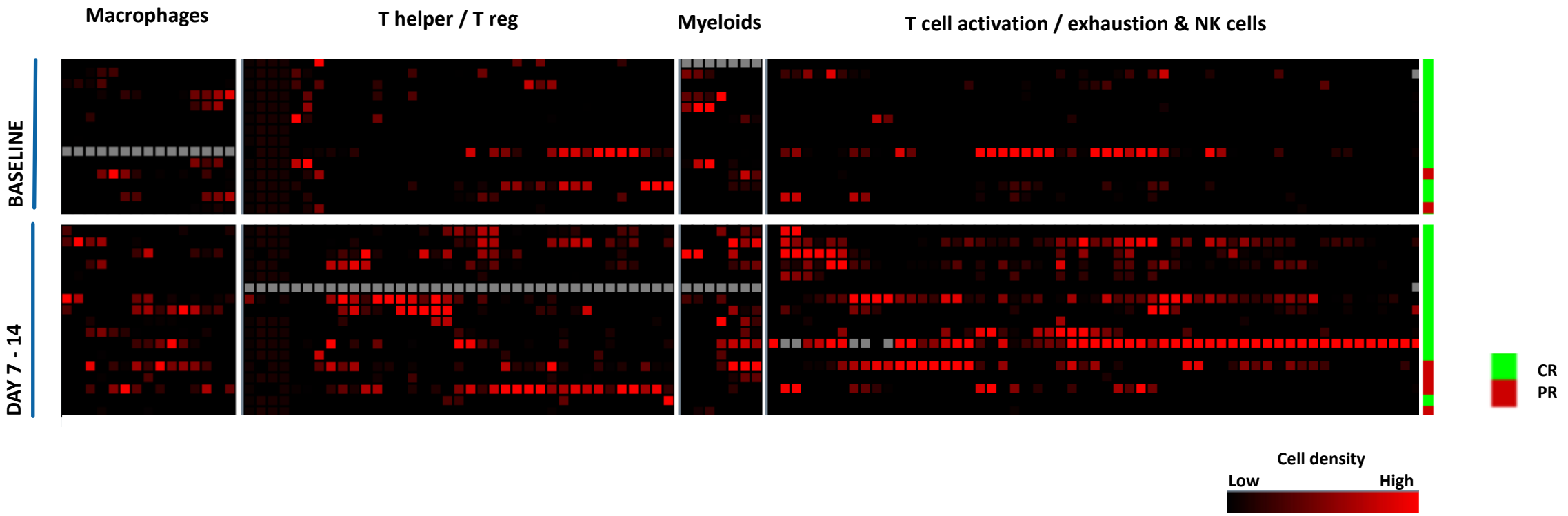
Global impact of axi-cel infusion on immune contexture – increased densities of immune cells post-infusion



Proteomic data based on Brightplex technology

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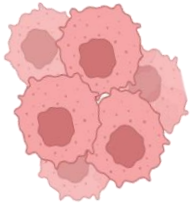
Brightplex® panel Macrophages & PD-L1

CD11b CD64, CD68, CD163, CD206, CD204, PDL1, PANCK

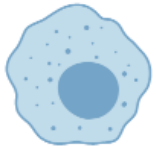


Tumor cells
PanCK+

Macrophages
CD68+

T cells
CD3+

anti-inflammatory



M1 Macrophages
CD68+CD64+
CD206-CD163-CD204-

M1M2 hybrid Macrophages
CD68+CD64+
with at least one positive M2 biomarker
(CD163, CD206, CD204)

- CD68+CD64+CD163+CD204+CD206-
- CD68+CD64+CD163+CD204-CD206+
- CD68+CD64+CD163+CD204+CD206+
- CD68+CD64+CD163+CD204-CD206-
- CD68+CD64+CD163-CD204-CD206+
- CD68+CD64+CD163-CD204+CD206+
- CD68+CD64+CD163-CD204+CD206-

M2 Macrophages
CD68+CD64-
with at least one positive M2 biomarker
(CD163, CD206, CD204)

- CD68+CD64-CD163+CD204-CD206-
- CD68+CD64-CD163-CD204-CD206+
- CD68+CD64-CD163-CD204+CD206-
- CD68+CD64-CD163+CD204+CD206-
- CD68+CD64-CD163+CD204-CD206+
- CD68+CD64-CD163-CD204+CD206+
- CD68+CD64-CD163+CD204+CD206+

And their PDL1 status

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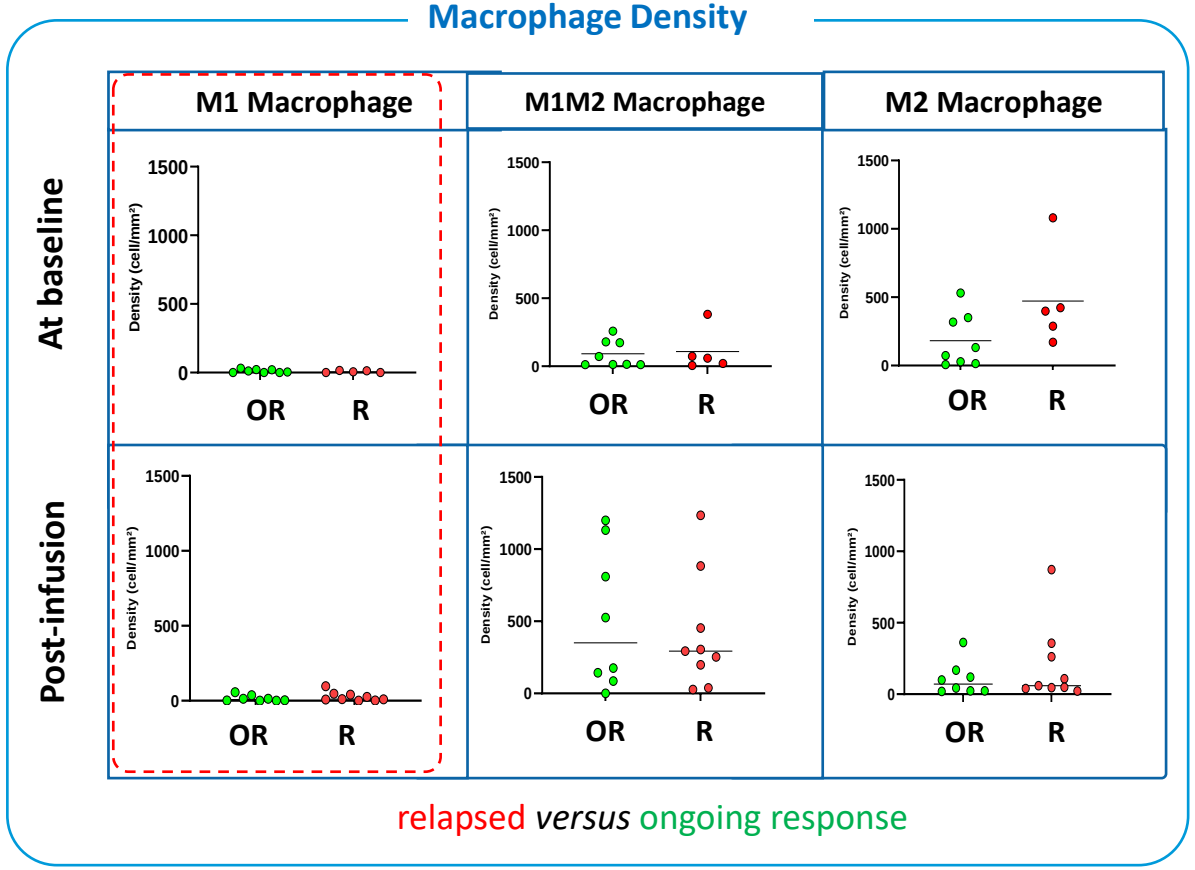
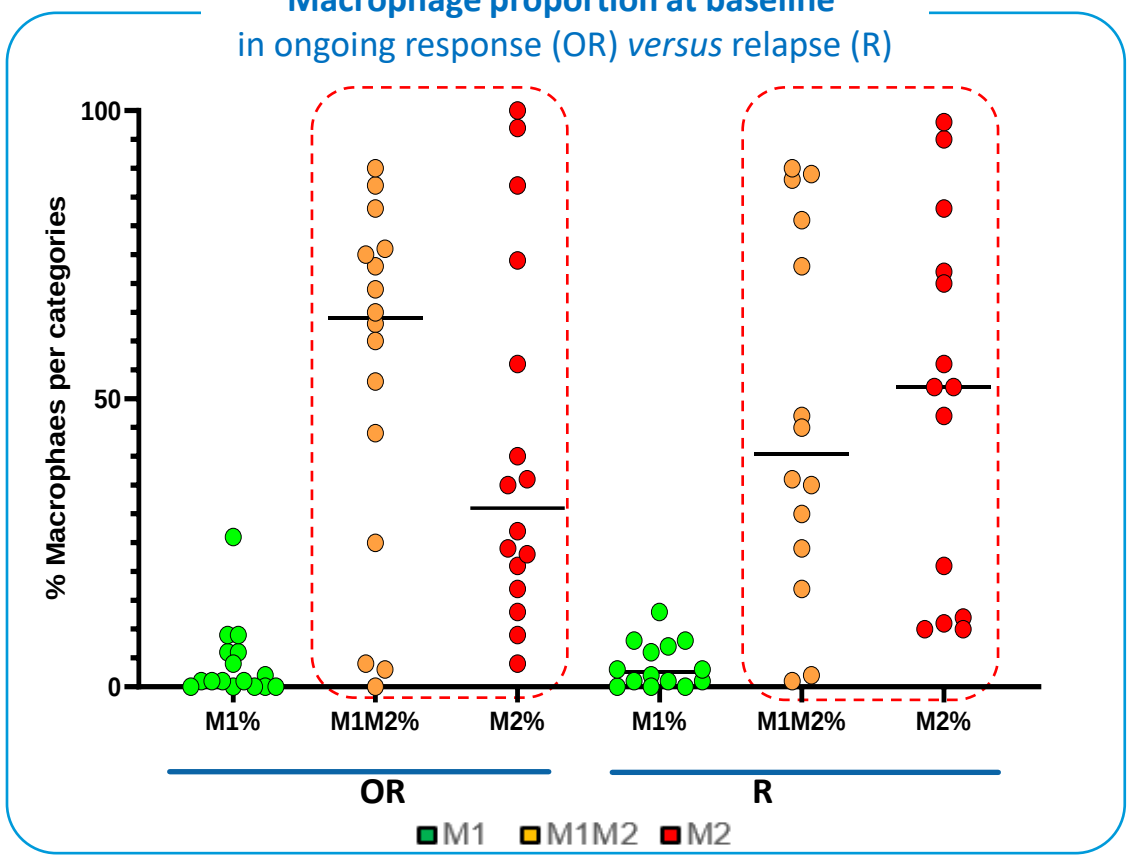
Tumor macrophage densities do not differ, but relative proportions skew differently between relapsed and ongoing responders





At baseline & post-infusion:

Low pro inflammatory M1 macrophage density in both groups. No differences in subtype densities.

At baseline:

Inverse Proportion of M1M2 *versus* M2 macrophages

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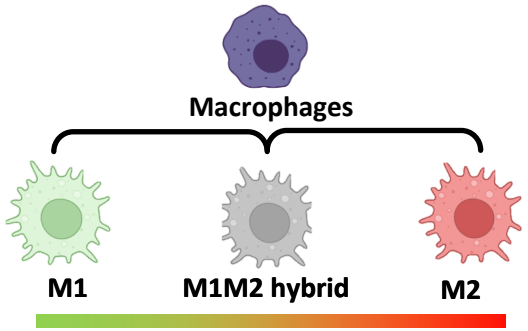
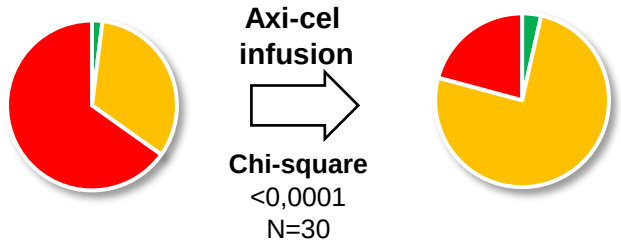
A higher proportion of protumoral macrophage at baseline is associated with relapse after axi-cel in patients with large B cell lymphoma

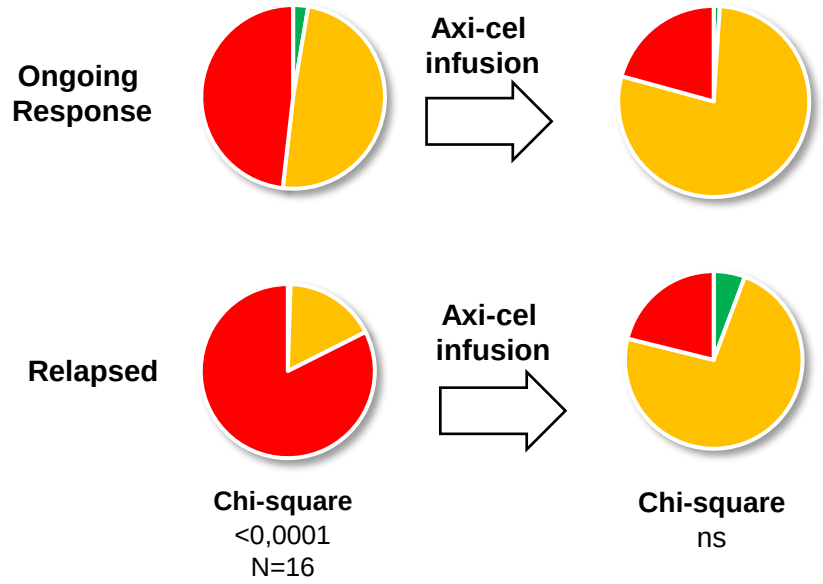
Macrophage lineage



Axi-cel infusion impacts macrophage plasticity



M2 macrophage proportion at baseline is potentially predictive of relaspe



M1 M1M2 M2

After axi-cel infusion
Significant switch from M2 to M1M2 macrophage phenotype

At baseline, a higher proportion of M2 macrophages is associated with relapse after axi-cel
→ M2 proportion as a putative predictive biomarker for axi-cel relapse

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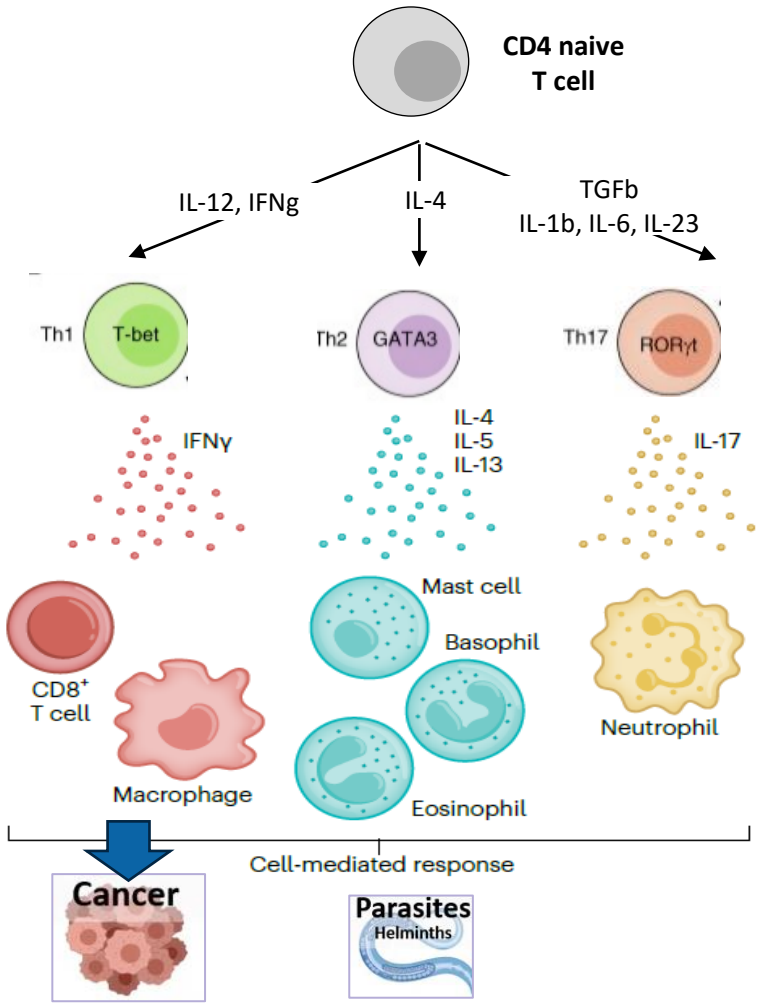
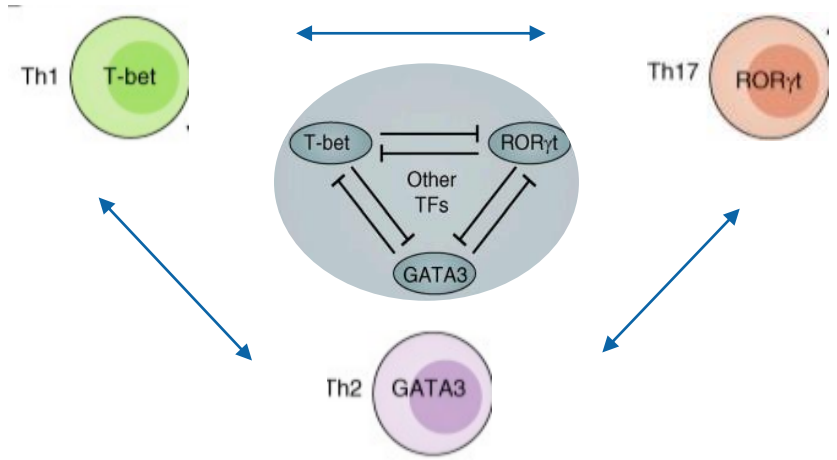
Lymphocyte T lineage – State of the art

Brightplex® regulatory T cell subtyping
CD3 CD8 GATA3 TBET RORg BCL6 FOXP3

T helper Lineage



T Helper Plasticity



T lymphocyte lineage

T helper lymphocytes (CD3+CD4+)		Cytotoxic T lymphocytes (CD3+CD8+)		Signature Effector Cytokines
T-bet	Th1	T-bet	Tc1	IFN-γ
GATA3	Th2	GATA3	Tc2	• (IL-4) • IL-5 • IL-13
RORγt	Th17	RORγt	Tc3	• IL-17 • IL-22

adapted from Fang & Zhu, JEM 2017, Künzli & Masopust, Nature Imm 2023

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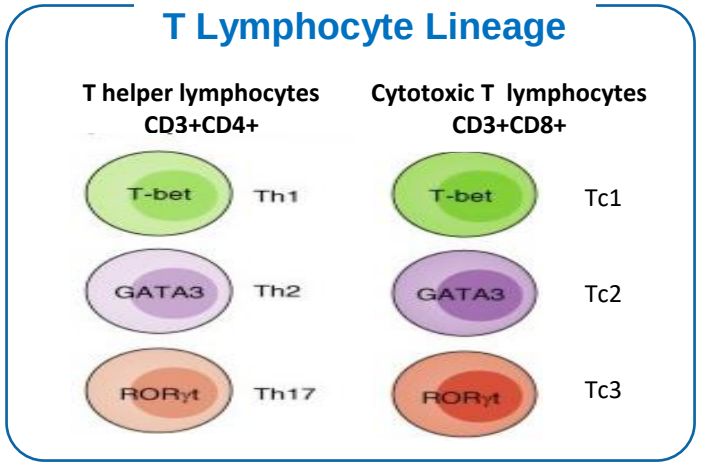
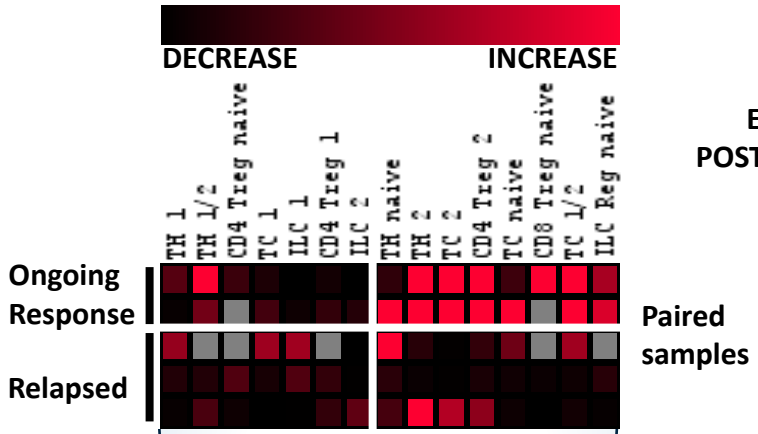
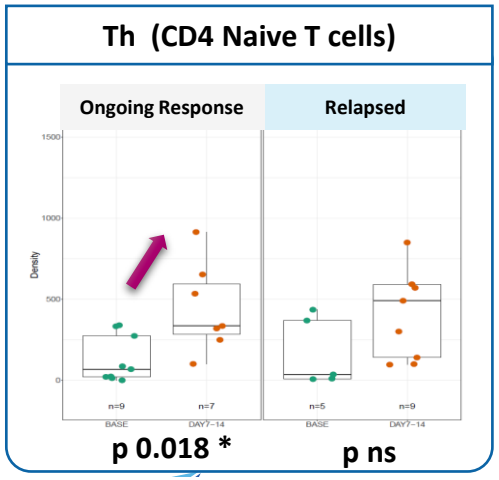
Global impact of axi-cel on T lymphocyte subpopulations

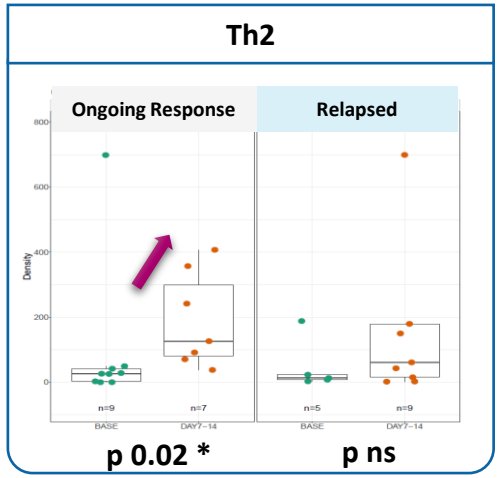


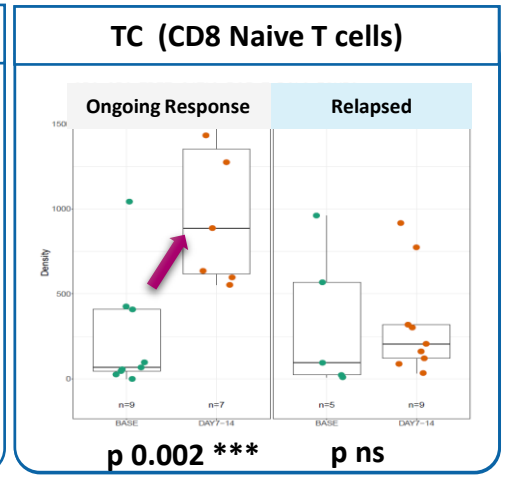


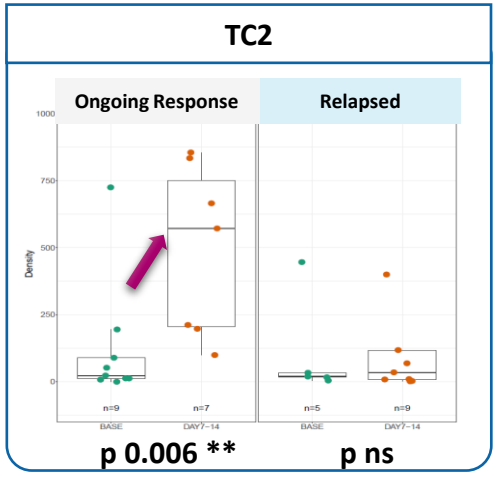
EVOLUTION
POST Axi-cel infusion
(FC)

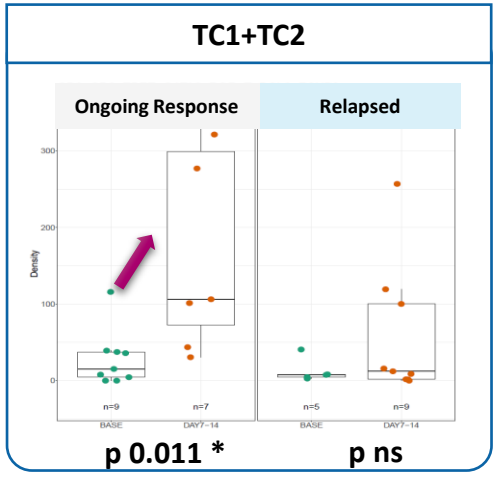
unpaired analysis











Significant Change < 0.05 * < 0.01 ** < 0.005 ***

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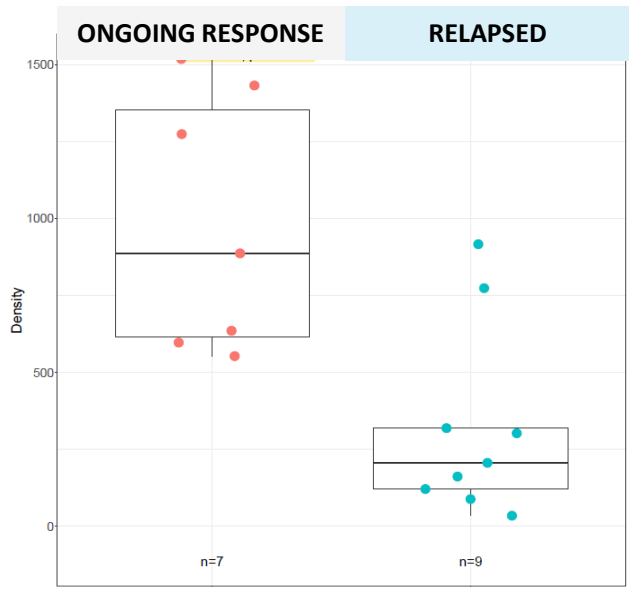
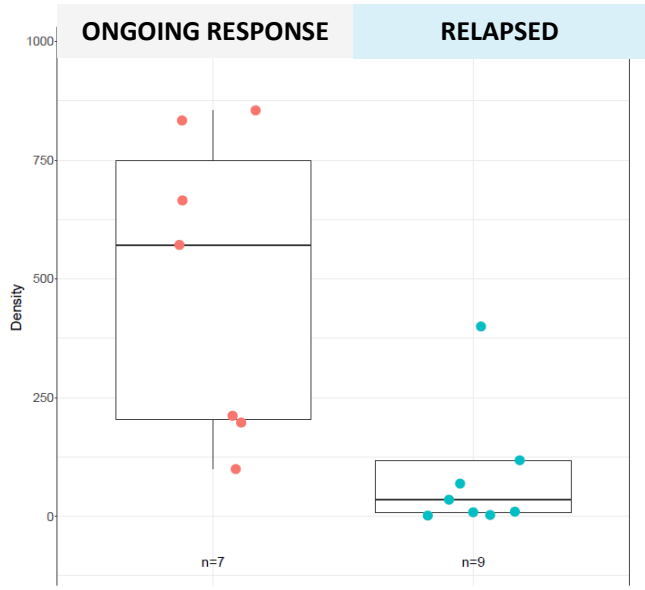
Higher CD8 naïve, TC2 and TC1+TC2 infiltration post-infusion in ongoing responders

CD8 Naive T cell



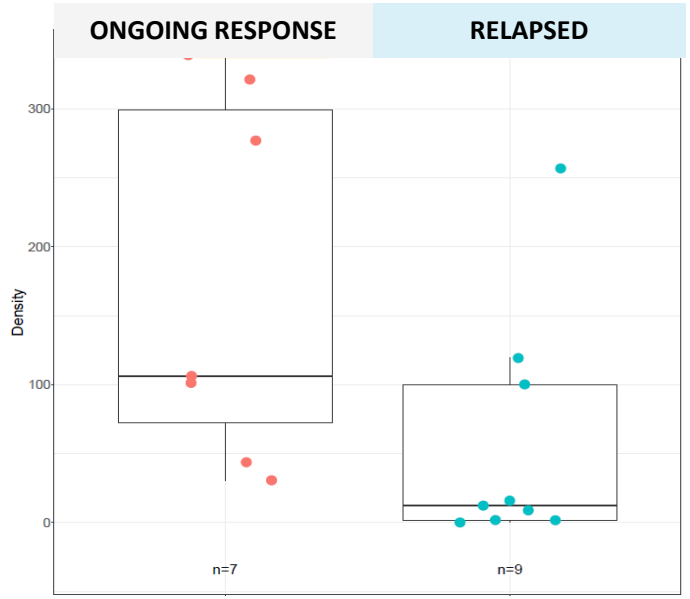
P-value : 0.0079

TC2 : GATA3+



P-value : 0.031

TC1+TC2 : GATA3+ TBET+



P-value : 0.023

(no significant difference observed in Th cell subpopulations)

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Axi-cel impact on Tumor Immune Contexture in DLBCL

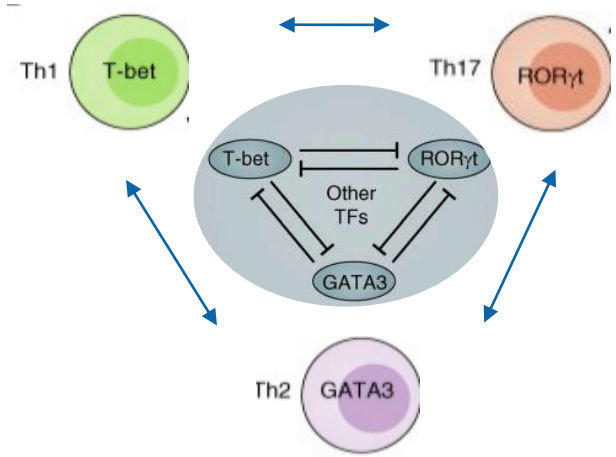
Th cell mediated response

- **Th1** : **Cancer** (Intracellular pathogens, Tissus repair, Foreign Bodies)

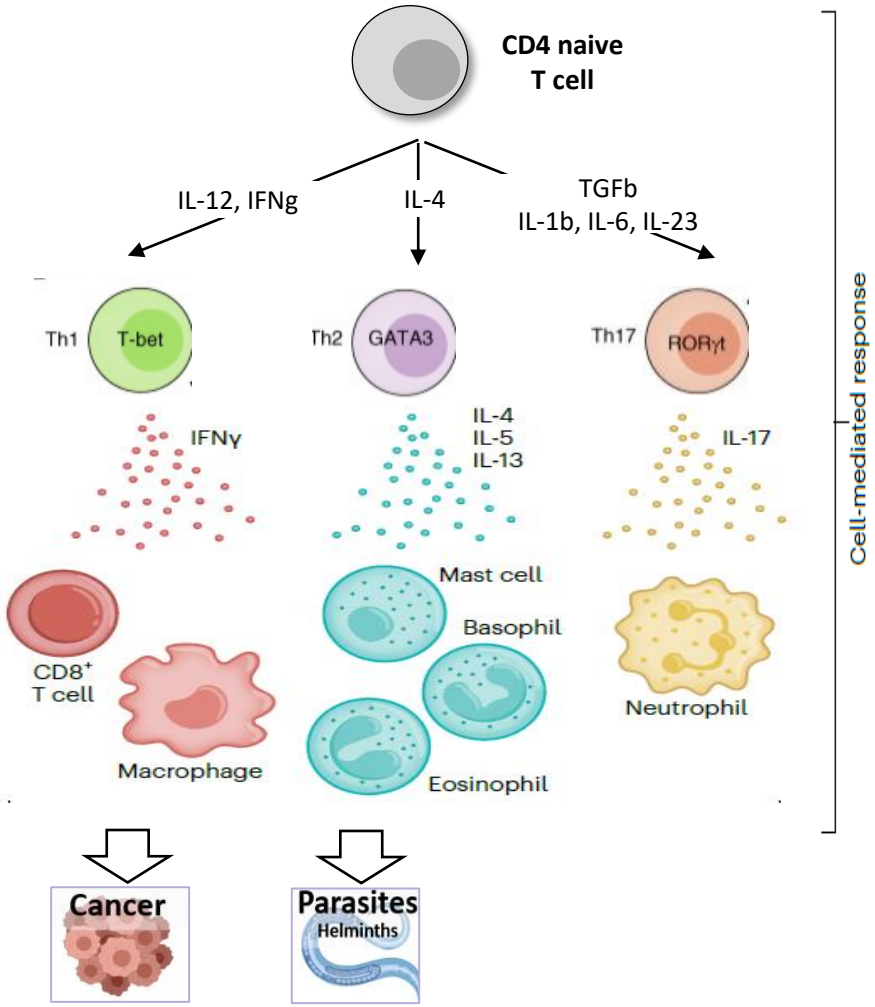
- **Th2** : **Allergen, Parasite**, ..

- **Th17** : **Extracellular pathogen**, chronic neutrophil inflammation, ..

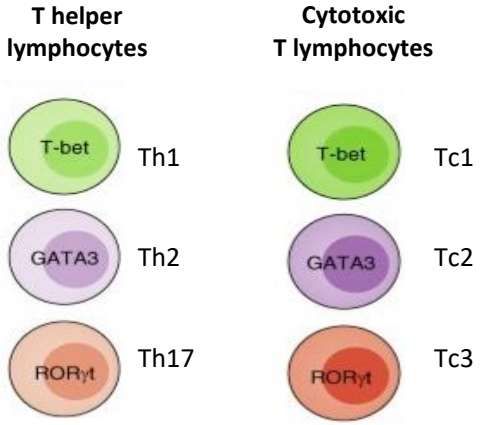
Impact of Axi-cel on Th Plasticity



Impact of Axi-cel on Th cell Lineage



Axi-cel induces increase in T cell subsets Th1/Th2 balance important



In DLBCL, Axi-cel infusion impacts Immune contexture,

Especially T lymphocyte subsets

Which correlates with Ongoing Response

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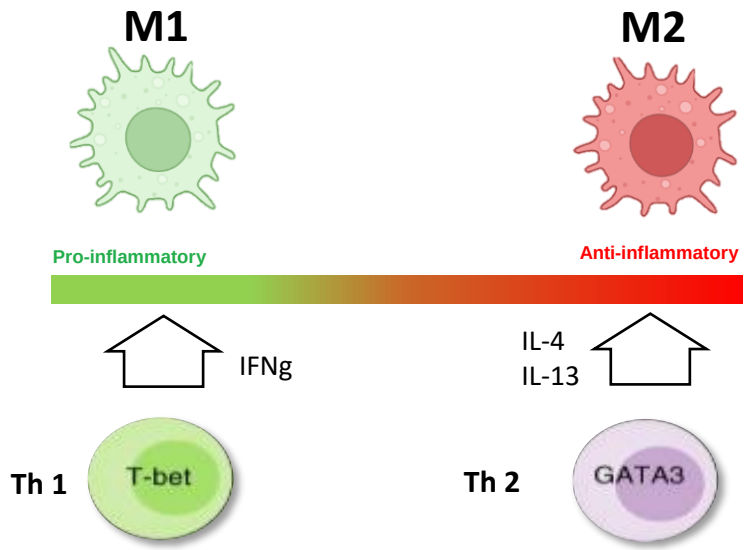
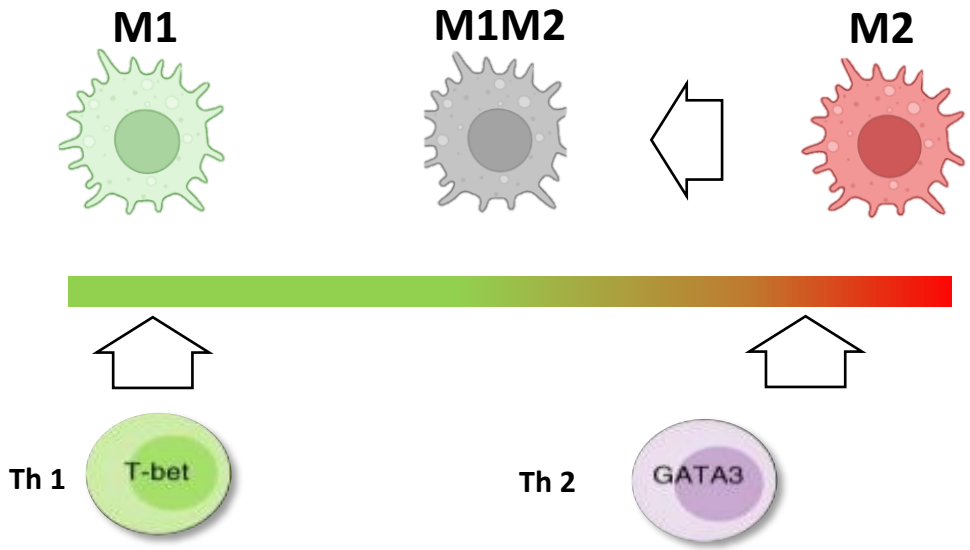
adapted from Fang & Zhu, JEM 2017, Künzli & Masopust, Nature Imm 2023

Axicel impact on Tumor Immune Contexture in DLBCL

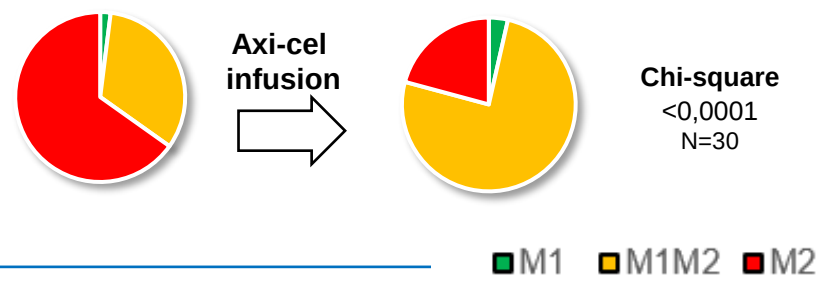
Th2 mediates M2 Polarization



Axi-cel promotes M2 to M1M2 polarization



Axi-cel infusion impacts macrophage plasticity



After Axi-cel infusion

- Switch from M2 protumoral macrophages to hybrid M1M2 macrophages phenotype ($p<0.0001$)
- Global increase of T lymphocyte subset cell density (Especially in Ongoing Responder: TC1+TC2 $p=0.023$)

→ **Axi-cel drastically impacts the tumor immune contexture correlated with ongoing response**

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SUMMARY

Results

- Low proinflammatory M1 macrophage density seen at baseline and post-infusion
- In relapsed patients, a higher proportion of protumoral M2 macrophage was observed at baseline (p<0.0001)

After axi-cel infusion

- Post-infusion, a significant shift in M2 to M1M2 macrophage proportions (M1, M1M2, M2) (p<0,0001) was observed.
- Ongoing response was associated with a significant increase of cell densities:
  - ✓ CD4 and CD8 naïve T cells
  - ✓ T helper Th2
  - ✓ Cytotoxic T lymphocyte TC2 and TC1+TC2

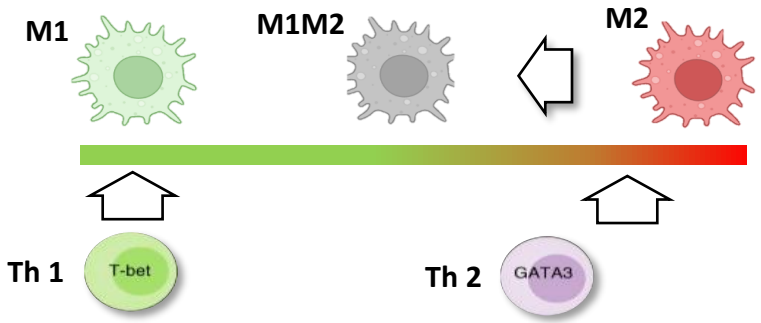
Conclusion

- Warrants validation to determine if baseline proportion of protumor M2 macrophage predicts axi-cel relapse.
- Axi-cel treatment significantly impacts densities of various T cell subpopulations and macrophage proportions

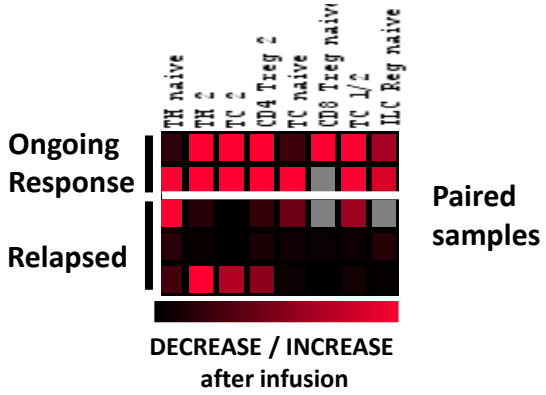
→ Leading to a drastic change of the tumor immune contexture correlated with ongoing response.

M2 macrophage proportion at baseline could predict axi-cel relapse

Axi-cel promotes M2 to M1M2 polarization



T lymphocyte change after infusion correlates with OR



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Thank you

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