GPCO

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2023

16 & 17 novembre

STRASBOURG

Hôpital Hautepierre

Clinical Pharmacology and modeling for allogeneic CAR-T cell with the impact of the lymphodepleting regimen

Case example of UCART19 in ALL

Thibaud Derippe

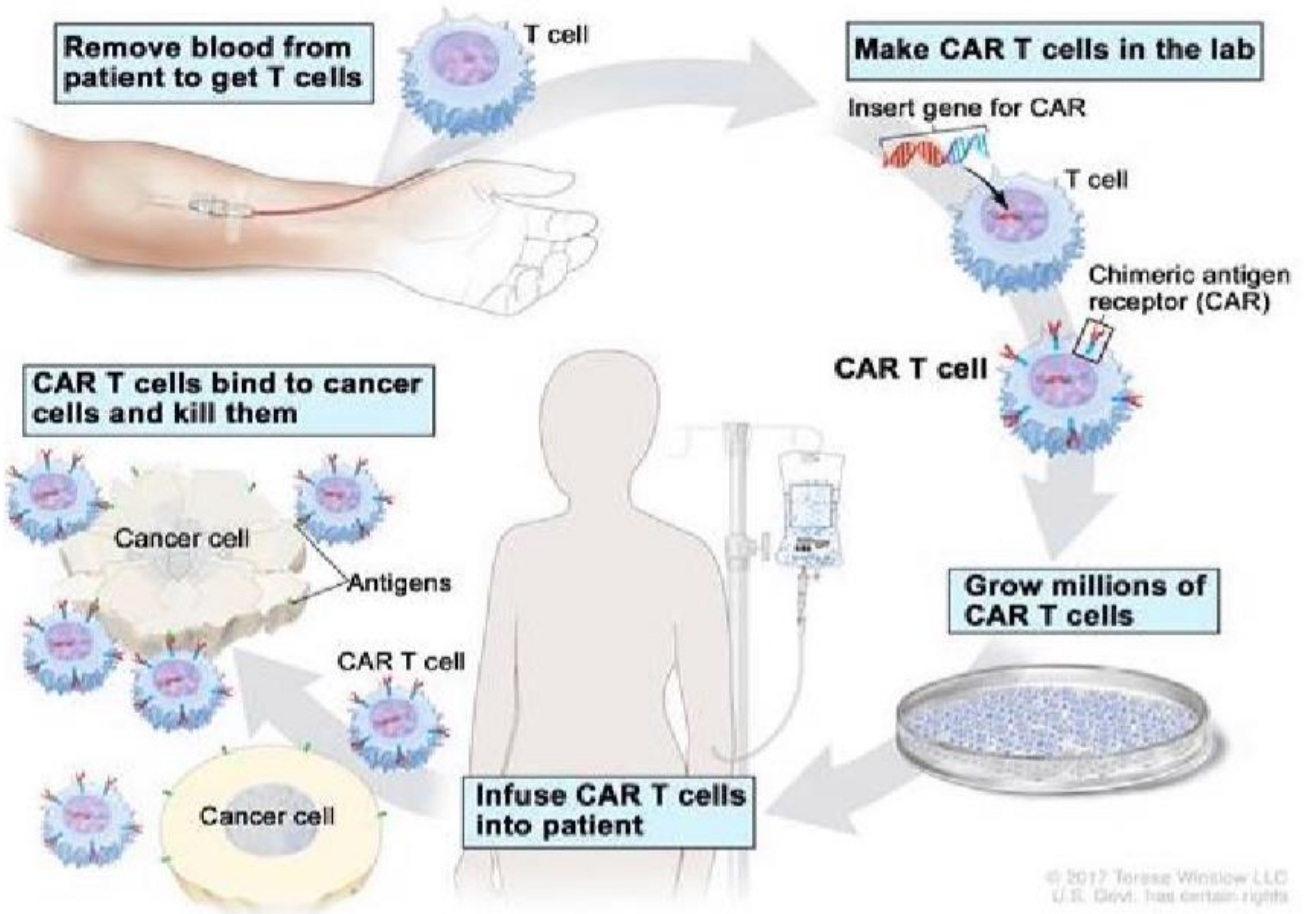
CAR-T cells are fundamentally T-cells enhanced in laboratory before reinfused in the patient

First possible source for original T cells:

- Directly from the patients (**autologous**)

↓

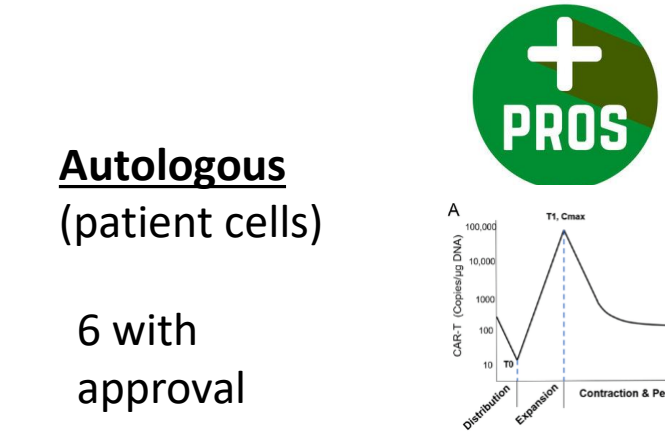
Pros & cons



Autologous CAR-T cells works great, but with important logistic caveats

Autologous
(patient cells)

6 with approval



Great efficacy and exposure

Quality of the original cell

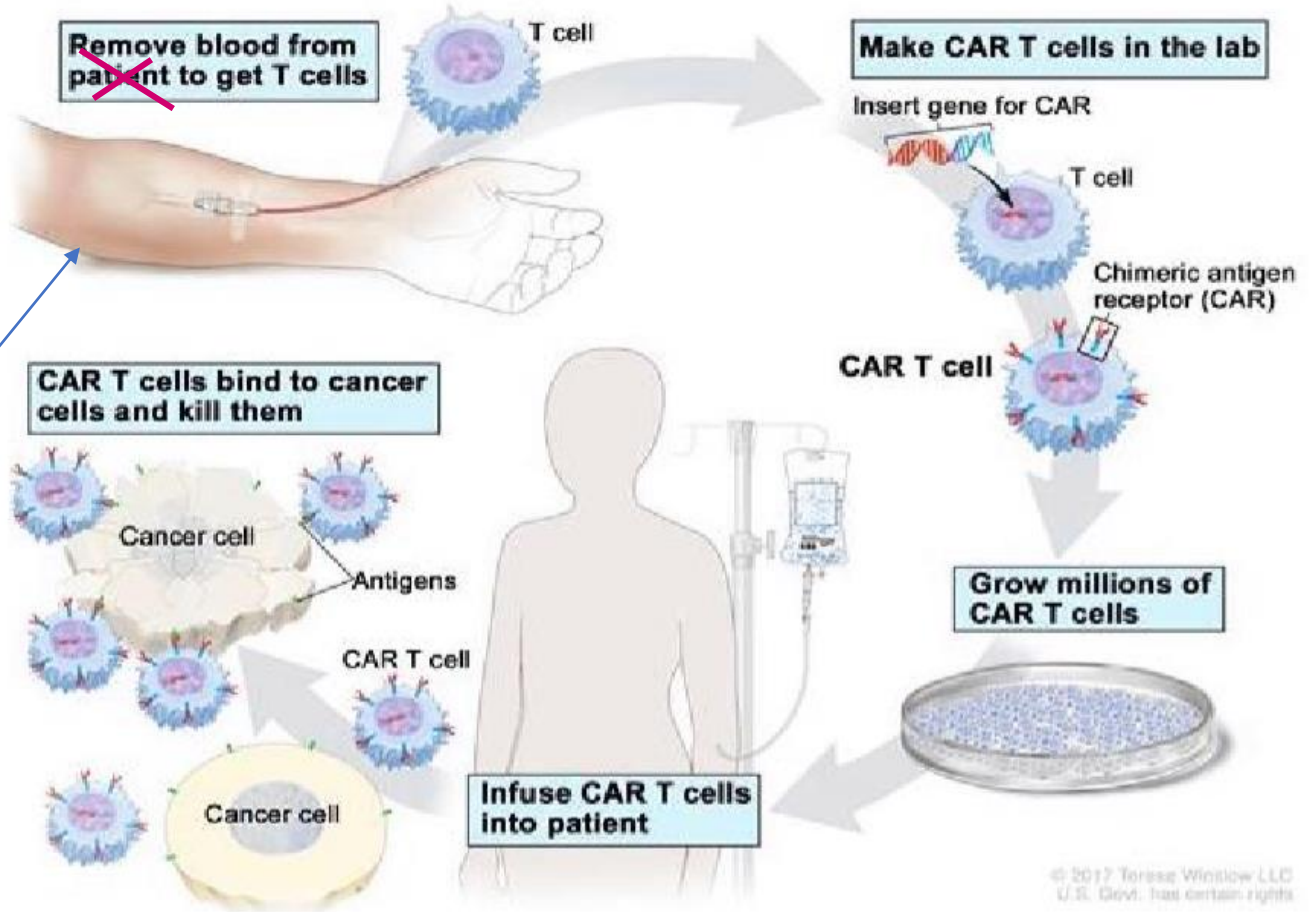
Logistically complex

Very expensive

Original T cells can also come from healthy donors !

<u>Two possible sources for original T cells:</u>

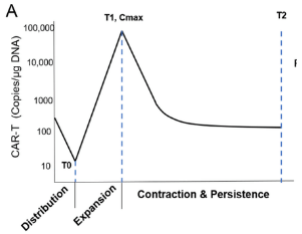
- Directly from the patients (autologous)
- **From a healthy donor (<u>allogeneic</u>)**



Allogeneic CAR-T cells theoretically solves all those issues

Autologous
(patient cells)

6 with approval



Great efficacy and exposure

Quality of the original cell

Logistically complex

Very expensive

Allogeneic
(healthy donor cells)

Healthy cell

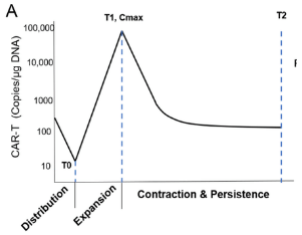
Immediate ‘Off the shelf’ availability

Reduced cost

But none of them on the market so far due to poor expansions

Autologous
(patient cells)

6 with approval



Great efficacy and exposure

Quality of the original cell

Logistically complex

Very expensive

Allogeneic
(healthy donor cells)

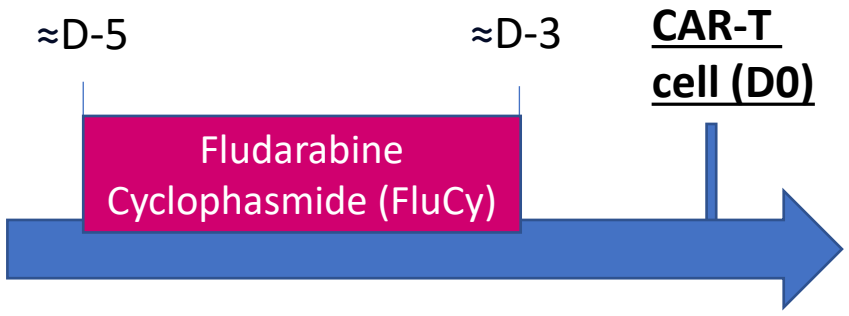
Too low expansion and persistence

Healthy cell

Immediate ‘Off the shelf’ availability

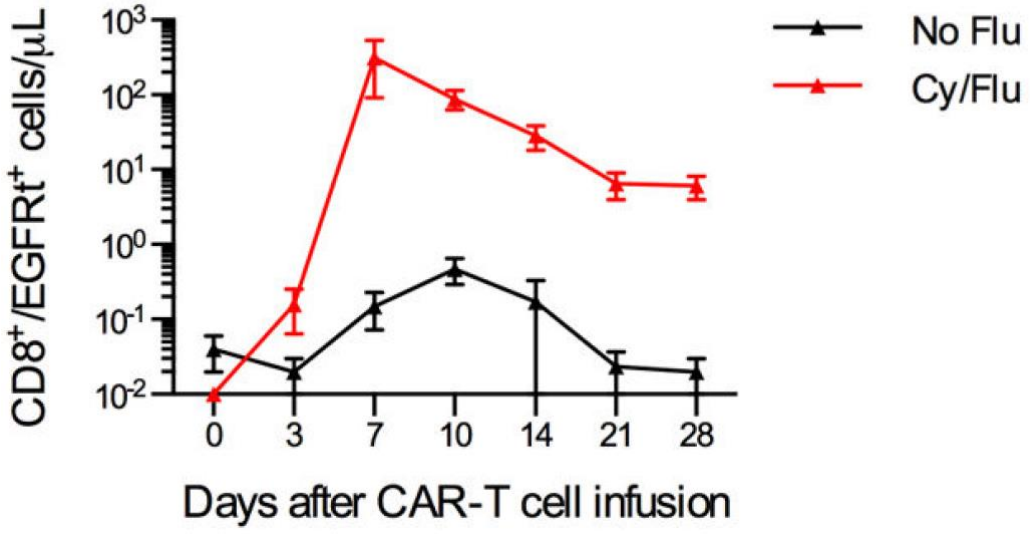
Reduced cost

CAR-T cell therapies require lymphodepletion few days prior the infusion to greatly improve cell expansion and efficacy



Fludarabine: around 30 mg/m2 per day
Cyclophosphamide: around 300-500 mg/m2 per day
(vary slightly for each product)

FluCy used in all 6 approved autologous CAR-T



Turtle et al (2016)

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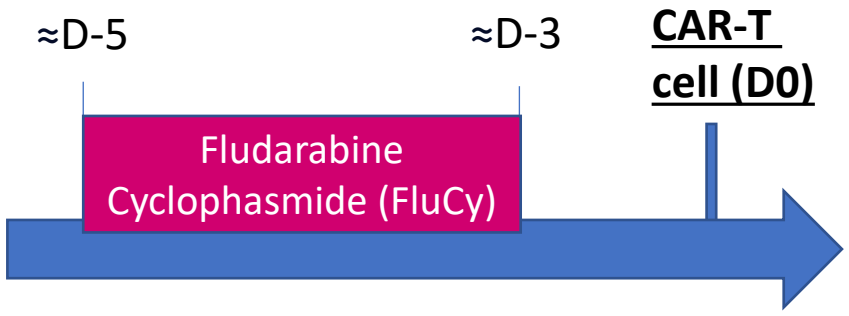

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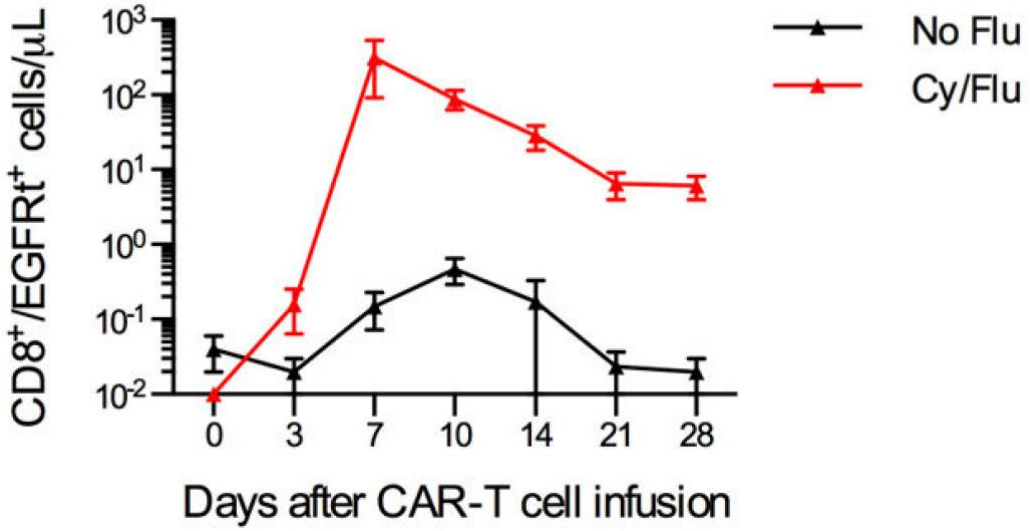


Turtle et al (2016)

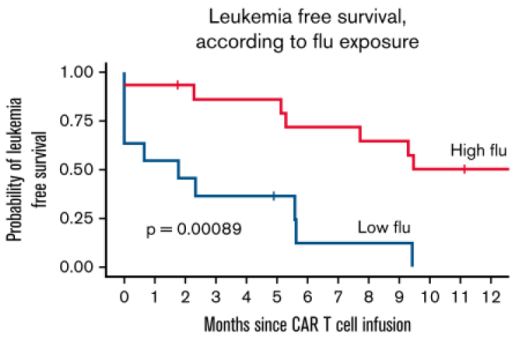
Should we increase this Flucy-based lymphodepletion for <u>allogeneic</u> CAR-T cells?

Different questions regarding LD for autologous and allogeneic CAR-T cells

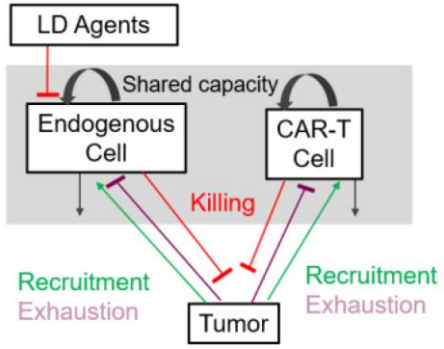
Autologous (using patient's cells)

PROS **Good exposure** (no allorejection) LD **FluCy gold standard**

Main question: individualization of FluCy regimen ?



Dekker et al. (2022)

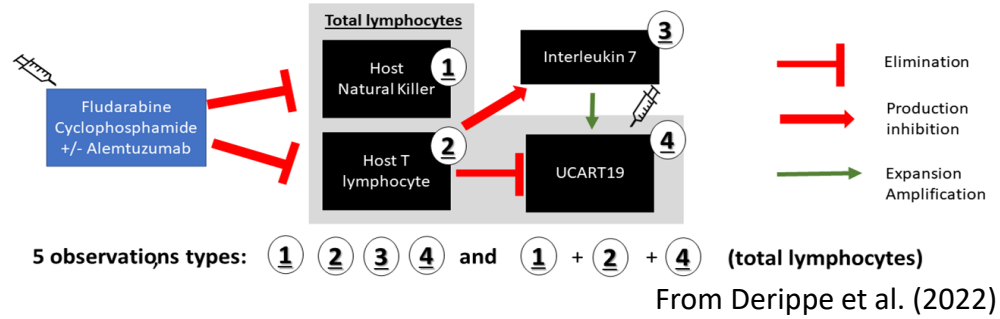


Adapted from Owens et al. (2020)

Allogeneic (healthy donors' cells)

CONS **Poor exposure** (**allorejection**) LD **FluCy not enough? need for a third drug?**

Main question: **What dosing regimen of third drug?**

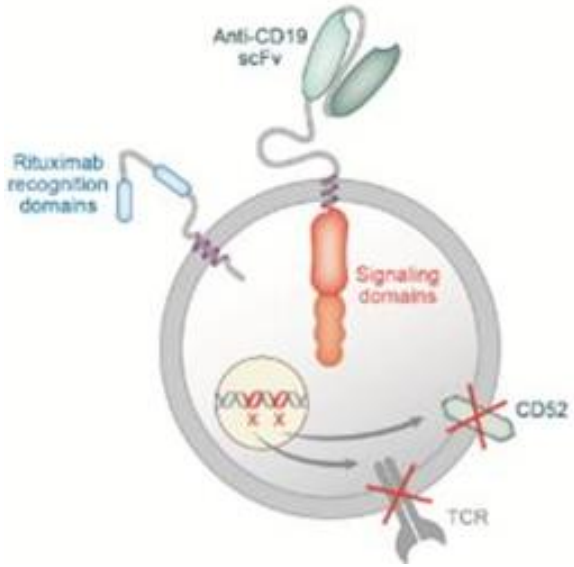


From Derippe et al. (2022)

Case example of UCART19

UCART19 is an allogeneic anti-CD19 CAR-T cells tested on 25 adults with B-cell Acute Lymphoblastic Leukemia (ALL)

UCART19 structure



- Anti CD19 scFv
- TCR knock out
- CD52 knock out

Targets CD19

- CD19 expressed on B lymphocytes
- CD19+ B cell ALL

Tested during phase 1 clinical trial CALM

- 25 adults (+ 3 re-dosing)
- 3 dose levels of CAR-Ts (6, 70, 200 millions)
- Lymphodepletion based on:
  - **FluCy (all patients) +/-**
  - **Alemtuzumab (0, 1mg/kg, 40 or 60mg)** (Anti-CD52**)**

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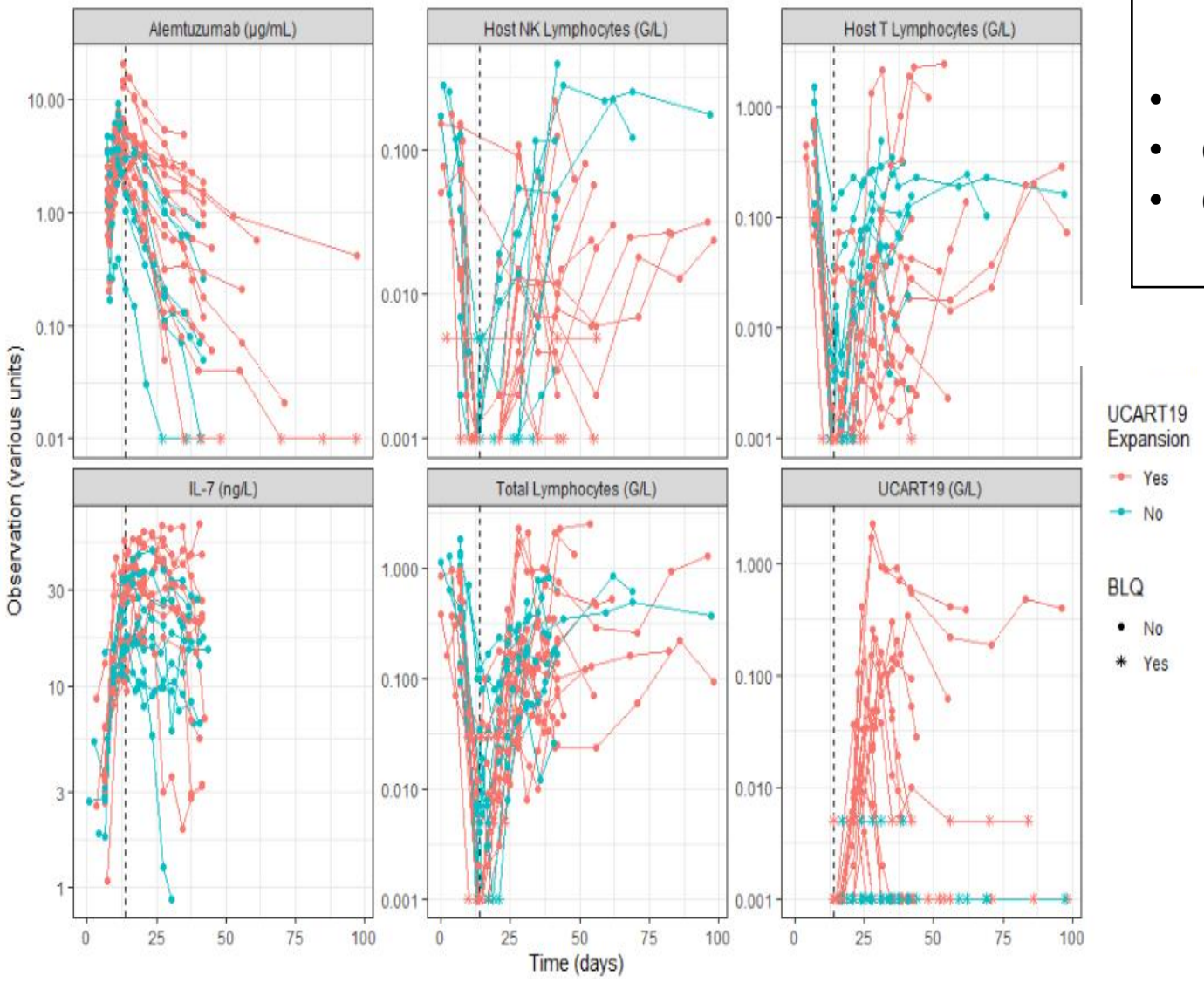
https://www.sec.gov/Archives/edgar/data/1737287/000156459019006991/allo-10k_20181231.htm

UCART19 was administered during CALM phase 1 study in adult ALL



A rich dataset was available:

- UCART19 (qPCR + FC)
- Cytokines (12 different)
- Cell counts (NK, T, B,…)
- Tumor burden
- Patient characteristics
- Alemtuzumab PK

Objective 1: understand UCART19 Clinical Pharmacology properties

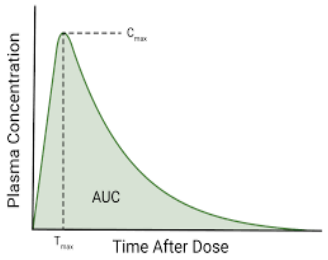
- Understand E-R relationship of UCART19
- Identify best biomarkers for mechanistic insight
- NCA/correlation analyses

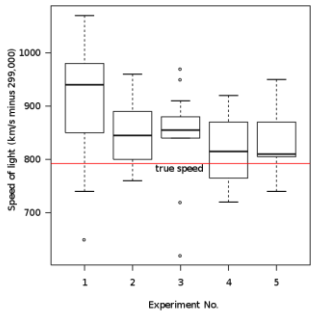
Objective 2: build a translational PKPD model based on new hypothesis

- Use conclusion of Objective 1 to build a mechanistic yet data driven model of UCART19

Data analyses and model development was made with a multidisciplinary team (iterative process)

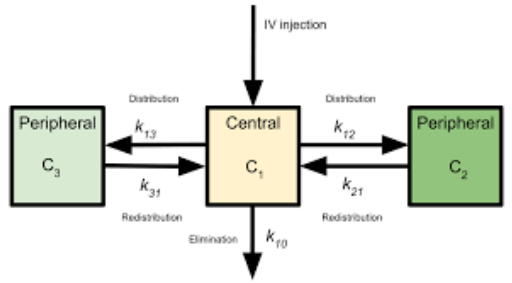
Data exploration,
NCA analysis & correlation





Interpretation & assumptions

Model building, calibration & diagnostic



$$C_t = C_0 e^{-k_e t}$$

$$k_e = \frac{-(\ln C_1 - \ln C_2)}{t_1 - t_2}$$

$$V = D/C_0$$

Multidisciplinary team

"ClinPharm" activities

- Thibaud Derippe
- Sylvain Fouliard

- Sandra Dupouy
- Maria Almena-Carrasco
- Ibtissam Marchiq
- Julia Geronimi
- Yasmina Adimy
- Sylvain Fouliard
- Thibaud Derippe

2 translational scientists

1 immunologist

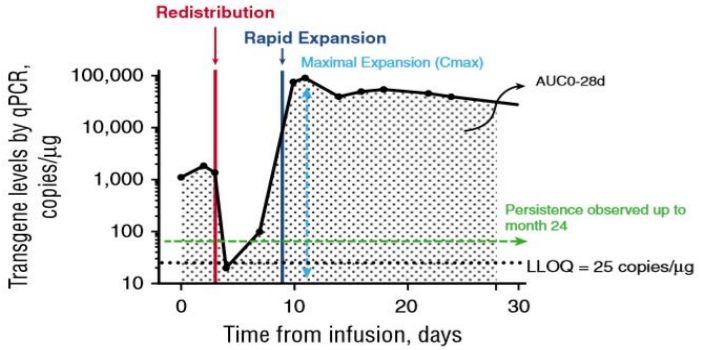
2 Data analysts

2 Pharmacometricians

Modeling activities

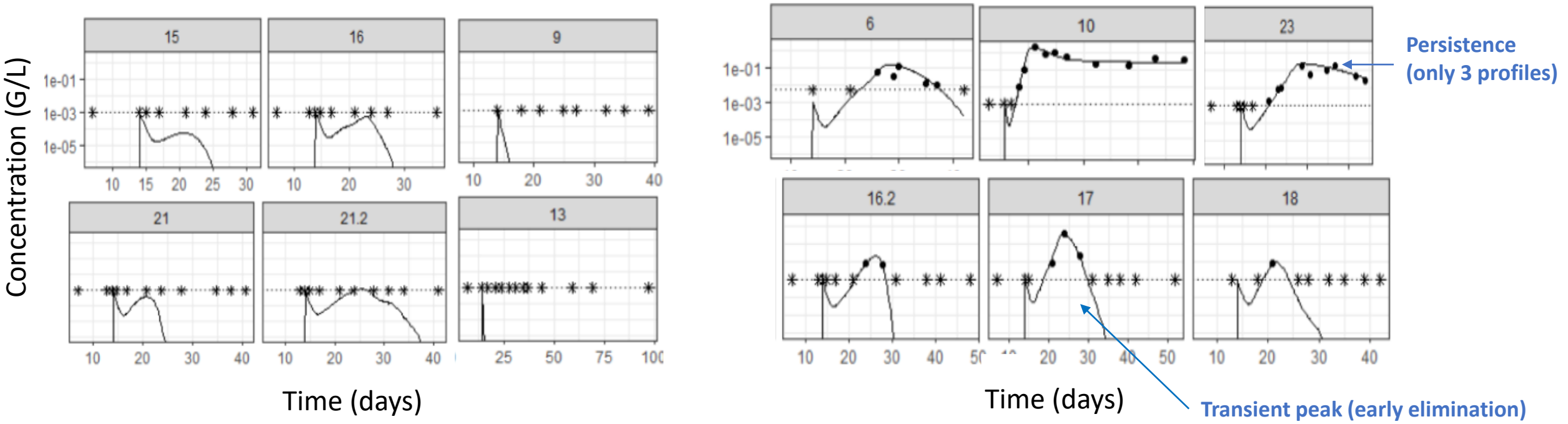
- Thibaud Derippe
- Sylvain Fouliard
- Pr. Donald E. Mager

Expansion was not seen in 46% of patients, and most of the remaining patients had a transient peak without persistence



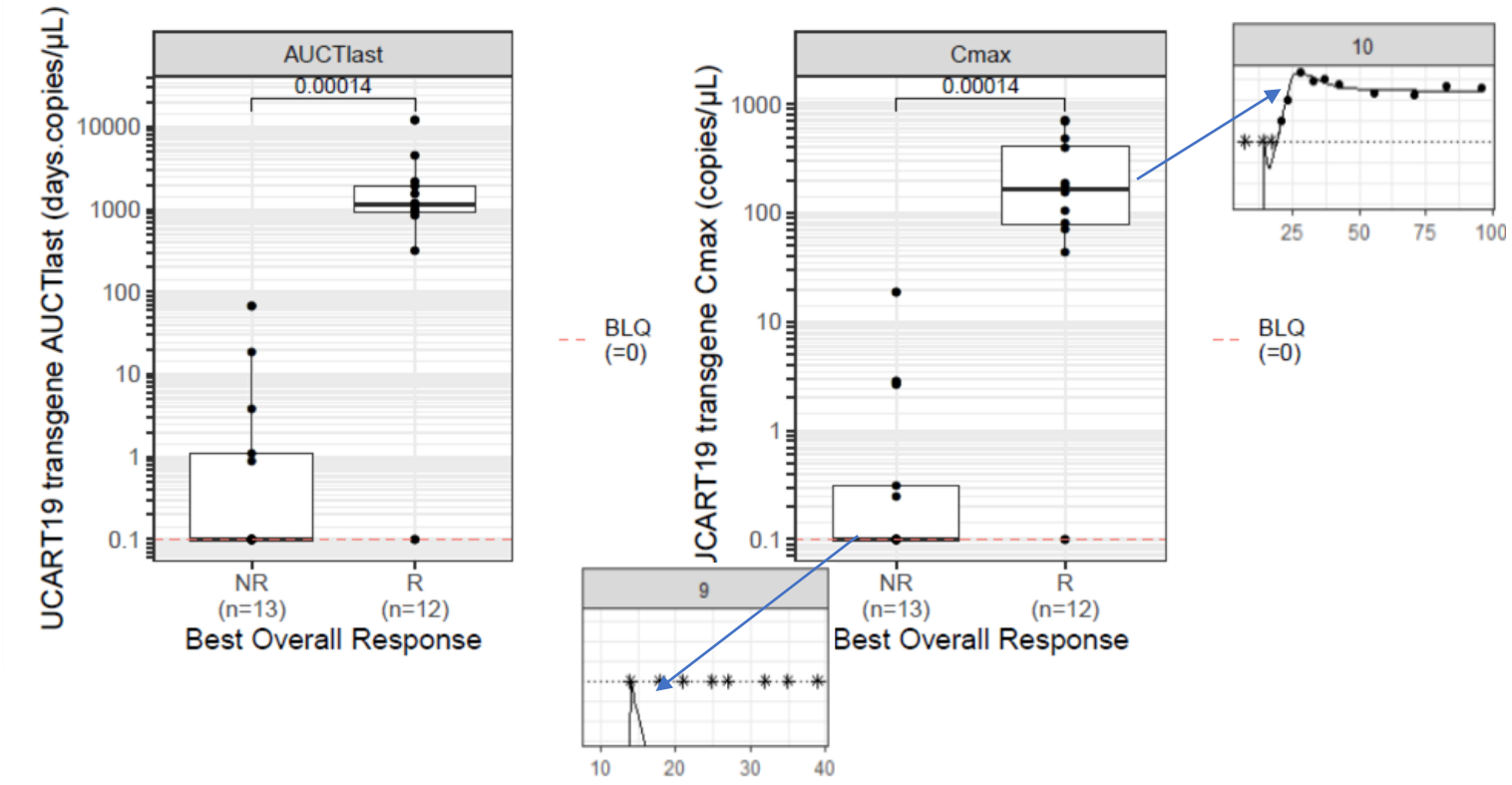
Non expanders (13/28)

Expanders (15/28)



Huge variability of CAR-T cells kinetics, higher than autologous

Best Overall Response was highly correlated to CAR-T exposure



Improving UCART19 efficacy = improving UCART19 PK

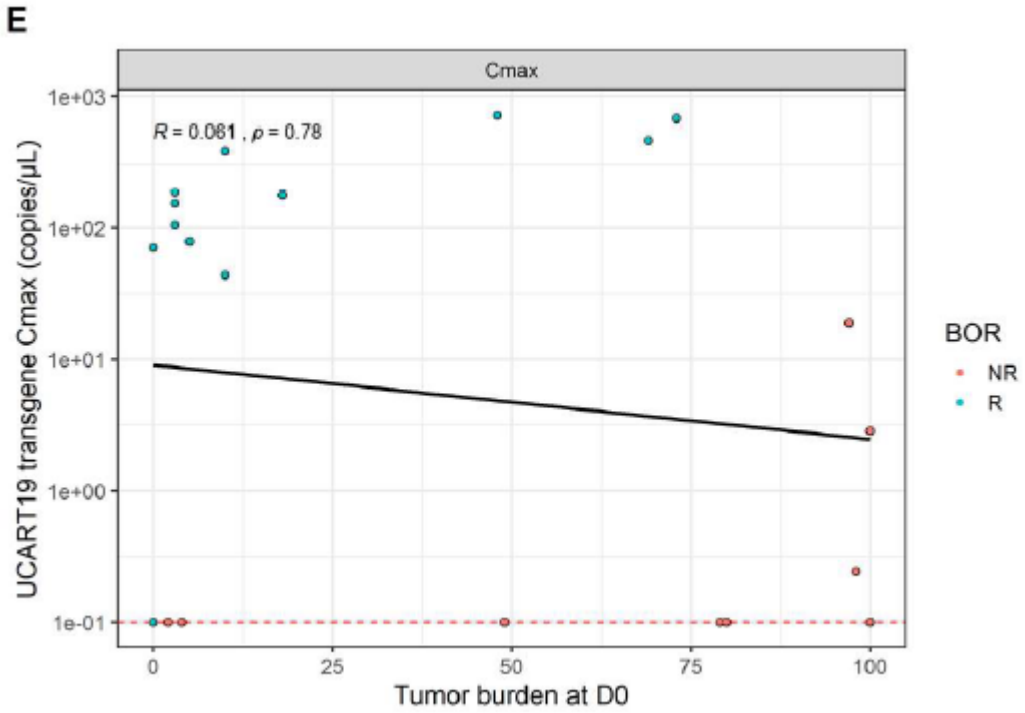
UCART19 PK was not correlated to the dose or tumor burden (variable across CAR-T product)

No correlation with the dose

Dose UCART19	Patient with expansion / N total
DL1 (6 millions)	5/6
DL2 (60-80 m)	6/13
DL3 (180-240 m)	4/9
Total	15/28

Not seen in most CAR-T cell therapies

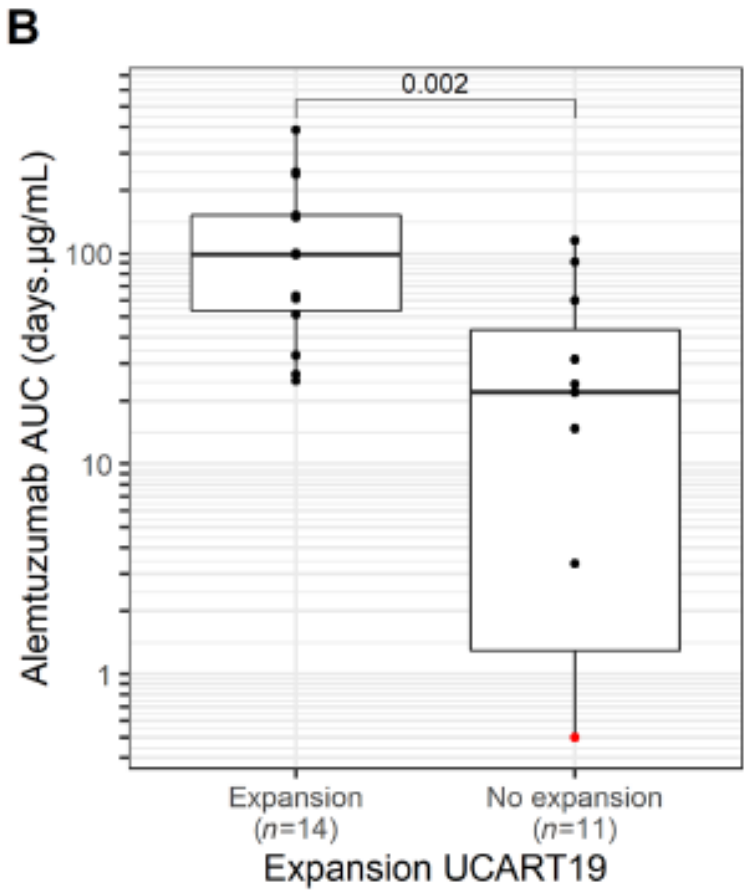
No correlation with the tumor burden

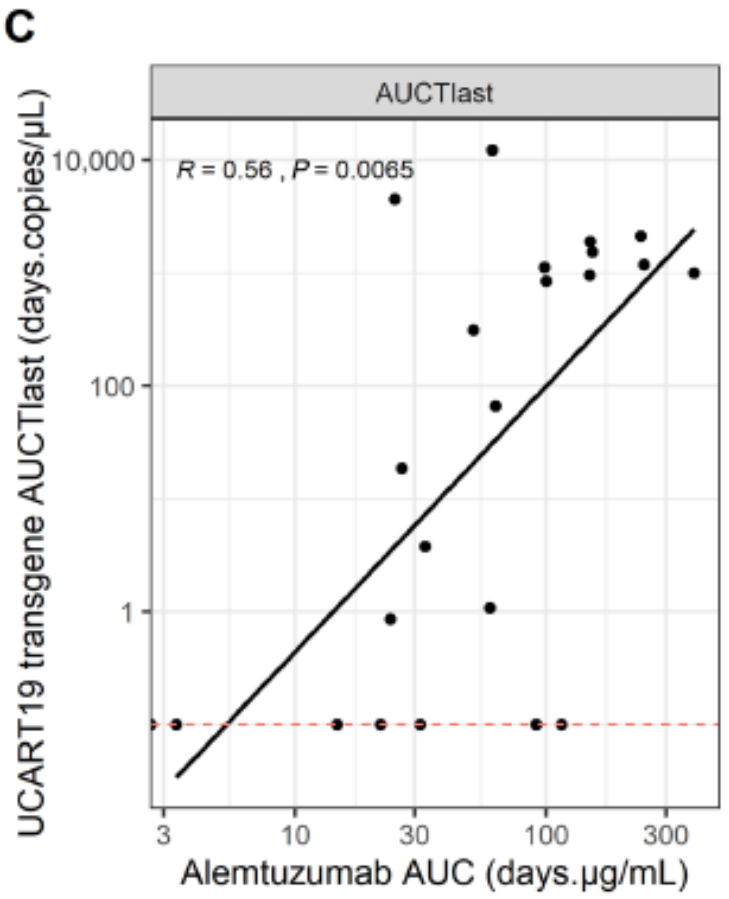


More variable across studies, some see a clear impact, some clear no-impact, some a bell-shape

Clear exposure-response correlation between UCART19 and alemtuzumab

Lymphodepleting regimen	Patients with expansions / N total
FluCy	0/3
FluCy + Alemtuzumab	15/25





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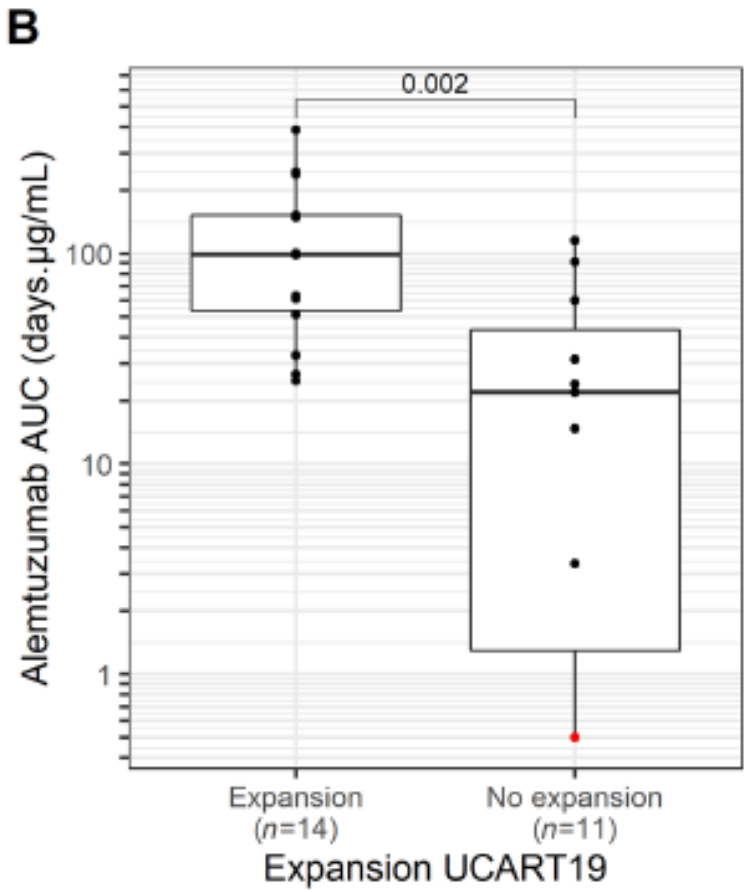
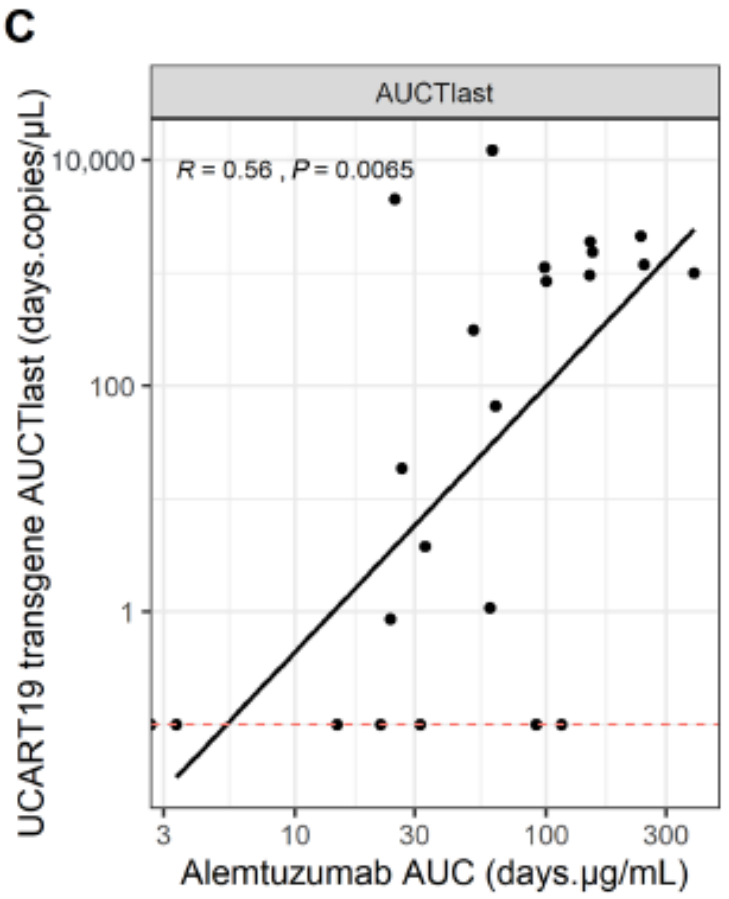


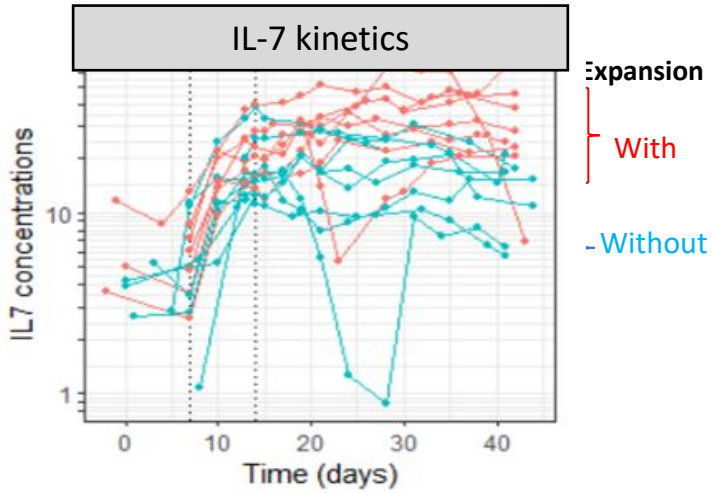


Summary: lymphodepletion much more impactful than CAR-T dose or tumor burden

IL-7 and host T-cells biomarkers were the most correlated biomarkers with both UCART19 and Alemtuzumab exposures

Main results

Interleukin 7 (IL-7)



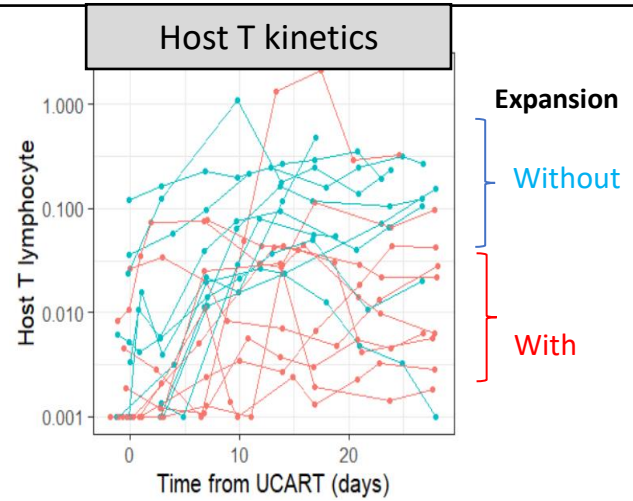
Correlated to

- Alemtuzumab (pos)
- UCART19 (pos)

Rationale

- IL-7 native role is to regulate the survival and growth of T lymphocytes
- Used for CAR-T cells in vitro expansion
- Correlation IL-7 CAR-T cells in clinics find in many studies (autologous or allogeneic)

Host T lymphocytes



Correlated to

- Alemtuzumab (neg)
- UCART19 (neg)

Rationale

- Intuitive host vs. graft (HvG)
- Explains the differences between autologous and allogeneic profile
- Explains the need of alemtuzumab

Summary of clinical pharmacology analyses

- **UCART19 efficacy is highly correlated to the PK**
- **The PK is highly variable, around 46% patient had no expansion**
- **Alemtuzumab highly increases the percentages of expansion**
- **The effect of the alemtuzumab can further explained through:**
  - **A decrease of host T cells that eliminate UCART19**
  - **An increase of IL-7 that increase UCART19 expansion**

From Clinical Pharmacology to Pharmacometrics/modeling

IL-7 and host T-cells biomarkers were the most correlated biomarkers with both UCART19 and Alemtuzumab exposures

Main results

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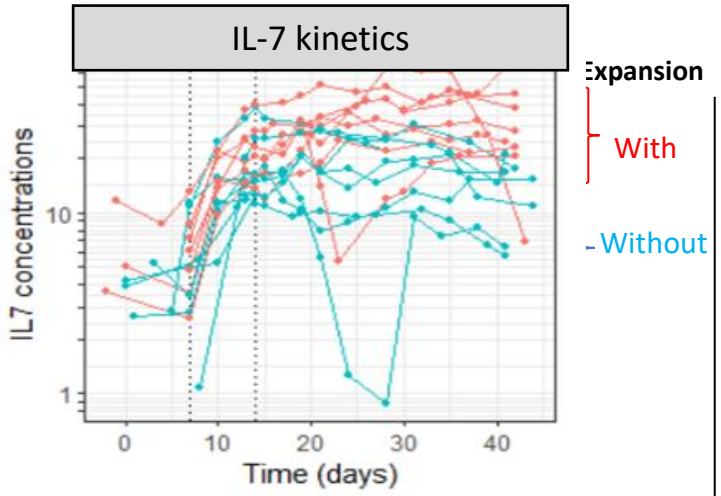

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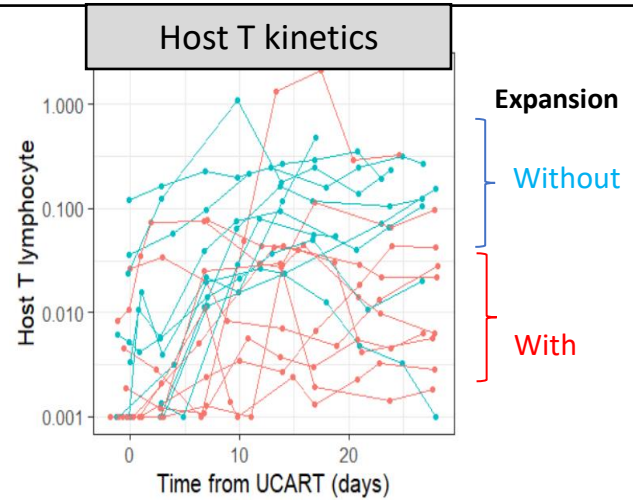

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(Model hypothesis) Lymphodepletion:

- Eliminates host T lymphocytes eliminating UCART19
- Increases IL7 kinetics stimulating UCART19 proliferation

The assumptions were translated into a mechanistic PK/PD model

(Model hypothesis) Lymphodepletion:

- Eliminates host T lymphocytes eliminating UCART19
- Increases IL-7 levels stimulating UCART19 proliferation

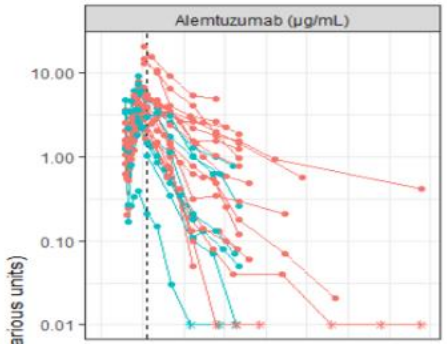
Mathematical translation

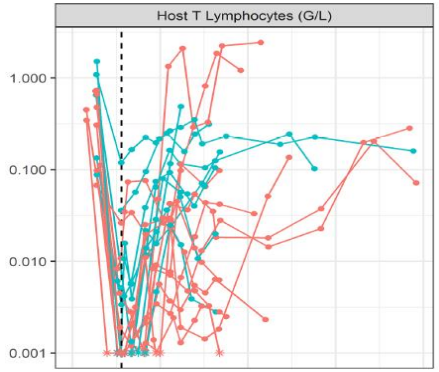
Fludarabine
Cyclophosphamide
+/- Alemtuzumab

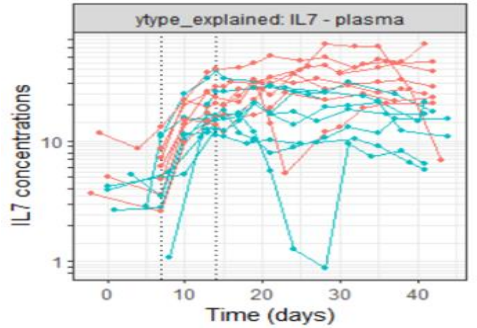
Host
T cells

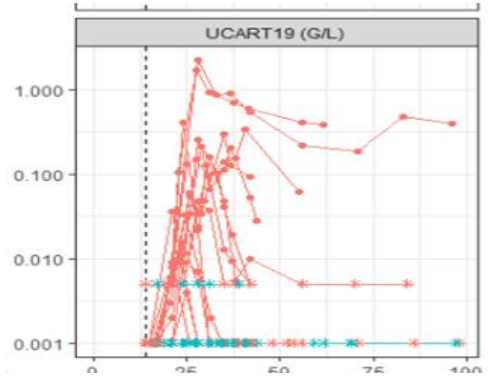
Interleukin 7

UCART19





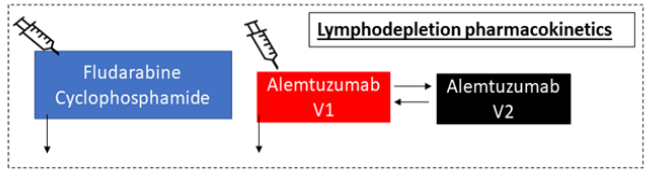


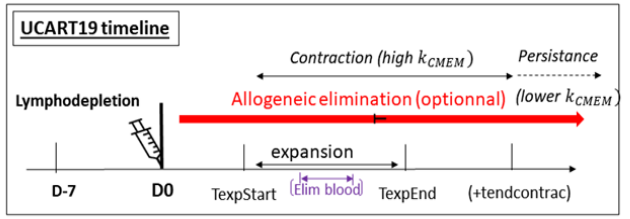


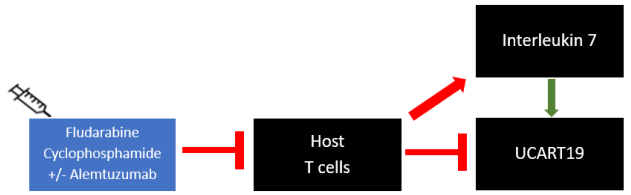
Final model

B

5 observations types: 1 2 3 4 and 1 + 2 + 4 (total lymphocytes)



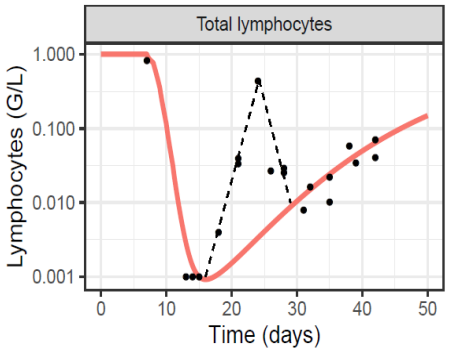


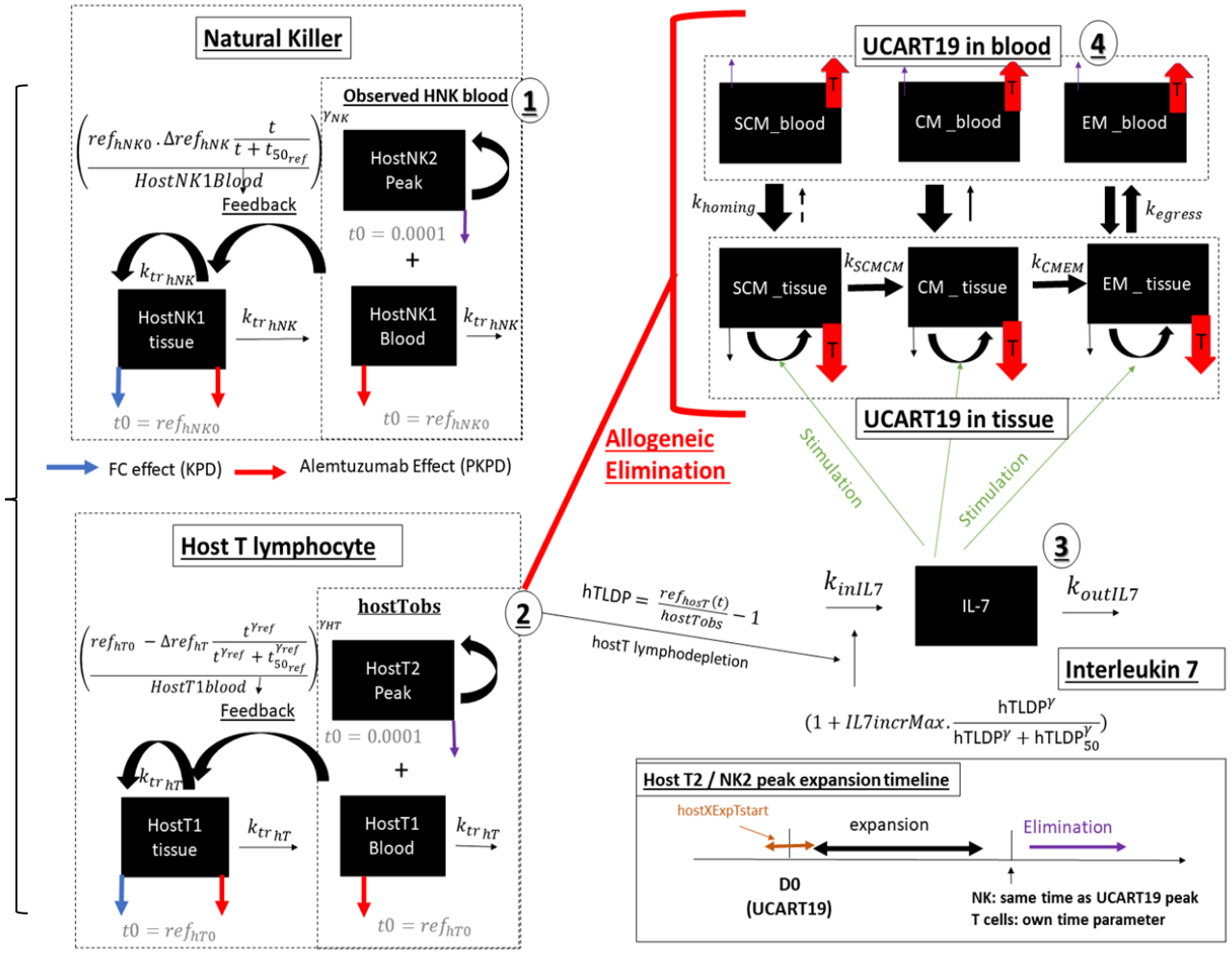


(Simplified model)

host T and NK(*)

- Close to HemTox / Friberg model (feedback system)
- Expansion systems to capture peaks





UCART19

- Distribution blood / tissue
- Progressive differentiation model (from naïve to effector cells)
  - SCM = stem cell memory
  - CM = central memory
  - EM effector memory

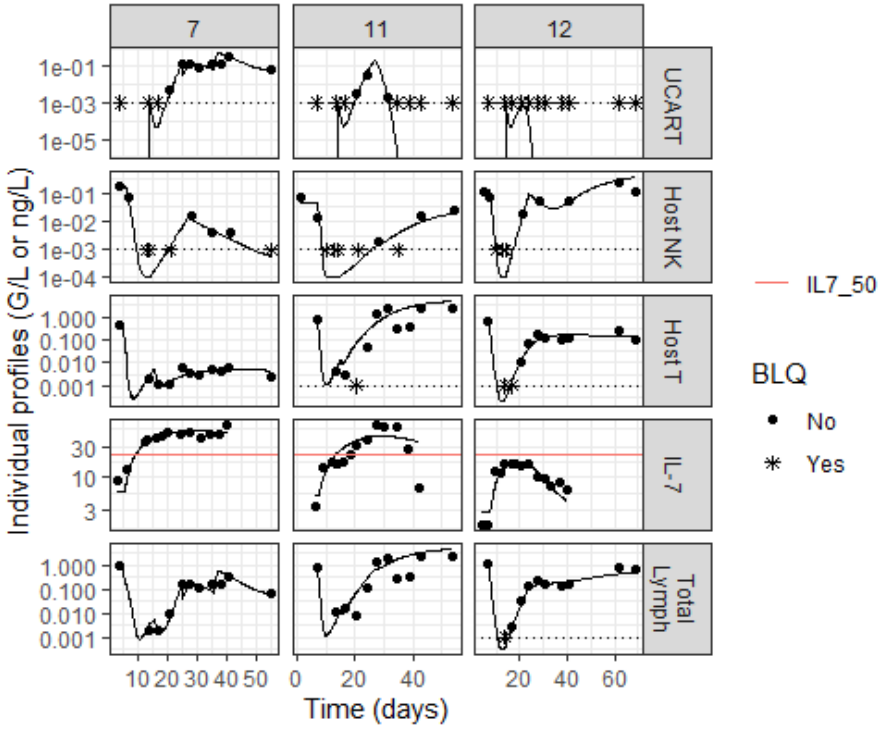
IL-7

Indirect Response Model (stimulation of production)

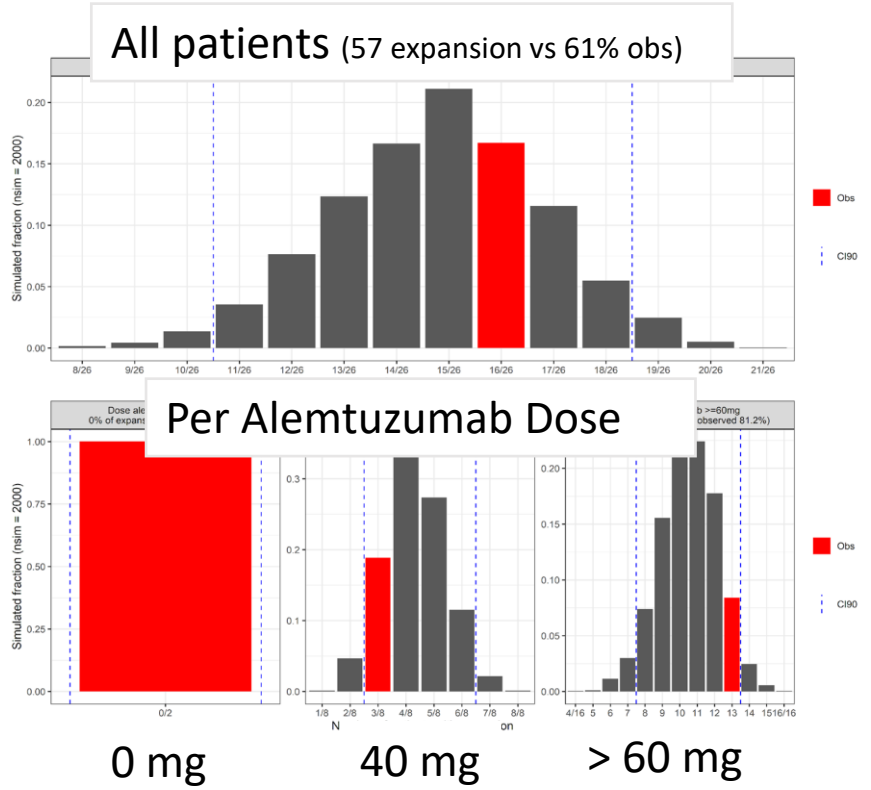
* Because of missing host-T profiles: Natural killer and total lymphocytes (sum NK, host T and CAR-T) data also added

The model was calibrated to capture both individual and population data

Captured well all types of individual profiles

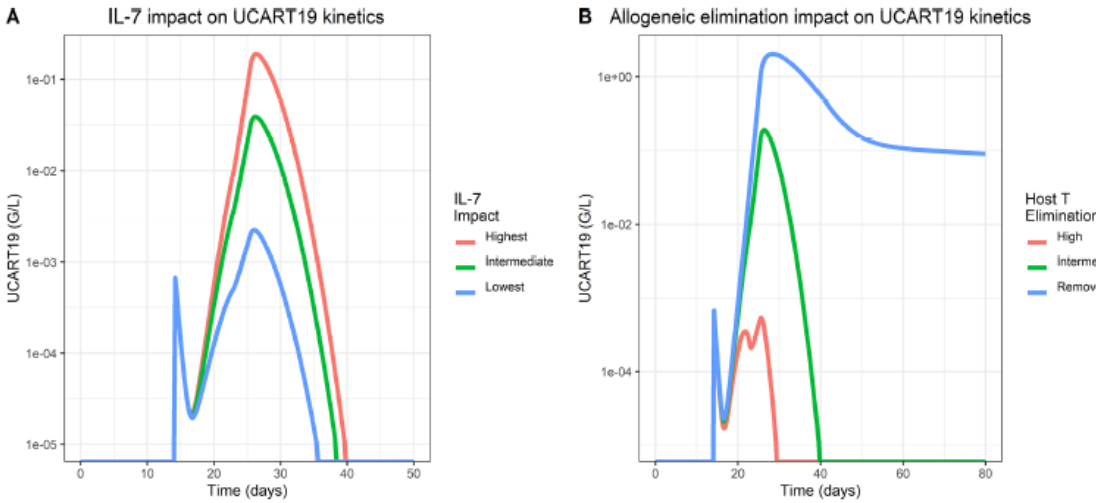


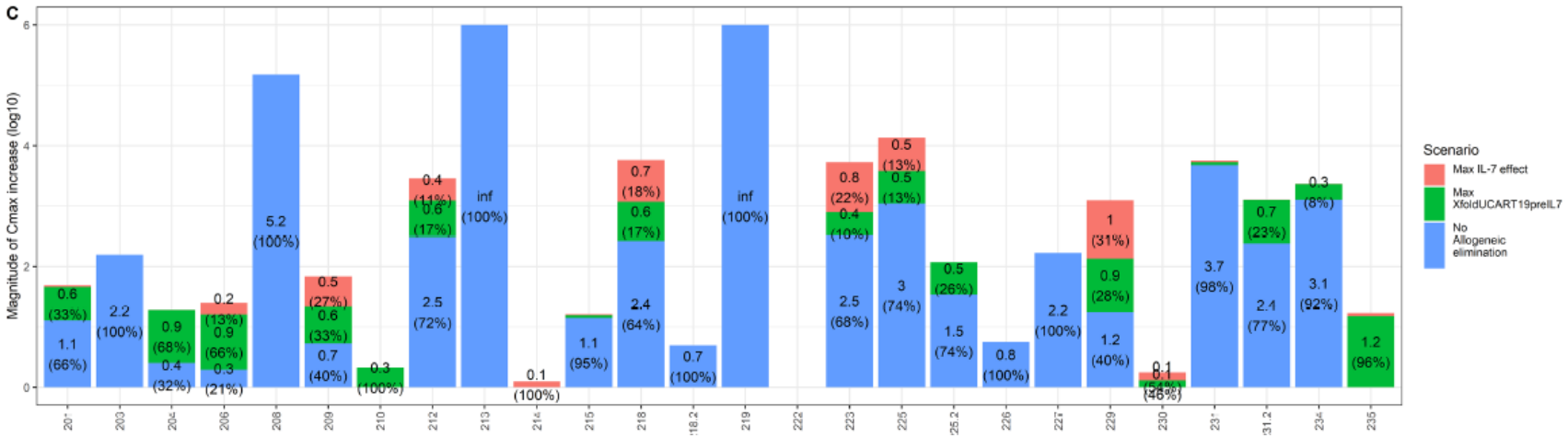
Good population description (number of expansions)



Support the assumptions of the model (IL-7, host T elimination)
Possibility to simulate alternative lymphodepleting regimens

Sensitivity analysis revealed allogeneic elimination has the strongest impact on CAR-T exposure



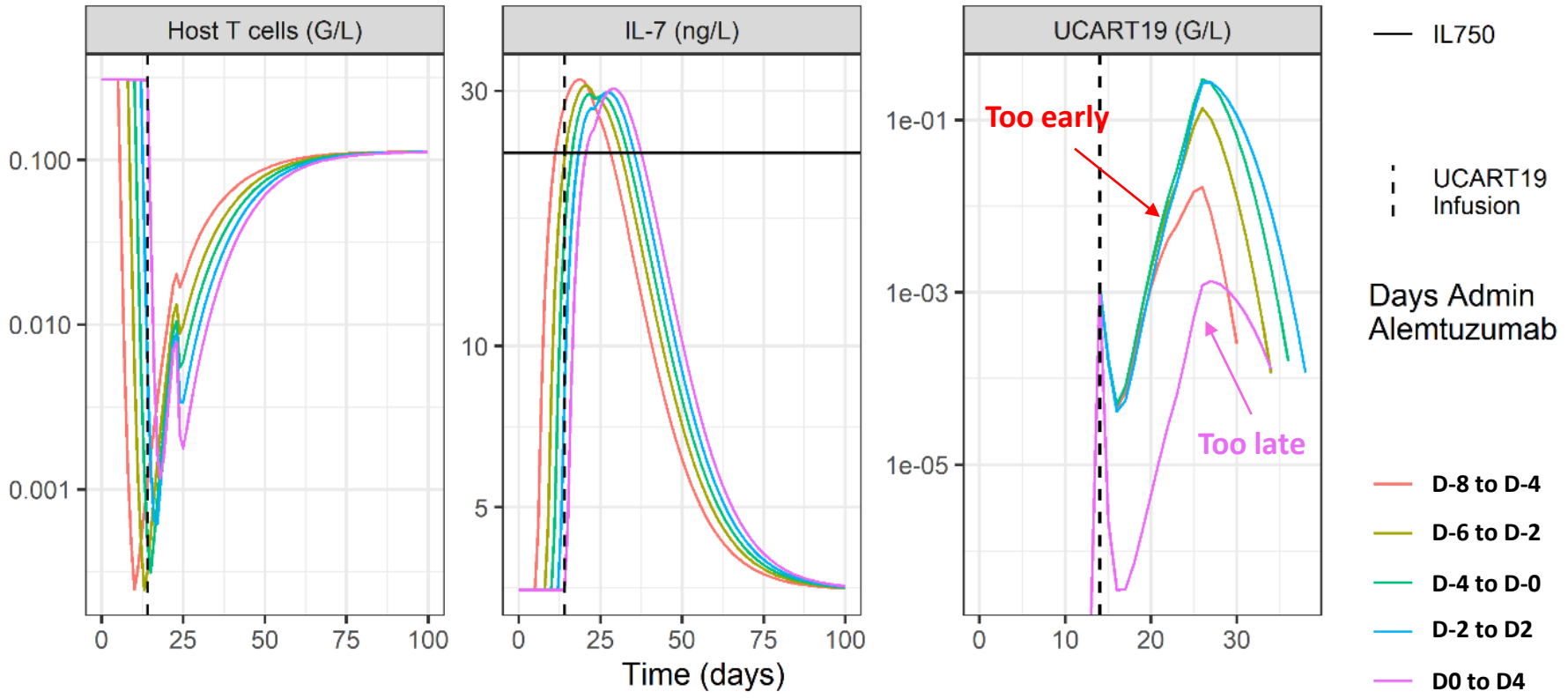


<u>For each patients, compute impact on Cmax</u>:

- without the allogeneic elimination
- with forced maximal IL-7 effect
- with forced maximal intrinsic expansion pre-IL7

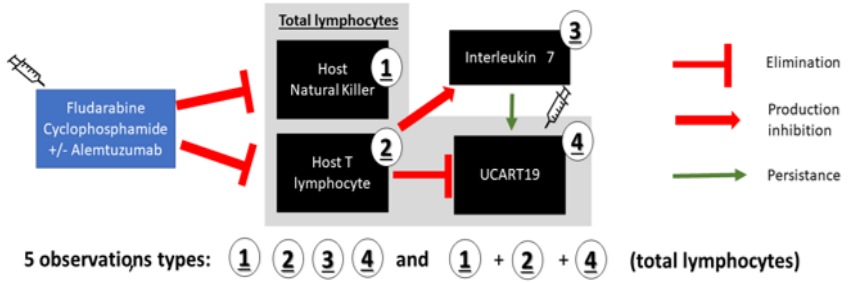
But some identifiability issue between IL-7 and host-T cells due to their intercorrelation

Example of simulations: modifying the time of lymphodepletion highly impacts UCART19 exposure

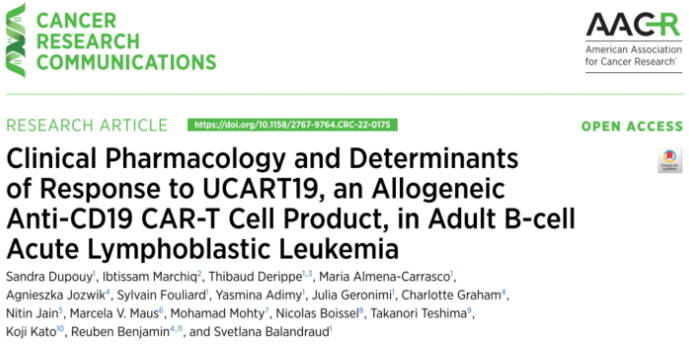


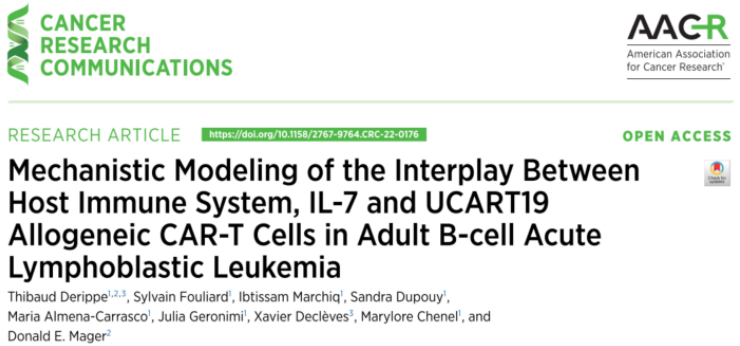
Conclusion

- **Lymphodepletion is mandatory** both in **autologous and allogeneic** CAR-T cell therapies
- **For allogeneic therapy, a third lymphodepleting drug can be critical,** in addition to standard FluCy. This shown with **Alemtuzumab increasing UCART19 cell kinetics**
- **Clinical pharmacology** analyses revealed the mechanism of Alemtuzumab: an **increase of IL-7 and a decrease of host-T cells**
- **A mechanistic PK/PD model for allogeneic UCART19** was built to capture the impact of FluCy + alemtuzumab lymphodepletion regimen on **host-T cell allorejection, IL-7 stimulations and UCART19 PK**



- The model can be used to **simulate optimal alternative pre-conditioning dosing regimen**
- For more information, **two companion papers** were published in Cancer Research Communication (2022)





Acknowledgment

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- All lab mates

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- Yasmina Adimy
- Marylore Chenel

Thank you !!

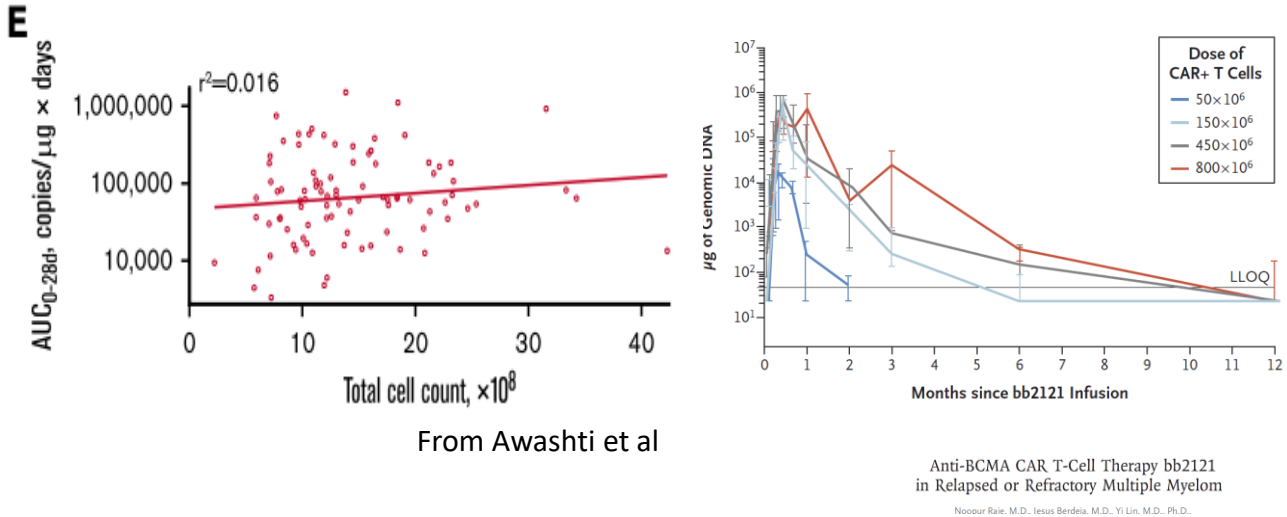
Backup

UCART19 PK was not correlated to the CAR-T dose (as frequently seen in CAR-T cell)

In UCART19

Dose UCART19	Patient with expansion / N total
DL1 (6 millions)	5/6
DL2 (60-80 m)	6/13
DL3 (180-240 m)	4/9
Total	15/28

Autologous CAR-T cells

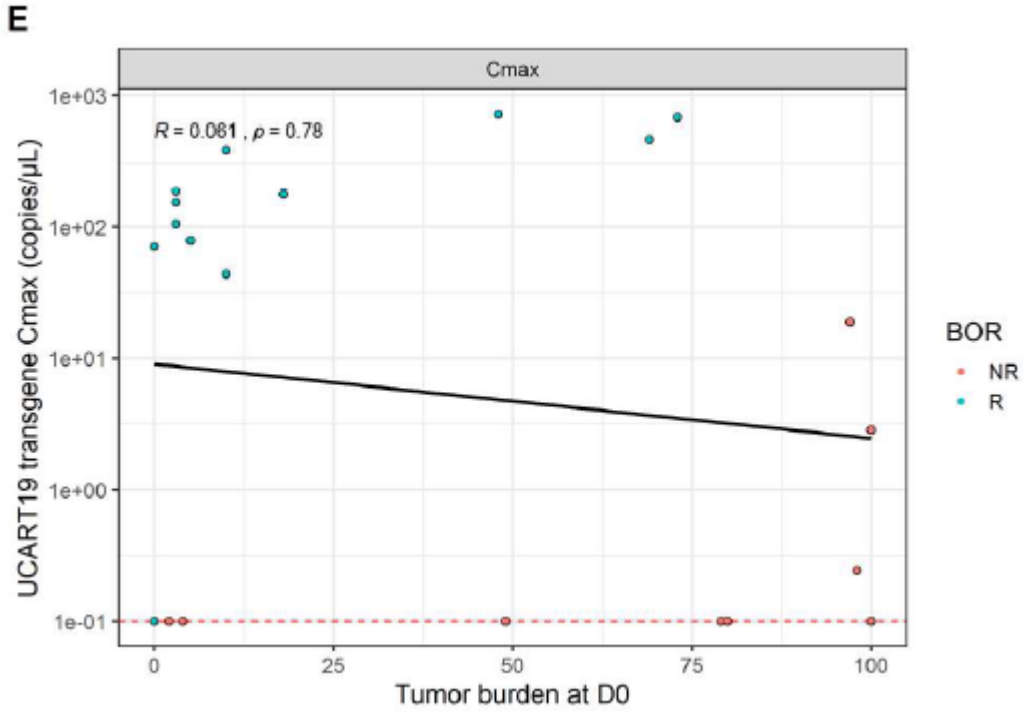


From Awashti et al

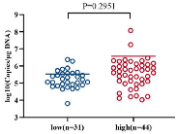
Most CAR-T cells do not show dose-PK relationship, excepted a 'dose threshold' if low DL1

UCART19 PK was not correlated to the tumor burden (variable across CAR-T product)

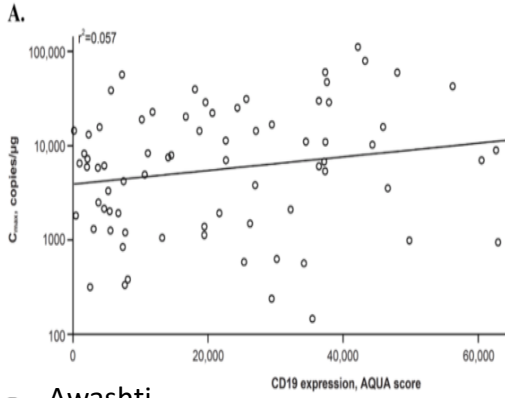
In UCART19



Other CAR-T cells = variable

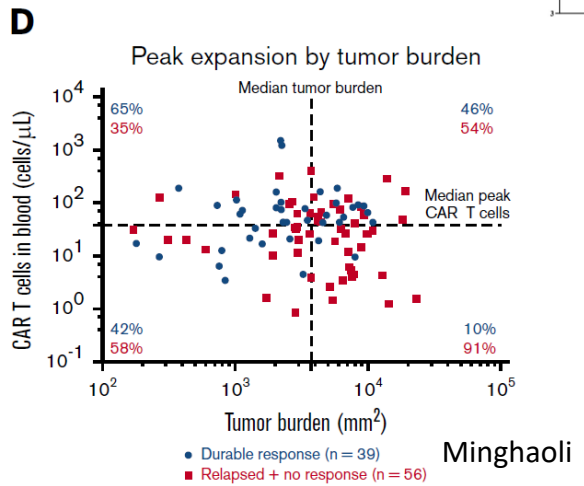


Also no correlation



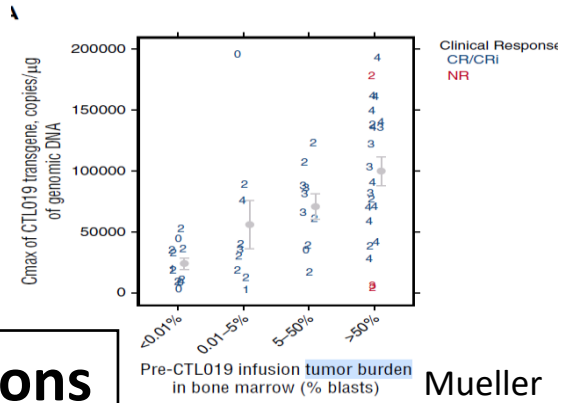
Awashti

Locke

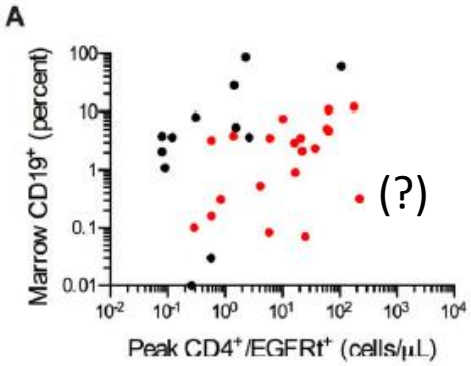


Minghaoli

Correlation



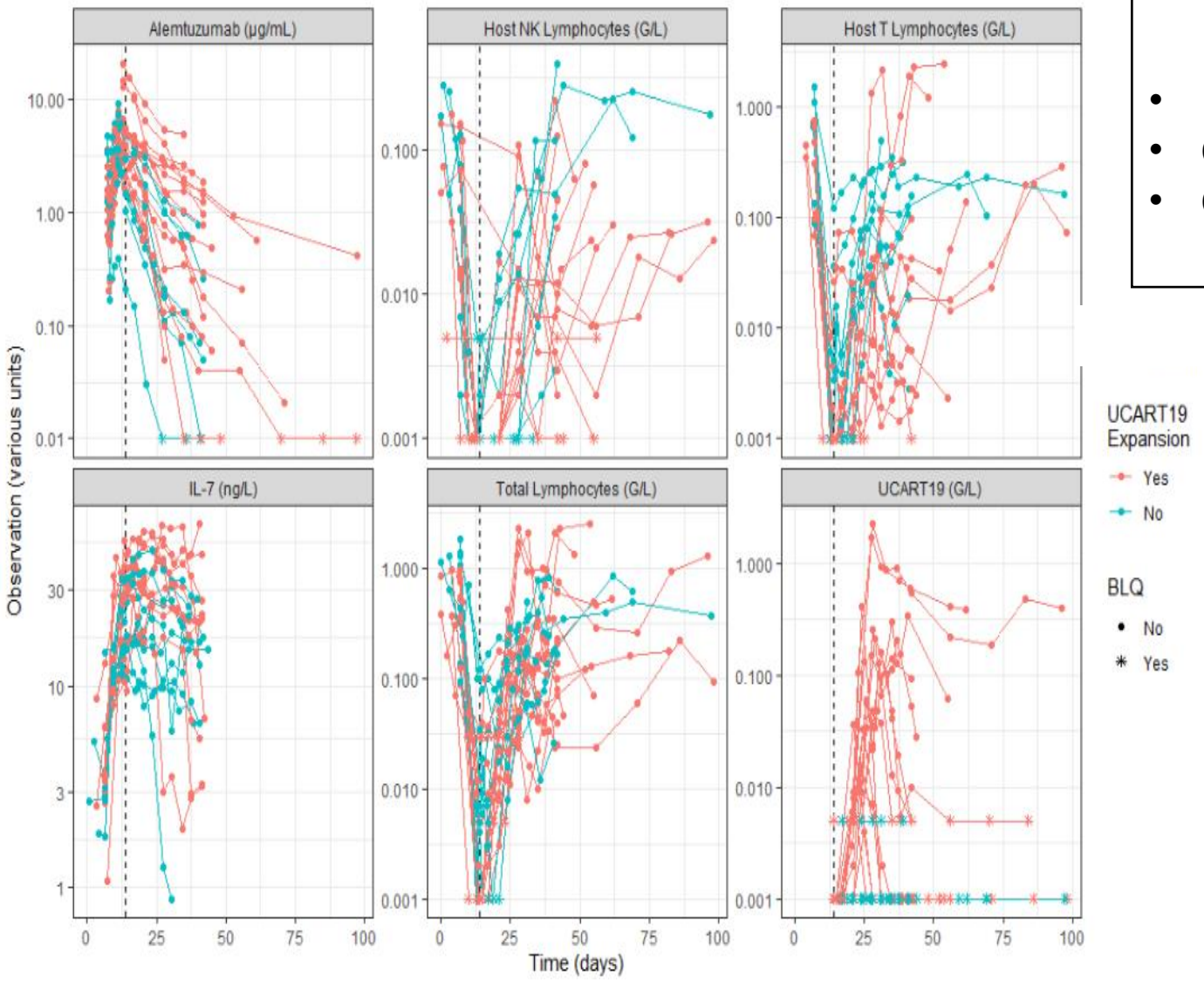
Mueller



Turtle

Unclear and complex tumor CAR-T cell interactions

To further explain the role of alemtuzumb/lymphodepletion…



<u>A rich dataset was available</u>:

- UCART19 (qPCR + FC)
- **Cytokines (12 differents)**
- **Cell counts (NK, T, B,…)**
- Tumor burden
- **Patient characteristics**
- Alemtuzumab PK
- **CAR-T subpopulation**

<u>Correlation of every possible biomarkers</u> with:

- Alemtuzumab exposure
- UCART19 exposure

To **further explain the mechanism of the lymphodepletion in UCART19 cell expansion**