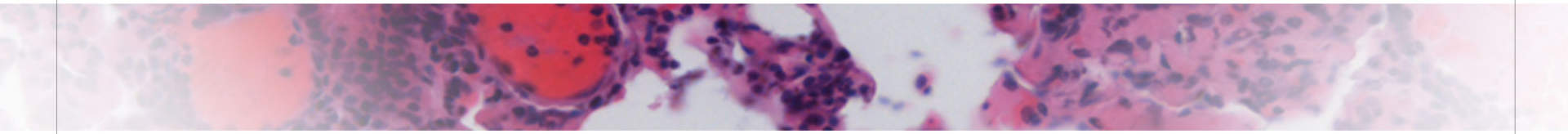
American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



Preliminary results of **UCART19**, an **allogeneic anti-CD19 CAR T-cell product**, in a first-in-human trial (CALM) in adult patients with CD19+ relapsed/refractory B-cell acute lymphoblastic leukemia

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King's College Hospital NHS Foundation Trust

SERVIER Oncology

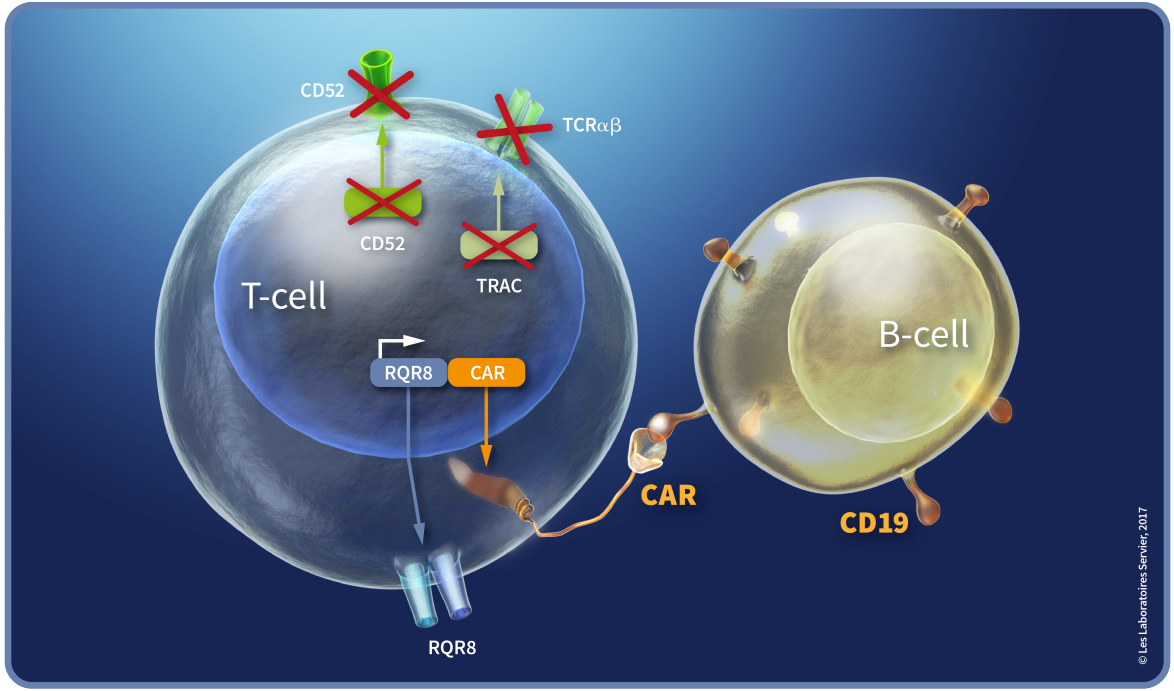
Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

Adult B-acute lymphoblastic leukemia (B-ALL)

- B-ALL is incurable in ~60% of adult patients
- At relapse, prognosis is very poor (<10% overall survival)
- Standard therapy involves combination chemotherapy ± allogeneic SCT
- Emerging treatments include BiTEs, monoclonal antibodies and CAR T-cell therapies

UCART19 (CD19CAR/RQR8+_TCRαβ-_T-cells)

Allogeneic, universal, adoptive T-cell therapy targeting CD19+ malignancies



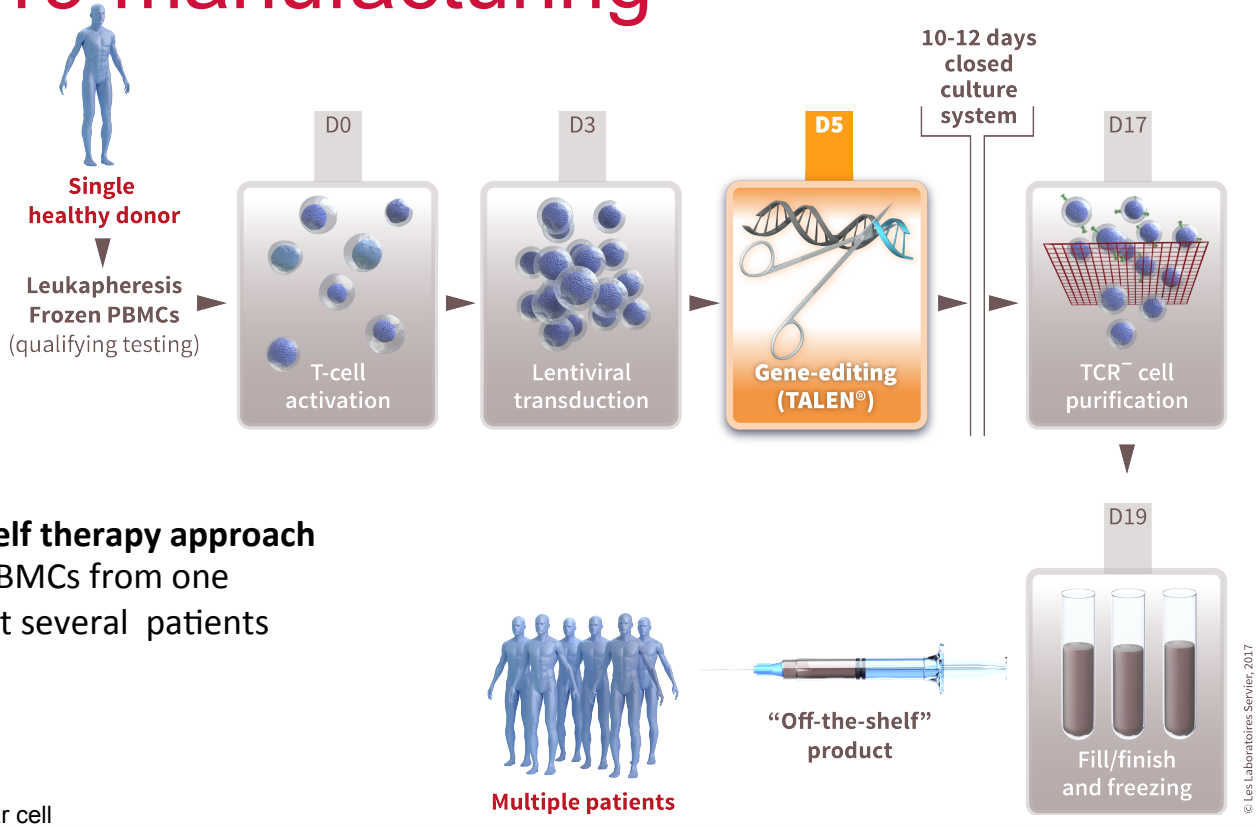
Transgene expression using lentiviral transduction

- **CAR**: anti-CD19 scFv and CD3ζ + 4-1BB
- **RQR8** (= CD20 mimotope): safety switch

Gene knock-out using TALEN® technology

- **TRAC KO**: to prevent TCR mediated recognition of patient's HLA antigens
- **CD52 KO**: to permit alemtuzumab use in lymphodepletion

UCART19 manufacturing

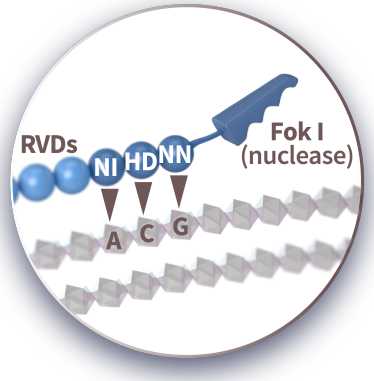


Ready-to-use, off-the-shelf therapy approach

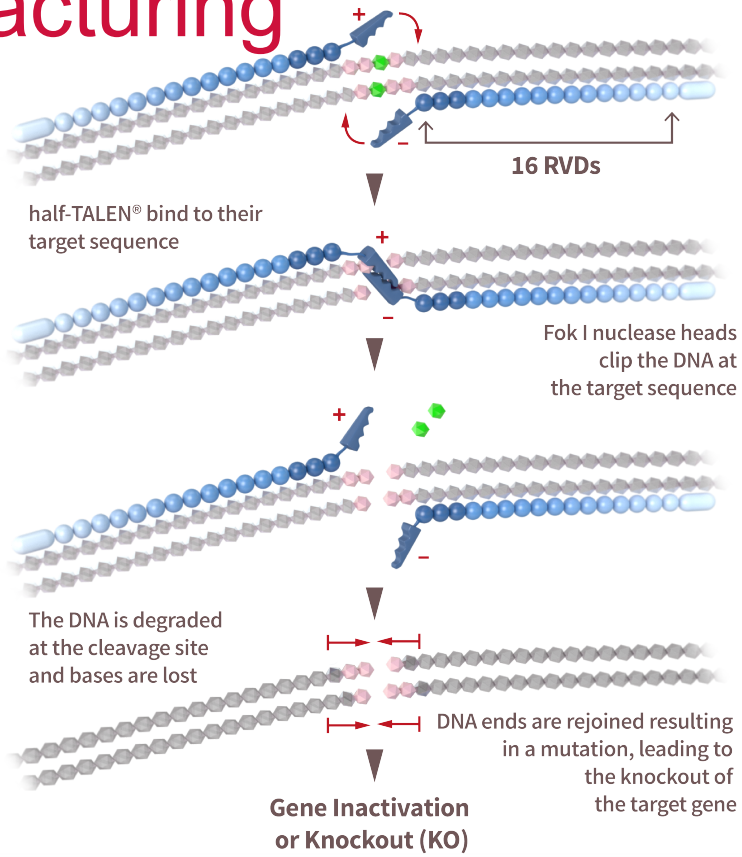
- Advantage of using PBMCs from one healthy donor to treat several patients

PBMC = peripheral blood mononuclear cell

UCART19 manufacturing



A custom TALEN® is created to target the precise gene sequence



TALEN® is a proprietary technology owned by cellectis

TALEN® = transcription activator-like effector nuclease

CALM main study objectives

Primary objectives

- Evaluation of safety and tolerability of UCART19 at different doses
- Determination of the maximum tolerated dose (MTD)

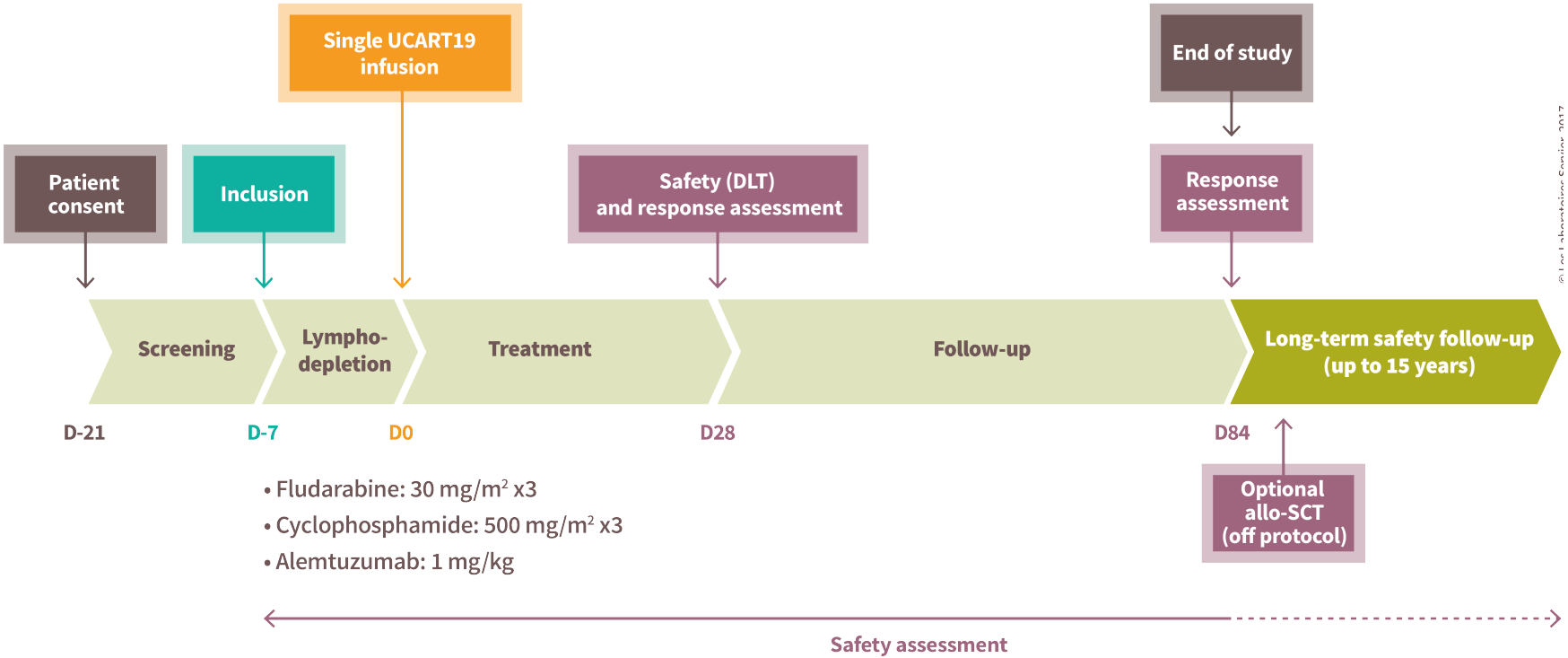
Secondary objective

- Assessment of anti-leukemic activity

Exploratory objective

- Expansion and persistence of UCART19

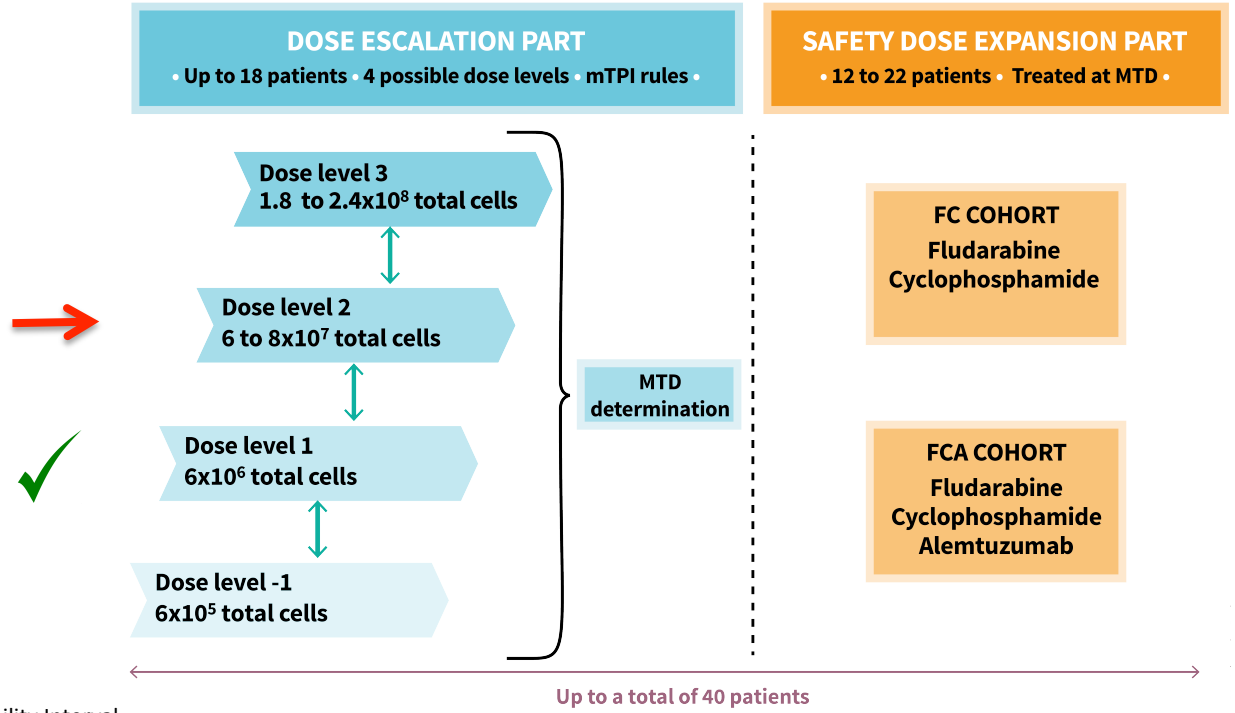
CALM study plan



DLT = dose-limiting toxicities SCT = stem cell transplant

CALM design

Phase I, open-label, non-comparative, dose-escalation study



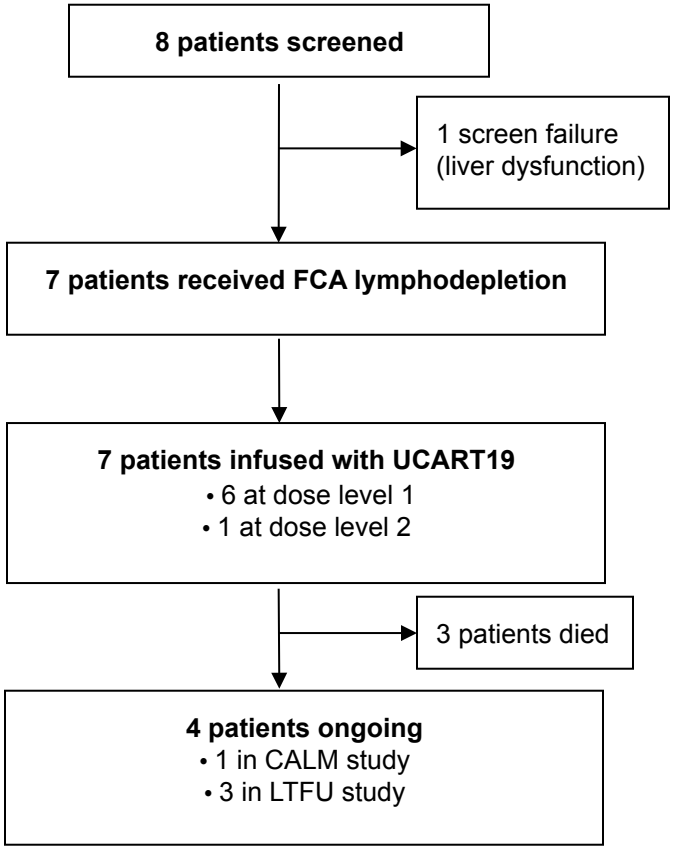
mTPI = modified Toxicity Probability Interval

Key eligibility criteria

- Age ≥16 years old
- Patient with $CD19^+$ R/R B-ALL
  - Morphological or MRD^+ (≥ $1x10^{-3}$ by flow cytometry and/or qPCR)
  - Who have exhausted available treatment options
- No previous treatment with investigational gene or cell therapy products
- No clinically suspected extra-medullary involvement
- Adequate renal, hepatic, pulmonary and cardiac function
- No active infection
- No active CNS leukemia

MRD = minimal residual disease

CALM study status



CALM population

high-risk, heavily pretreated

Characteristic	N =7
Median age (range) - years	23 (18-49)
Disease at screening	
B-ALL relapsed/refractory	7
Number of prior treatment lines	
1 to 3	3
≥ 4	4
Previous allogeneic stem cell transplantation (SCT)	6
Time to relapse following previous SCT	
< 6 months	3
≥ 6 months	3
Median (range)	7.8 months (4.1-11)
Disease burden at inclusion (% of bone marrow blasts)	
< 5	3
5 to 25	2
> 25	2
Median (range)	8 % (0-90)

Main toxicities post-UCART19 infusion

N=7	Worst grade G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	All grade n (%)
Cytokine release syndrome	1 (14)	5 (71)	-	1 (14)	-	7 (100)
Neurotoxic events	2 (29)	-	-	-	-	2 (29)
Neutropenic sepsis	-	-	-	1(14)	1(14)	2 (29)
CMV infection	-	3 (43)	-	-	-	3 (43)
Adenovirus infection	2 (29)	-	-	-	-	2 (29)
Graft-versus-host disease*	1 (14)	-	-	-	-	1 (14)
Prolonged cytopenia	-	-	-	2 (29)	-	2 (29)

* Acute cutaneous GvHD n: number of patients with at least one event by worst grade

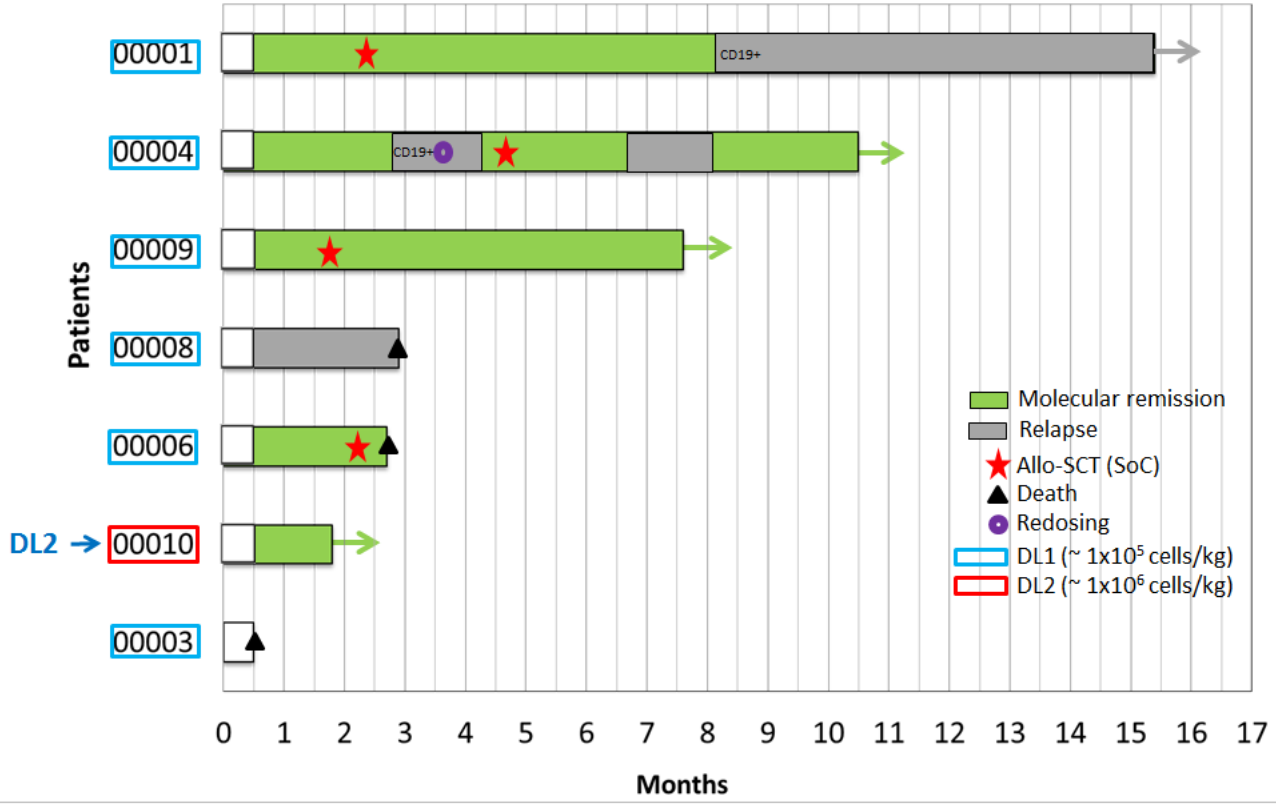
1 DLT: death at D15 from Grade 5 neutropenic sepsis following Grade 4 CRS at D7 (dose level 1)

Cytokine release syndrome (CRS)

	N= 7
Time to onset (median and range in days)	8 (5-12)
Duration (median and range in days)	5 (2-9)
Cytokine elevation (IL-6, IFN-γ, IL-10)	7*
Specific treatment	**4/7**
Tocilizumab	4/4
Corticosteroids	2/4
Vasopressors	1/4
Outcome – Number making full recovery	6

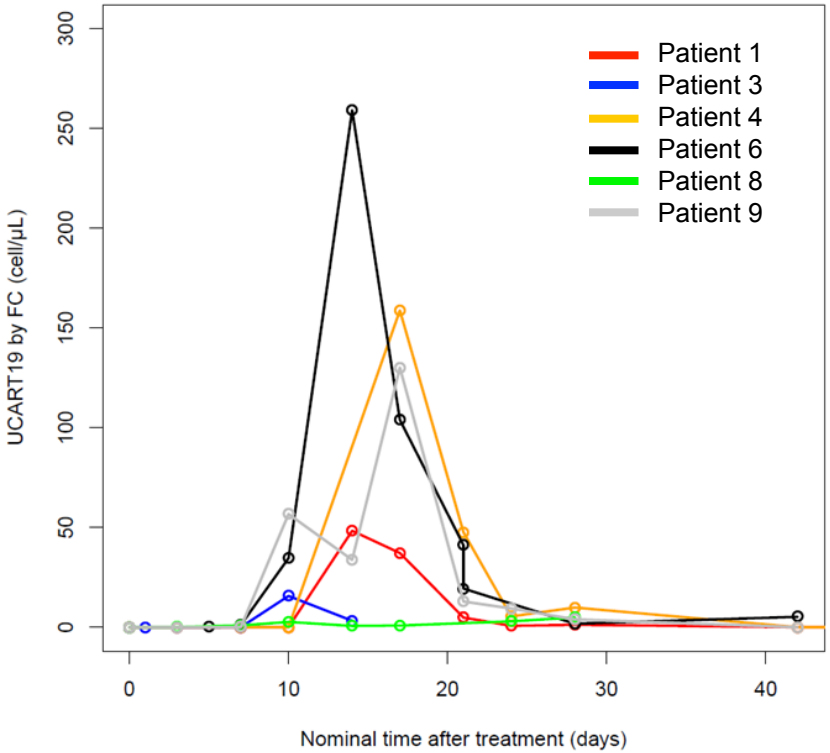
*Fold increase from D0 between 1.4 and 403

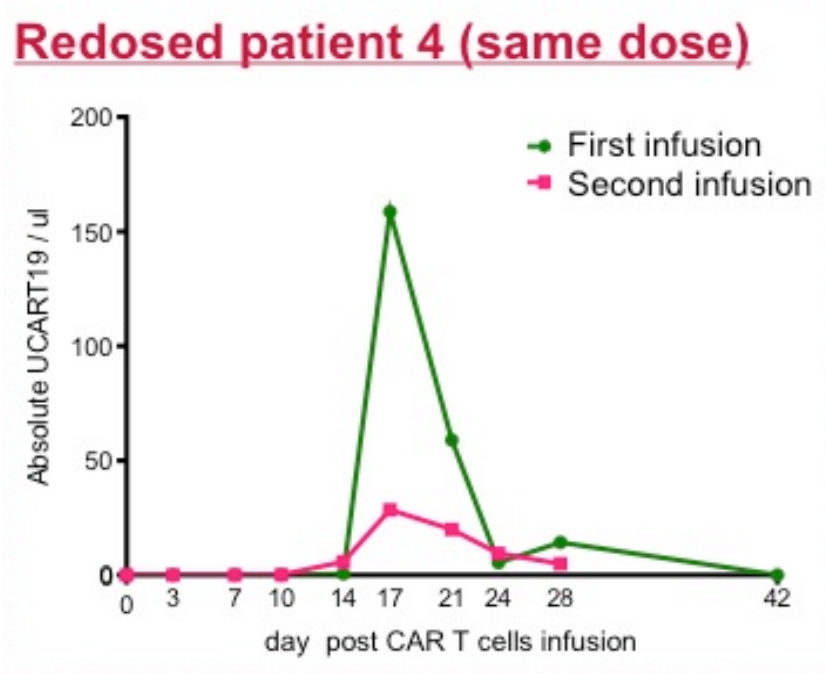
Anti-leukemic activity



- Molecular remission in 5/7 patients
- 4 patients alive at 15.4, 10.5, 7.6 and 1.8 months after UCART19 infusion
- 3 deaths: 1 DLT at D15, 1 PD, 1 transplant related infection

UCART19 levels at DL1 (~ 1 x 10^5 cells/kg)





Conclusion

- First allogeneic, off-the-shelf, CAR T-cell therapy in high risk, heavily pretreated, R/R adult B-ALL
- 1 DLT at dose level 1 (grade 4 CRS complicated by infection)
- Other mild/manageable expected toxicities: 1 G1 acute skin GvHD, 6 G1-2 CRS, 3 G2 viral reactivations, 2 G1 neurotoxic events
- Molecular remission in 5/7 patients
- UCART19 expansion in blood seen in all patients
- Redosing resulted in successful expansion and efficacy
- Promising results at dose level 1 (~ $1x10^5$ cells/kg)

Acknowledgements

- Patients participating in this early-phase trial and their families
- Teams involved in UCART19 studies at KCL, Servier and Pfizer

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