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Preliminary Results of UCART19, an Allogeneic Anti-CD19 CAR T-Cell Product in a First-in-Human Trial (PALL) in Pediatric Patients with CD19+ Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

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BACKGROUND

CD19 is a good target antigen for CAR T-cell therapy against B-cell malignancies due to its highly restricted pattern of expression. UCART19 is a lentiviral-transduced CAR T-cell expressing:

- a second generation anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3ζ), and
- a RQR8 «safety switch» intended to allow targeted elimination of RQR8+ cells by rituximab.

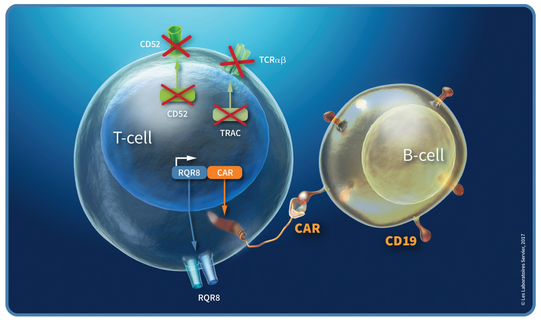

Figure 1. UCART19, an engineered allogeneic anti-CD19 CAR T-cell medicinal product

Additionally, UCART19 has been modified to disrupt the T-cell receptor alpha constant (*TRAC*) and *CD52* genes with the help of mRNA coding for transcription activator-like effector nuclease (*TALEN*®), Cellectis' gene-editing technology. Inactivation of the *TRAC* gene is intended to prevent TCR- mediated recognition of patient HLA antigens. The *CD52* knock-out permits the use of UCART19 in patients treated with alemtuzumab aiming to induce a profound and prolonged lymphodepletion.

We previously reported with Cellectis the success of UCART19 in two infants with R/R ALL treated under a special license granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). They achieved molecular remission ahead of allogeneic stem cell transplantation and were in complete remission at last assessments at 18 and 24 months.

UCART19 MANUFACTURING

UCART19, a ready-to-use, off-the-shelf therapy, offers the advantage of using peripheral blood mononuclear cells (PBMCs) from one healthy donor to treat several patients.

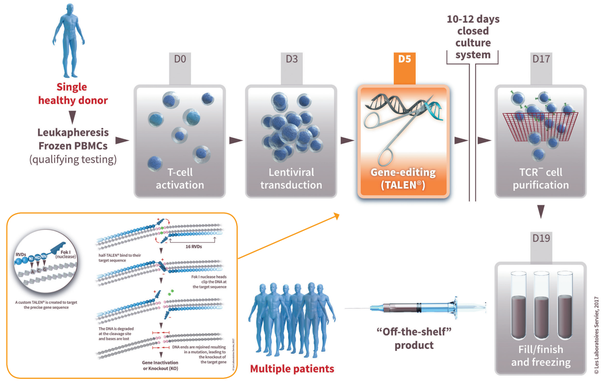

Figure 2. UCART19 manufacturing process and TALEN® technology

UCART19 is manufactured from frozen PBMCs obtained by leukapheresis from healthy volunteer donors. A number of steps are performed:

- T-cells are activated/expanded ex vivo by addition of anti-CD3/anti-CD28 beads
- The cells are then transduced with a recombinant lentiviral vector cassette driving the expression of both anti-CD19 CAR and the RQR8 epitope
- mRNA TALEN® are introduced by electroporation into target cells to induce disruption of *TRAC* and *CD52* genes
- Residual TCRαβ+ cells are depleted
- Drug product is aliquoted into cryovials that are stored at a temperature below -135°C in vapor phase liquid nitrogen until thawing prior to intravenous administration

METHODOLOGY

This is a phase I multicenter, open-label, non-comparative study to evaluate the safety and the ability of UCART19 to induce molecular remission at day (D) 28 and enable allogeneic stem cell transplantation (allo-SCT) in pediatric patients with relapsed or refractory (R/R) CD19+ B-ALL. The lymphodepletion regimen combining cyclophosphamide (60 mg/kg/day for 2 days), fludarabine (30 mg/m²/day for 5 days), and alemtuzumab (0.2 mg/kg/day for 5 days) starts during the week preceding UCART19 infusion (from D-7 to D-1). A flat dose of UCART19 ($2x10^7$ total cells equivalent to 1.1 to $2.3x10^6$ cells/kg) in 4 different weight-bands is evaluated. UCART19 is administered at D0 as a single non-split dose, by slow IV infusion over 5 minutes.

A risk mitigation plan has been set up to manage potential safety risks associated with the administration of UCART19.

Key Eligibility Criteria

Patients must fulfil the following main eligibility criteria:

- Age between 6 months and < 18 years
- High-risk relapsed or refractory (R/R) CD19+ B-ALL with morphological or residual disease load ≥$1x10^{-3}$ (by qPCR and/or FC)
- Eligible for allo-SCT with suitable donor available
- No other therapeutic options

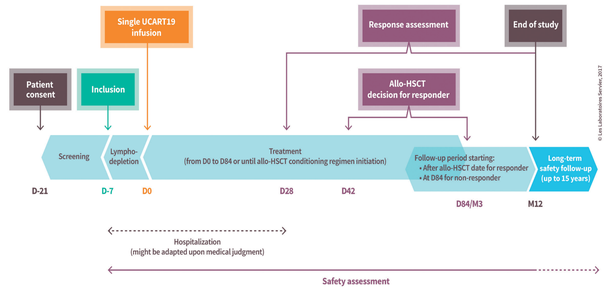

Figure 3. Study design

PRELIMINARY RESULTS

As of October 13, 2017, 5 high-risk R/R ALL pediatric patients have been treated (baseline characteristics are described in Table 1). 4 out of 5 patients received 3 or more previous lines of treatment and 2 had undergone a previous allo-SCT. All had received debulking chemotherapy and/or inotuzumab ozogamicin (2 patients) before UCART19.

Patient Characteristics n (%)	All (n=5)
Age mean (years)-range	4.8 [0.8-16.4]
Disease at diagnosis	
NOS	3
with t(12;21)(p13;q22) TEL-AML1 (ETV6-RUNX1)	1
with t(v;11q23);MLL rearranged	1
Prior treatment	
3	2
≥ 4	3
Previous allo-SCT	2
Time of relapse after previous graft	
> 6 months	2
Bone marrow blasts before lymphodepletion	
<10%	4
>50%	1

Table 1. Baseline characteristics

Safety

A total of 84 emergent adverse events (EAEs) were reported. Of these, 34 events occurring in 5 patients were considered as severe, and 68 events in 5 patients as serious. 19 events were related to UCART19 in which 3 were considered as severe.

One patient died due to transplant-related complications (including thrombotic microangiopathy and BK hemorrhagic cystitis and nephritis).

As detailed in Figure 4, the most frequent AE reported were cytokine release syndrome (CRS) related to UCART19; and neutropenia and infusion-related reaction related to lymphodepletion.

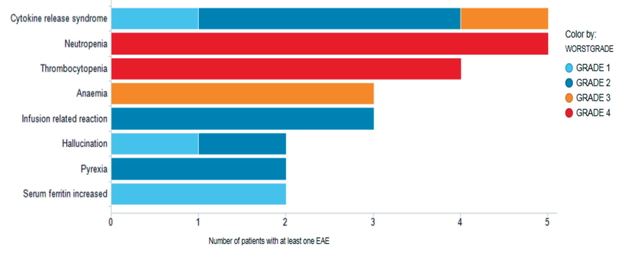

Figure 4. Emergent Adverse events related to UCART19 or Lymphodepletion reported in ≥ 2 patients

PRELIMINARY RESULTS

5 out of 5 patients experienced an adverse event of special interest (AESI) (Table 2).

	All Grade n°/N	Grade 1	Grade 2	Grade 3
Cytokine release syndrome	5/5	1	3	1
Graft-versus-host disease	1/5	1		
Infections	4/5			4
Neurotoxicity events	2/5	1	1	

n°=nb of pts with at least one event

Table 2. Adverse events of special interest in 5 patients

All patients experienced reversible CRS related to UCART19. CRS symptoms occurred between D4 and D8. One grade 3 CRS was observed and managed with 2 doses of tocilizumab. Acute grade 1 graft-versus-host disease related to UCART19 was seen in 1 patient, restricted to skin and recovered with topical steroids. Four children experienced viral complications (CMV, ADV, BK, metapneumovirus) related to lymphodepletion. Neurotoxicity of grade 1 or 2 related to UCART19 was observed in 2 patients and rapidly recovered within 1 to 3 days without treatment.

Anti-leukemic activity

All patients completed the 28-day evaluation period and were evaluable for anti-leukemic activity. By D28-42, 5/5 pts had achieved complete remission with incomplete blood count recovery albeit with hypoplastic marrows (all patients were MRD negative (<0.01%) by flow cytometry or qPCR). All patients proceeded to allo-SCT between 7 to 9 weeks after UCART19 infusion. Two children relapsed 3 months after transplantation (one CD19- and one CD19+) and died 7 and 7.5 months after UCART19 infusion, respectively. One subject died in remission due to transplant complications, and two remain in molecular remission 5 and 5.5 months post-transplant.

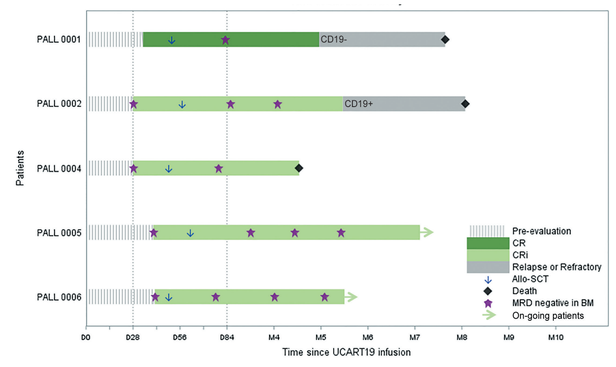

Figure 5. Anti-leukemic activity

PRELIMINARY RESULTS

Preliminary cellular kinetics

Levels of UCART19 vector copy number (VCN) are measured in blood and bone marrow by qPCR in all patients. Measurements in bone marrow correlated with measurements in blood. Consistently with data in adults (CALM study) VCN in pediatrics showed a peak around D14 for all patients. UCART19 was detected until D28 except for patient 1, in whom UCART19 was still observable at D42. PK assessment of patient 1 at further time-points was not possible due to UCART19 elimination by conditioning regimen for allo-SCT at D52.

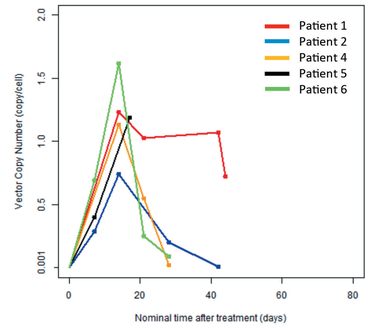

Figure 6. VCN data in blood

Chimerism data

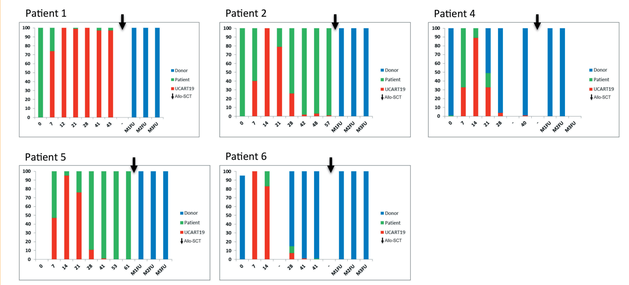

Figure 7. Chimerism data in blood

UCART19 was detectable in blood from D7 to at least D42 in all patients by molecular signatures of T-cell donor chimerism.

CONCLUSION

- **To date UCART19 related toxicities have been manageable.**
  - **Grade 1 acute GvHD in one patient, restricted to skin and resolved with topical steroids.**
  - **Single grade 3 CRS occurred and resolved within 13 days with 2 doses of tocilizumab.**
  - **No grade 3/4 neurotoxicity reported.**
- **Lymphodepletion-related viral complications and persisting neutropenia were encountered.**
- **UCART19 has resulted in flow MRD- in 5/5 and PCR MRD- in 3/5 subjects. This allowed allo-SCT to be attempted in all these heavily pre-treated children.**
- **The trial is active in UK and Belgium (NCT02808442).**
- **Another trial (CALM) is currently evaluating UCART19 in R/R B-ALL adult patients.**

ACKNOWLEDGEMENTS

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DISCLOSURES

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