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CALM study

Phase I study of UCART19, an allogeneic anti-CD19 CAR T-cell product, in high risk adult patients with CD19+ relapsed/refractory (R/R) B-cell ALL: Preliminary results of phase I CALM study

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BACKGROUND

UCART19 is a second generation anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3z), that has been genetically 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®), a Cellectis gene-editing technology (Figure 1).

UCART19 is expressing a RQR8 "safety switch" intended to allow targeted elimination of RQR8+ cells by rituximab.

This is a ready-to-use, off-the-shelf therapy that has the advantage that peripheral blood mononuclear cells (PBMCs) isolated from a single healthy donor can be used to treat multiple patients

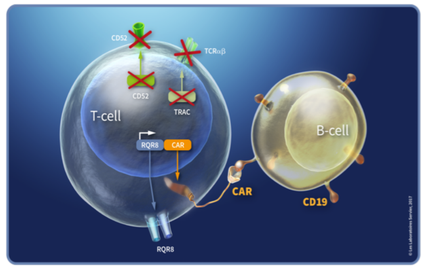

Figure 1. UCART19, an engineered allogeneic anti-CD19 CAR T-cell medicinal product

As previously reported with Cellectis, preliminary efficacy for UCART19 was demonstrated with two infants suffering from R/R ALL. Both infants were treated with UCART19 under a special license granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). Both infants remain in remission 24 and 30 months after subsequent transplant.

Updated data for UCART19 administered to a pediatric population suffering from R/R ALL (PALL study) are presented in EHA 2018 (abstract #PF175).

METHODS

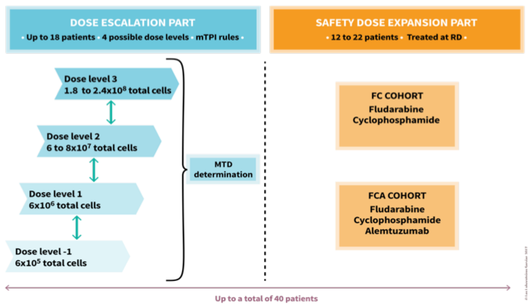

Figure 2. Study plan

- Phase I multicenter, dose-escalating, open-label, non-comparative study, to evaluate up to 4 dose levels (DL) of UCART19 and to determine the maximum tolerated dose (MTD) in adult patients with R/R B-ALL.
- Dose-escalation is followed by a safety expansion part, patients dosed at MTD or at the recommended dose (RD) (Figure 2)
- The lymphodepletion (LD) regimen starts from D-7 preceding UCART19 infusion and combines: cyclophosphamide 1500 mg/m² and fludarabine 90 mg/m², without alemtuzumab (FC) or with alemtuzumab 1 mg/kg (FCA)
- During the expansion part, the role of alemtuzumab will be investigated in 2 cohorts of patients (LD with FC or FCA)
- At D0, UCART19 is administered as a single non-split dose, by slow IV infusion (5 minutes)
- Evaluation of dose limiting toxicities is performed 28 days after infusion (D28)
- Bone marrow aspiration/biopsy is performed before LD, at D-1, at D28 and D84
- Minimal residual disease (MRD) is defined by < 10^{-4} blasts in bone marrow, assessed by flow cytometry (FLC) and/or by qPCR
- At study completion (D84 after infusion), the patient is rolled-over to the long term follow-up study (LTFU) for a 15-year duration

OBJECTIVES

Primary objective

- To evaluate the safety and tolerability of UCART19 and to determine the maximum tolerated dose (MTD) in relapsed or refractory B-ALL adult patients

Secondary objective

- To assess the anti-leukemic activity:
  - ✓ rate of objective response at Day 28, Day 84 and overall,
  - ✓ duration of response, time to remission, progression free survival

Exploratory objectives

- To assess the proportion of patients who underwent an allogeneic stem cell transplant (allo-SCT) at Day 84.
- To analyse the expansion, phenotype, trafficking and persistence of UCART19 in blood, in bone marrow

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- Age ≥ 16 years
- Patient with R/R CD19 positive B-ALL
  - ✓ Morphological disease or MRD$^+$ (≥ 1x10^{-3} by flow cytometry (FLC) and/or qPCR)
  - ✓ Who has exhausted available treatment options

Exclusion criteria

- Previous treatment with investigational gene or cell therapy medicine products
- Active systemic infection
- Active CNS leukemia
- Extra-medullary disease

RESULTS

STUDY STATUS

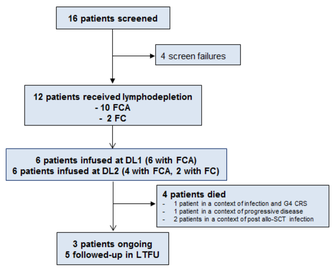

Figure 3. Study status

- As of April 24, 2018, 12 patients have been treated in the dose escalation part, with 6 patients at DL1 with 6x10^6 total cells (approximately 1x10^5 cells/kg) and 6 patients at DL2 with 6 to 8x10^7 total cells (approximately 1x10^6 cells/kg). Patient characteristics are presented in Table 1.
- 4 patients had recurrent genetic abnormalities including hyperdiploidy and translocations
- Patients had received a median of 3.5 prior treatment lines (range 1-5)
- Recruitment in dose escalation is active in 3 countries (UK, U.S. and France)

SAFETY

N=12	Worst grade G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	All grades n (%)
AEs related to UCART19						
Cytokine release syndrome	1 (8.3)	8 (66.7)	1 (8.3)	1 (8.3)	-	11 (91.7)
Neurotoxicity events	3 (25)	-	-	-	-	3 (25)
Graft-versus-host disease in skin	1 (8.3)	-	-		-	1 (8.3)
AEs related to lymphodepletion and/or UCART19						
Prolonged cytopenia*	-	-	-	3 (25)	-	3 (25)
Neutropenic sepsis	-	-	-	1 (8.3)	1(8.3)	2 (16.7)
CMV infection	-	3 (25)	-	-	-	3 (25)
Adenovirus infection	1 (8.3)	-	1 (8.3)	-	-	2 (16.7)

* Persistent Grade 4 neutropenia and/or thombocytopenia beyond Day 42 post UCART19 infusion, except if >5% bone marrow blasts
n: number of patients with at least one event by worst grade

Table 2. Most relevant AEs post-UCART19 infusion/ before allo-SCT

- 11/12 patients experienced CRS (G1 to G4) (Table 2) .
  - ✓ Tocilizumab was administered in 6/11 patients
  - ✓ CRS correlated with serum cytokine increase (IL-6, IL-10 and IFNγ) and UCART19 expansion in blood in all patients but one
- 1 patient developed G1 skin GvHD at D31, that resolved with topical steroids
- Viral reactivations (CMV and/or adenovirus) occurred in 4 patients (G1 to G3)
- 3/12 patients developed prolonged cytopenia defined as persistent grade 4 beyond D42 post UCART19
- 2 DLTs have been observed, one at DL1 related to UCART19: G4 CRS associated with G5 neutropenic sepsis (death at D15 post-infusion) and one at DL2 related both to UCART19 and LD: G4 prolonged cytopenia associated with infection and pulmonary hemorrhage (death at D82 post-infusion)
- Deaths: 4 deaths have been reported: 1 patient with CRS G4 associated with infection, 1 patient had progressive disease and 2 patients in a context of post allo-SCT infection

BASELINE CHARACTERISTICS

	All (N=12)
Median age in yrs (range)	29.50 [18-62]
Nb of prior treatment lines	
1 or 2	4
≥3	8
incl. prior inotuzumab ozogamicin	6
incl. prior blinatumomab	3
Previous allo-SCT	7
Time of relapse following previous allo-SCT	
< 6 months	4
≥ 6 months	3
Median (range)	5.9 months (4.1-11)
Bone marrow blasts prior to lymphodepletion	
<5%	3
5-25%	3
>25%	6
Median (range)	34% (0-98)

Table 1. Patient characteristics

UCART19 KINETICS

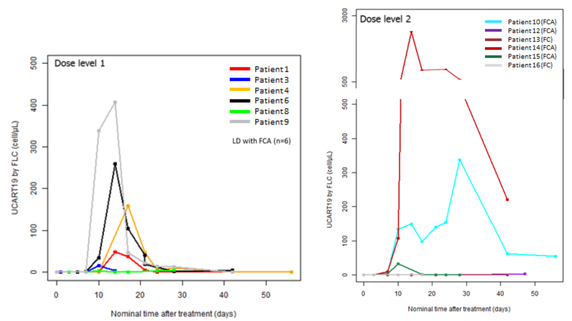

Figure 5. Flow cytometry PK profile

- Preliminary data on flow cytometry at DL1 and DL2 show that UCART19 was detectable in blood from D3 to D14 with a proliferation peak between D10 and D17. One patient at DL2 showed the highest peak linked to longest persistence (Figure 5)
- Among those patients with cell expansion, at DL1: 1 patient showed UCART19 persistence up to D42; at DL2: 2 patients showed persistence up to D42 and ongoing persistence at D56
- Preliminary data suggests that the level of UCART19 expansion does not correlate with response on D28; instead, MRD$^-$ CR at D28 was observed even with low levels of UCART19 expansion
- After the first dose of UCART19, no expansion was observed in 2 out of 10 patients who received LD with FCA and 2 out of 2 patients who received FC
- The role of alemtuzumab in UCART19 expansion is under investigation.

RESULTS

ANTI-LEUKEMIC ACTIVITY

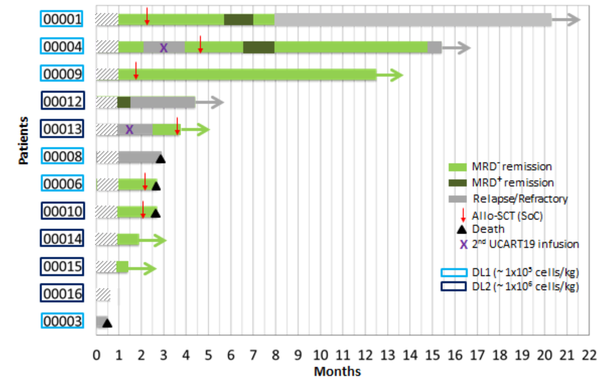

Figure 4. Anti-leukemic activity

- 12 patients received at least one UCART19 infusion as of April 24, 2018
- 10/12 patients were evaluable for anti-leukemic activity at D28 post UCART19 infusion. One patient died at D15 and one patient did not reach D28 evaluation
- At D28, 8 out of 10 evaluable patients achieved CR, including 7 patients in MRD$^-$ CR. Those 2 patients with refractory disease had no UCART19 expansion
- 4 out of 7 patients in MRD$^-$ CR underwent an allo-SCT. One patient remains in MRD$^-$ CR 12.4 months post UCART19 infusion, one patient relapsed 100 days post transplant
- Re-dosing with UCART19 was permitted on a compassionate use basis:
  - ✓ The 1st patient had relapsed with CD19$^+$ disease at D61 following 1st dose (LD with FCA); the 2nd dose (LD with FC) allows this patient to achieve MRD$^-$ at D28
  - ✓ The 2nd patient had no UCART19 expansion after the 1st dose (LD with FC) and had refractory disease at D28; the 2nd dose (LD with FCA) allows this patient to achieve MRD$^-$ at D28
  - ✓ Both patients proceeded subsequently to an allo-SCT
- 4 patients remain in molecular remission at data cut-off

CONCLUSIONS

- **First allogeneic, off-the-shelf, CAR T-cell therapy in high risk, heavily pretreated, R/R adults B-ALL**
- **All patients but one experienced manageable CRS, grade 1 neurotoxicity and skin GVHD were observed in 3 and 1 patients, respectively**
- **10 out of 12 patients were evaluable for anti-leukemic activity at D28 post UCART19, one patient did not reach D28 evaluation**
- **8 out of 10 evaluable (80%) patients achieved CR at D28 (88% MRD$^-$ CR)**
- **2 patients received a 2nd dose of UCART19 (off-protocol), whom both achieved MRD$^-$ CR at D28**
- **6 patients proceeded to an allo-SCT, including 4 patients after the 1st dose of UCART19, and 2 patients after the 2nd dose**
- **4 patients remain in MRD$^-$ CR at 12.4, 3.6, 1.8 and 1.3 months respectively, post UCART19**
- **Viral complications and prolonged cytopenia were encountered related to lymphodepletion and/or UCART19**

ACKNOWLEDGEMENTS

Patients and their families participating in this early phase trial.
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Teams involved in UCART19 studies at Servier and Allogene Therapeutics.
TALEN® is a proprietary technology owned by Cellectis.

Disclaimer: Part of these data were presented during an oral session at the EBMT congress on 21 March, 2018.