Stockholm – June 14-17, 2018

PALL Study

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

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Poster # PF175

BACKGROUND

UCART19 is a genetically modified CAR T-cell product manufactured from healthy donor cells expressing:

- a second generation anti-CD19 CAR (anti-CD19 scFv- 41BB- CD3z), and
- a RQR8 «safety switch» intended to allow targeted elimination of RQR8+ cells by rituximab.

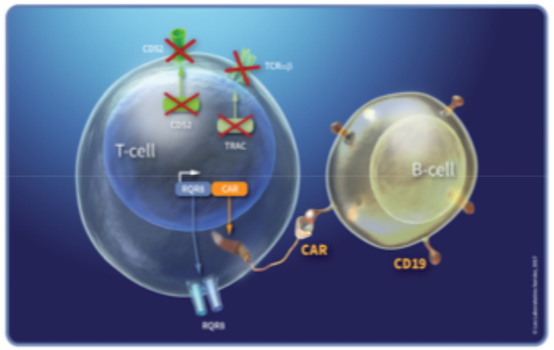

Figure 1. UCART19, an engineered allogeneic anti-CD19 CAR T-cell medicinal product

In addition, 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.

UCART19 is a ready-to-use, off-the-shelf therapy that has the added advantage that peripheral blood mononuclear cells (PBMCs) isolated from a single healthy donor can be used to treat multiple patients. As previously reported with Cellectis, preliminary efficacy for UCART19 was demonstrated the with two infants with 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.

METHODS

OBJECTIVES

Primary objective

- To evaluate the safety of UCART19 at a fixed dose in pediatric patients with relapsed or refractory B-ALL

Secondary objective

- To determine the ability of UCART19 to achieve molecular remission at D28

Exploratory objectives

- To determine the ability of UCART19 to achieve molecular remission at D56, D84 or ahead of allo-SCT conditioning regimen initiation
- To assess the remission rate, duration of remission, time to remission, disease specific survival, and progression free survival
- To assess the proportion of patients who underwent allo-SCT

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- Age between 6 months and < 18 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
- Eligible for allo-SCT with suitable donor available

Exclusion criteria

- No previous treatment with investigational gene or cell therapy products
- No active infection
- No active CNS leukemia

METHODS

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 high-risk relapsed or refractory (R/R) CD19+ B-ALL.

The lymphodepletion regimen starts from D-7 (during the week preceding UCART19 infusion) and combines:

- cyclophosphamide (C) (60 mg/kg/day for 2 days),
- fludarabine (F) (30 mg/m²/day for 5 days),
- w/wo alemtuzumab (A) (0.2 mg/kg/day for 5 days).

At D0, a flat dose of UCART19 ($2x10^7$ total cells equivalent to 1.1 to $2.3x10^8$ cells/kg) is administered as a single non-split dose, by slow IV infusion over 5 minutes.

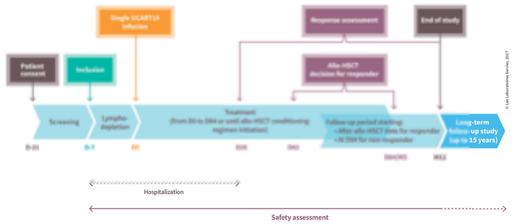

Figure 2. Study design

Safety assessment is performed at D28 post UCART19 administration.

BMA is performed at baseline, D-1, D14 (optional), D28, D56, D84 or ahead of allo-SCT conditioning regimen initiation or at the withdrawal visit (at the investigator's discretion).

During the 12-month follow-up period, a BMA will be performed at M1, M2, M3, M6 and M12 post allograft for the disease assessment.

For refractory patients, the BMA will be performed optionally according to investigator's judgment.

RESULTS

As of April 24, 2018, a total of 6 R/R ALL pediatric patients have been treated in the study. Patients' characteristics are presented in Table 1.

	All (N=6)
Median age (range)-Years	3.75 [0.8-16.4]
Disease at screening	
B-ALL relapsed	6
Disease at diagnosis	
NOS	4
with t(12;21)(p13;q22) TEL-AML1 (ETV6-RUNX1)	1
with t(v;11q23);MLL rearranged	1
Nb of prior treatment lines	
2 prior treatment lines	1
3 prior treatment lines	2
≥4 prior treatment lines	3
Previous allogeneic stem cell transplantation (SCT)	**2**
Time of relapse following previous SCT	
>6 months	2
Bone marrow blasts at inclusion	
<10%	5
>50%	1

Table 1. Patients characteristics

STUDY STATUS

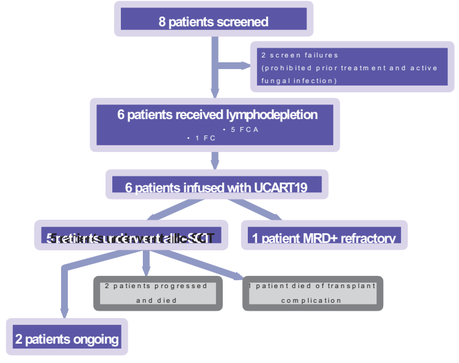

Figure 3. Study status

SAFETY

As detailed in Table 2, the most frequent AE related to UCART19 were cytokine release syndrome (CRS), neurotoxic events and skin GvHD; prolonged cytopenia were reported as related to lymphodepletion and in some cases possibly related to UCART19; viral reactivation (CMV, ADV, BK, metapneumovirus) was reported as related to lymphodepletion.

n= number of patients with at least one event by worst grade

All (N=6)	Worst grade G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	All grades
AEs related to UCART19					
Cytokine release syndrome	1 (17)	4 (67)	1 (17)	-	6 (100)
Neurotoxic events	2 (33)	1 (17)	-	-	3 (50)
Graft-versus-host disease*	1 (17)	-	-	-	1 (17)
AEs related to lymphodepletion and/or UCART19					
Prolonged cytopenia**	-	-	-	3 (50)	3 (50)
BK virus hemorrhagic cystitis	-	-	2 (33)	-	2 (33)
Metapneumovirus infection	-	-	-	1 (17)	1 (17)
CMV infection	-	-	1 (17)	-	1 (17)
Febrile neutropenia	-	-	1 (17)	-	1 (17)
Adenovirus infection	1 (17)	-	-	-	1 (17)

*Acute cutaneous GvHD
** Persistent Grade 4 neutropenia and/or thrombocytopenia beyond Day 42 post UCART19 infusion, except if >5% bone marrow blast

Table 2. Most frequent AE post-UCART19 infusion/before allo-SCT

ANTI-LEUKEMIC ACTIVITY

All patients completed the 28-day evaluation period and were evaluable for anti-leukemic activity. 5/6 pts had achieved complete remission with incomplete blood count recovery and were MRD negative (<0.01%) by flow cytometry or qPCR. Three patients died post-transplant, 2 for progression and one died in remission due to transplant complications.

Alemtuzumab's benefit/risk in lymphodepletion prior to UCART19 is under investigation.

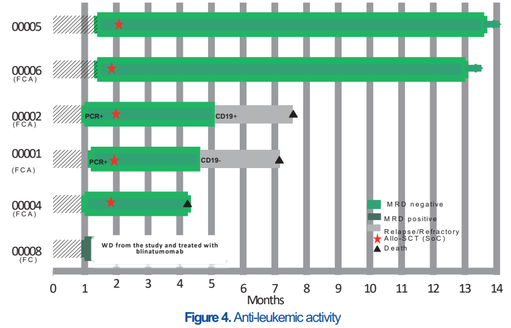

Figure 4. Anti-leukemic activity

RESULTS

PRELIMINARY CELLULAR KINETICS

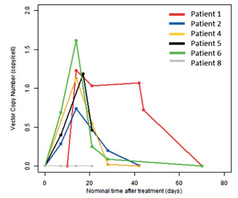

Figure 5. VCN data in blood

UCART19 vector copy number (VCN) are measured in blood and bone marrow by qPCR. Preliminary data showed that for 5 out of 6 patients, UCART19 was detectable in blood by D7, with a proliferation peak observed around D14. No UCART19 was detected for one patient who subsequently relapsed. For 3 out of 5 patients, UCART19 persisted in blood until D28. For 2 out of 5 patients, UCART19 remained detectable in blood on D42. Persistence beyond D42 was not measured since UCART19 was eliminated by conditioning regimen for allo-SCT.

CYTOKINES KINETICS

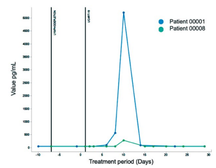

Figure 6. Levels of IFNγ in two patients

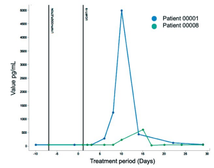

Figure 7. Levels of IL-6 in two patients

2 out of 6 patients had IL-6 and IFNγ elevation. No cytokine elevation was observed in 4 out of 6 patients by local lab. All 6 patients experienced CRS. CRS G3 was observed in patient 1 and CRS G2 in patient 8. Time to onset of first CRS symptoms ranged between D5 and D9.

CHIMERISM DATA

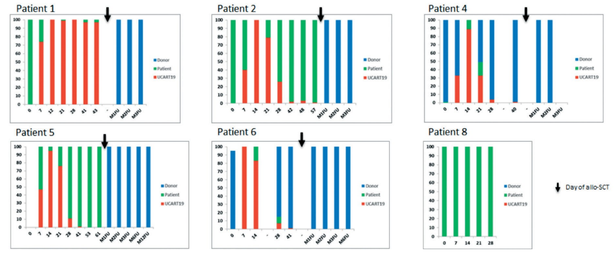

Figure 8. Chimerism data in blood

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

CONCLUSION

- **First allogeneic, off-the-shelf, CAR T-cell therapy in high risk, heavily pretreated, R/R pediatric B-ALL.**
- **To date UCART19 related toxicities have been manageable:**
  - **Grade 1 acute GvHD (restricted to skin) observed in one patient and resolved with topical steroids.**
  - **Grade 3 CRS observed in one patient and resolved within 13 days following treatment with tocilizumab.**
  - **No grade 3/4 neurotoxicity reported.**
- **UCART19 has resulted in flow cytometry MRD- CR in 5/6 patients.**
- **Lymphodepletion-related viral complications and prolonged cytopenia were encountered.**
- **Two patients are still in remission > 13 months post-UCART19 infusion.**

ACKNOWLEDGEMENTS

Patients and their families participating in this early phase trial.
Nurses, study personnel and investigators working with us on the study.
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.