Preliminary Data on Safety, Cellular Kinetics and Anti Leukemic Activity of UCART19, an Allogeneic Anti-CD19 CAR T-cell Therapy in Adult and Pediatric Patients with CD19⁺ Relapsed/Refractory B-cell Acute Lymphoblastic Leukemia – A Pooled Analysis of the CALM and PALL Phase 1 Trials

Reuben BENJAMIN, MD, PhD, Principal Investigator

R/R B-cell ALL in Children and Adults

• Prognosis of R/R ALL is very poor (<10% overall survival)

• Standard therapy involves combination of chemotherapy ± allogeneic SCT

• New treatments include BiTEs, ADCs and autologous CAR T-cell therapies

• Still unmet medical need in advanced R/R ALL

• The “off-the-shelf” UCART19 may overcome some hurdles faced with autologous CAR T-cell therapies
UCART19: the First “Off the Shelf” Anti-CD19 Allogeneic CAR T-cell Therapy

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 anti CD52 mAb use in lymphodepletion

TALEN® (= transcription activator-like effector nuclease) is a proprietary technology owned by Cellectis
## PALL / CALM – Study Main Objectives

<table>
<thead>
<tr>
<th>Objectives</th>
<th>PALL (pediatric study)</th>
<th>CALM (adult study)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>• Safety and tolerability of UCART19</td>
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<tr>
<td></td>
<td>• Determine maximum tolerated dose (MTD) and lymphodepleting (LD) regimen</td>
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<tr>
<td><strong>Secondary</strong></td>
<td>• Remission rate at D28</td>
<td></td>
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<tr>
<td><strong>Exploratory</strong></td>
<td>• Anti-leukemic activity at each time-point up to M12</td>
<td>• Proportion of patients undergoing allo-SCT</td>
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<tr>
<td></td>
<td>• Proportion of patients undergoing allo-SCT</td>
<td>• Expansion and persistence of UCART19</td>
</tr>
<tr>
<td></td>
<td>• Expansion and persistence of UCART19</td>
<td>• Proportion of patients undergoing UCART19 redosing</td>
</tr>
</tbody>
</table>
PALL / CALM Study Schema

**Single UCART19 infusion**

**Response and Safety/DLT assessments**

**Response assessments**

**Optional redosing with UCART19**

**End of Study**

**Response assessment**

<table>
<thead>
<tr>
<th>LD regimen (FC or FCA)</th>
<th>Doses in PALL</th>
<th>Doses in CALM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine (F)</td>
<td>150 mg/m²</td>
<td>90 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide (C)</td>
<td>120 mg/kg</td>
<td>1500 mg/m²</td>
</tr>
<tr>
<td>Alemtuzumab (A)</td>
<td>1 mg/kg</td>
<td>1 mg/kg or 40 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PALL dose</th>
<th>CALM dose levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight-banded dose</td>
<td>DL1: 6x10⁶</td>
</tr>
<tr>
<td>[range 1.1 to 2.3x10⁶]</td>
<td>DL2: 6 or 8x10⁷</td>
</tr>
<tr>
<td>cells/kg]</td>
<td>DL3: 1.8 or 2.4x10⁸</td>
</tr>
<tr>
<td></td>
<td>≈ 1x10⁵ cells/kg</td>
</tr>
<tr>
<td></td>
<td>≈ 1x10⁶ cells/kg</td>
</tr>
<tr>
<td></td>
<td>≈ 3x10⁶ cells/kg</td>
</tr>
</tbody>
</table>

**Patient consent**

**Inclusion**

**Screening**

**Lymphodepletion**

**Treatment period**

**Follow-up period**

**LTFU study**

**Safety assessments**
PALL / CALM Key Eligibility Criteria

Inclusion Criteria

• Age: PALL from 6 months to <18 yrs; CALM from 16 yrs to <70 yrs
• Patients with CD19+ relapsed or refractory (R/R) B-ALL
  ✓ R/R defined as ≥ 2nd BM relapse or any BM relapse after allo-HSCT or chemorefractory
  ✓ morphologically confirmed (≥ 5% leukemic blasts) or quantifiable MRD+ (≥ 1x10^-3)
  ✓ and who have exhausted available treatment options

Exclusion Criteria

• Clinically suspected extra-medullary involvement, CNS-3
• Evidence of active infection within 7 days of inclusion
• Presence of UCART19 donor-specific anti-HLA antibodies
# High-Risk, Heavily Pretreated Patients

<table>
<thead>
<tr>
<th></th>
<th>PALL (N =7)</th>
<th>CALM (N =14)</th>
<th>POOLED (N =21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range) - years</strong></td>
<td>2.7 (0.8-16.4)</td>
<td>29.5 (18-62)</td>
<td>22 (0.8-62)</td>
</tr>
<tr>
<td><strong>Number of previous lines of therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 3</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>≥ 4</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>4 (2-6)</td>
<td>4 (1-5)</td>
<td>4 (1-6)</td>
</tr>
<tr>
<td><strong>High cytogenetic risk</strong></td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Prior allo-SCT</strong></td>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td><strong>Time to relapse following prior allo-SCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td><strong>Bone marrow tumor burden prior to LD (% of blasts)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>5 to 25</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 25</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>6 [0-80]</td>
<td>19 [0-96]</td>
<td>8 [0-96]</td>
</tr>
</tbody>
</table>

* High cytogenetic risk includes complex karyotypes, MLL rearrangements, Ph+
**PALL / CALM - Patients Status**

**Enrolled (N=21)**  
Lymphodepletion (17 FCA - 4 FC)

**Treated (N=21)**

**PALL** N=7 (fixed dose)
- Ongoing (N=4)  
  - 2 still in remission  
  - 1 in relapse  
  - 1 refractory  
- Non treatment-related deaths (N=3)  
  - 2 progressive disease  
  - 1 viral infection in post allo-SCT setting  
- No treatment-related death

**CALM** N=14
- 6 DL1  
- 6 DL2  
- 2 DL3

- Ongoing (N=8)  
  - 3 still in remission  
  - 3 in relapse  
  - 2 refractory

- Non treatment-related deaths (N=4)  
  - 3 progressive disease  
  - 1 viral infection in post allo-SCT setting

- Treatment-related deaths (N=2)  
  - 1 pulmonary haemorrhage in post allo-SCT setting  
  - 1 neutropenic sepsis + CRS G4

*1 additional death was reported post cut-off date

**Screened (N=31)**  
10 screen failures (7 CALM, 3 PALL)

**Cut-off date: 23 Oct 2018**
## UCART19 Shows an Acceptable Safety Profile

<table>
<thead>
<tr>
<th>N=21</th>
<th>G1 n (%)</th>
<th>G2 n (%)</th>
<th>G3 n (%)</th>
<th>G4 n (%)</th>
<th>G5 n (%)</th>
<th>All grades n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs related to UCART19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>4 (19.0)</td>
<td>12 (57.1)</td>
<td>2 (9.5)</td>
<td>1* (4.8)</td>
<td>-</td>
<td>19 (90.5)</td>
</tr>
<tr>
<td>Neurotoxicity events</td>
<td>7 (33.3)</td>
<td>1 (4.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Acute skin graft-versus-host disease **</td>
<td>2 (9.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>AEs related to lymphodepletion and/or UCART19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged cytopenia***</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 † (28.5)</td>
<td>-</td>
<td>6 (28.5)</td>
</tr>
<tr>
<td>Viral infections †</td>
<td>1 (4.8)</td>
<td>2 (9.5)</td>
<td>4 (19.0)</td>
<td>1 (4.8)</td>
<td>-</td>
<td>8 (38.1)</td>
</tr>
<tr>
<td>Neutropenic sepsis</td>
<td>1 (4.8)</td>
<td>1* (4.8)</td>
<td>2 (9.5)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia/ septic shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>1† (4.8)</td>
<td>1 (4.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* 1 DLT at DL1 related to UCART19: G4 CRS associated with G5 neutropenic sepsis (death at D15 post-infusion)

** GvHD confirmed by biopsy in 1 out of 2 cases

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

† 1 DLT at DL2 related both to UCART19 and LD: G4 prolonged cytopenia associated with infection and pulmonary hemorrhage (death at D82 post-infusion)

† Viral infections: CMV, ADV, BK virus, metapneumovirus
82% Achieved CR/CRi in FCA-treated Population

- CR/CRi: 14/17 pts in FCA-treated pts
- MRD-: 10/14 pts (71%)
- Allo-SCT: 11/14 pts (78%)
- Overall CR/CRi: 14/21 pts (67%)

* This patient died post cut-off date
** Patient in MRD- status after 2nd dose, underwent allo-SCT (data reported post cut-off date)
UCART19 Kinetics Measured by qPCR and Flow

- UCART19 expansion observed in 15/17 pts with FCA
- UCART19 expansion observed in 0/4 pts with FC
- 3 pts had UCART19 persistence beyond D42 and upto D120 in 1 pt
- Response is linked to expansion observed in D0-28 period
Trend for a Deeper and More Sustained Host T-cell Depletion with FCA

Maximum value of the cell range is plotted from the CALM study.
Redosing Allowed Further UCART19 Expansion and 2 out of 3 pts Achieved MRD-

✓ Patient 1
  • MRD- at D28
  • Relapse and 2nd infusion 3 months after 1st dose
  • MRD- at D28 after redosing

✓ Patient 2
  • Refractory at D28
  • 2nd infusion 1.6 months after 1st dose
  • MRD- at D28 after redosing

✓ Patient 3
  • Refractory at D28
  • 2nd infusion 2.4 months after 1st dose
  • Progression at D28
Key Messages

• 82% (14/17) CR/CRi rate in FCA-treated pts
  – 71% (10/14) achieved MRD-status
  – 67% (14/21) CR/CRi rate in overall population
  – No UCART19 expansion and no response in 4/4 FC-treated pts

• UCART19 has shown an acceptable safety profile:
  – no moderate/severe acute GvHD, no severe neurotoxicities, and mainly moderate CRS
  – viral reactivations and prolonged cytopenias are observed

• FCA lymphodepletion appears to be required for UCART19 expansion

• Redosing with UCART19 resulted in cell expansion and MRD-status in 2/3 pts

• UCART19 evaluation in pediatric and adult B-ALL is ongoing
Acknowledgements

- Patients participating in CALM & PALL trials and their families
- Teams involved in UCART19 studies at study centres, Servier and Allogene teams

PALL trial active centers
- Great Ormond Street Hospital, London, UK - W. Qasim
- Hospital Robert Debré, Paris, France - A. Baruchel

CALM trial active centers
- Kings College Hospital NHS Foundation Trust, London, UK - R. Benjamin
- MD Anderson Cancer Centre, Houston, US - N. Jain
- Massachusetts General Hospital, Boston, US - M. Maus
- Hospital Saint Louis, Paris, France - N. Boissel
- Hospital Saint Antoine, Paris, France - M. Mohty