CD19 CART-cells for the treatment of acute lymphoblastic leukemia in children and young adults

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NOVARTIS, USA
Chimeric Antigen Receptor (CAR) T cells: a living drug

Mechanism of action data is based on in vitro/in vivo data
B cell malignancies are ideal targets for CART cell therapies

• B cell – T cell interactions are hardwired into the immune response
  – Multiple bi-directional costimulatory signals provide ideal conditions for T cell expansion, function, and maintenance

• Ongoing B cell lymphopoiesis likely contributes to induction of long-lived memory CAR T cells

• B cell aplasia, while not desirable, can be medically managed with Ig replacement and antibiotics
CTL019 expresses chimeric antigen receptors

- Antigen binding domain
  - Recognizes CD19 on B cells
- CD3-zeta signaling domain
  - Initiates T-cell activation
  - Mediates antitumor activity
- 4-1BB costimulatory domain
  - Augments antitumor activity
  - Enhances proliferation and persistence of CAR T cells
CTL019 is an autologous immunocellular therapy
CAR T-cell development and collaboration with Penn

- In 2012, Novartis & University of Pennsylvania partnered for CAR-T therapies
- New treatment paradigm in oncology
- Designed to harness the patient’s own immune system to eliminate cancer cells
- Novartis set up a 180,000-sq. ft. cell-manufacturing site specific for cellular therapies in Morris Plains, NJ, USA
Relapsed/refractory B-cell ALL in pediatric and young adult patients

- B-cell acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children
- Despite current treatment options, ~15% pediatric and young adult patients with ALL experience relapsed/ refractory (r/r) disease\(^1\)
  - Median overall survival is 3 to 9 months
- Unmet medical need for novel treatment options for pediatric and young adult patients with r/r ALL to provide
  - Deep and durable remission
  - Curative treatment opportunities
  - Improved quality of life

Efficacy, long-term safety, and persistence demonstrated in CHOP Study B2101J

- First academic trial establishing feasibility of CTL019 manufacturing
- Demonstrated high rate of durable complete remissions (CR/CRi=95%) and long-term safety in pediatric ALL patients
  - First use of tocilizumab to successfully reverse severe CRS
- Demonstrated long-term persistence of CTL019 cells
  - 1st pediatric patient treated has been in remission for 5 years
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Key eligibility criteria & Primary Endpoint: Study B2202

**Inclusion**
- 2nd or greater bone marrow relapse or primary refractory B-cell ALL
- ≥5% bone marrow lymphoblasts
- Age 3 years at the time of screening to age 21 years at the time of initial diagnosis
- Adequate organ function

**Exclusion**
- Prior gene therapy
- Prior anti-CD19 therapy
- Active CNS involvement

**Primary endpoint**
- Overall remission rate (ORR=CR+CRi) within 3 months after CTL019 administration (by IRC)
Trial design: Study B2202 (ELIANA)

- Lymphodepleting chemotherapy: fludarabine (30 mg/m² IV daily for 4 doses) plus cyclophosphamide (500 mg/m² IV daily for 2 doses)
Global, multicenter trial

**B2202 ELIANA**

**North America**
- United States: 13
- Canada: 2

**Europe**
- Austria: 1
- Belgium: 1
- France: 2
- Germany: 1
- Italy: 1
- Norway: 1
- Spain: 1

**Asia**
- Japan: 1

**Oceania**
- Australia: 1

FPFV: 8 APR 2015
Patient disposition
Study B2202

Enrolled (N=92)

Discontinued prior to CTL019 infusion (N=17)
- CTL019 product could not be manufactured 7
- Death 7
- Adverse event 3

CTL019 infused (N=75)

Discontinued study follow-up (N=27)\(^1\)
- Death 11
- Lack of efficacy 9
- New therapy for ALL while in remission 5
- Patient/guardian decision 2

Follow-up ongoing (N=48)

- Median follow-up time was 13.1 months

\(^1\) Patients alive are still followed for survival status.
Baseline characteristics
Study B2202

<table>
<thead>
<tr>
<th>Select baseline characteristics</th>
<th>N=75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>11 (3-23)</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>57</td>
</tr>
<tr>
<td>Previous lines of therapy, median (range)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>Prior HSCT, %</td>
<td>61</td>
</tr>
<tr>
<td>Disease Status</td>
<td></td>
</tr>
<tr>
<td>Primary refractory, %</td>
<td>8</td>
</tr>
<tr>
<td>Chemo-refractory, %</td>
<td>92</td>
</tr>
<tr>
<td>Morphologic blast count in bone marrow, %, median (range)</td>
<td>74 (5-99)</td>
</tr>
</tbody>
</table>
## B2202: CTL019 efficacy in infused patients

<table>
<thead>
<tr>
<th>N=75</th>
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</table>

### Primary efficacy endpoints

<table>
<thead>
<tr>
<th>Overall remission rate (ORR: CR+CRi) within 3 mos</th>
<th>81</th>
<th>71, 89</th>
<th>&lt;0.0001</th>
</tr>
</thead>
</table>

### Best overall response (BOR)

<table>
<thead>
<tr>
<th></th>
<th>%</th>
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<tbody>
<tr>
<td>CR</td>
<td>60</td>
</tr>
<tr>
<td>CRi</td>
<td>21</td>
</tr>
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</table>

### Secondary efficacy endpoints

<table>
<thead>
<tr>
<th>MRD negative (in BM among CR/CRi patients)</th>
<th>81</th>
<th>58, 61</th>
<th>&lt;0.0001</th>
</tr>
</thead>
</table>

MRD negative = MRD < 0.01%

BOR, best overall response; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DOR, duration of remission; MRD; minimal residual disease
B2202: Duration of Remission, EFS, OS

Relapse free survival at 12 months 59%

Overall survival at 12 months 76%
## B2202 Safety: Adverse Events of Special Interest within 8 Weeks

<table>
<thead>
<tr>
<th>Events</th>
<th>Any Grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>77</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Neurological toxicities</td>
<td>40</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>43</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>35</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Cytopenias not resolved by day 28</td>
<td>37</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Tumor lysis</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
B2202 (ELIANA): Conclusions

• High efficacy with primary endpoint met (CR/CRi 81%)
• Durable complete remissions observed, all MRD-negative
• Median survival 19 months, follow-up ongoing
• Global trial with central manufacturing
• CRS manageable
  – Management guidelines developed and executed globally
• New treatment for pediatric & young adult r/r B-cell ALL
  – FDA approval: Aug 30, 2017
What's next in the Novartis CAR-T portfolio: Front Line Pediatric ALL

Pediatric ALL:
- Newly diagnosed
- High risk (age, WBC)
- Completed induction & consolidation chemotherapy
- End of Consolidation MRD positive (> 0.01%)

Induction & Consolidation Chemotherapy

- Lymphodepleting chemotherapy:
  - Fludarabine (25 mg/m² i.v. daily for 4 days)
  - Cyclophosphamide (500 mg/m² i.v. daily for 2 days starting with the first dose of fludarabine)

Dose in G2201J (same as ELIANA)
- Single IV infusion
- ≤50 kg body weight: 0.2 to 5 x 10⁶ tisagenlecleucel transduced cells/kg
- >50 kg body weight: 0.1 to 2.5 x 10⁷ tisagenlecleucel transduced cells
What’s next in the Novartis CAR-T portfolio: Pediatric B-NHL study

**r/r B-NHL**
- Aged ≤ 18 y
- r/r to prior therapies
- Failed or ineligible for SCT
- Burkitt, DLBCL, PMBCL, Grey Zone lymphoma, and FL.

**Dose in C2202 (same as ELIANA)**
- Single IV infusion
- ≤50 kg body weight: 0.2 to 5 x 10^6 tisagenlecleucel transduced cells/kg
- >50 kg body weight: 0.1 to 2.5 x 10^6 tisagenlecleucel transduced cells

* B-NHL: B-cell non Hodgkin Lymphoma
Manufacturing matters

**Leading edge**
180,000 sq./ft. facility in Morris Plains, New Jersey facility

**22-day**
Target turnaround time of manufacturing KYMRIA H in the US 22 days from receipt

**Manufactured**
CAR-T cells for more than 300 patients across 11 countries

**Reliable**
And integrated manufacturing and supply chain platform

**Allows for**
An individualized treatment approach on a global scale using cryopreservation
CAR-T cell therapy: Reimagining medicine

- Efficacy demonstrated in
  - pediatric & young adults with r/r ALL
  - adults with r/r DLBCL
- Well characterized and manageable safety profile, at trained sites
- Next generation CAR-T therapies planned:
  - Faster manufacturing
  - Developments to improve efficacy
  - Strategies to reduce toxicity
  - Additional hematologic indications
  - Development to target solid tumors
Acknowledgments

• Patients and families taking part in our trials
• Investigators around the world
• Colleagues at University of Pennsylvania and CHOP: Drs. June, Levine, Grupp, Maude, Schuster
• Colleagues at Novartis: NIBR, Global Drug Development, BTDM, Novartis Oncology
We are focused on engineering the future of cancer care for patients in need

“Each light on our Wall of Hope represents a person for which KYMRIA H has been manufactured. Those lights are a reminder to us that every product we manufacture represents our hope for a unique cancer patient, and of our responsibility to them.”

Vasant (Vas) Narasimhan, MD
Novartis
Thank You
“They believed she had less than a 1-in-1,000 chance of surviving to the next morning.”

Tom Whitehead
Father of Emily Whitehead

“I was given three to six months to survive and I’m 16 months in remission … I’m a walking miracle.”

Scott McIntyre, Patient
“We’re making the immune system do things it never could ... it’s unlike anything the pharmaceutical industry has ever done.”

Carl H. June, MD
Richard W. Vague Professor of Immunotherapy at the Perelman School of Medicine and Director of the Center for Cellular Immunotherapies at the Abramson Cancer Center, University of Pennsylvania

“This is the most exciting thing I have seen in my lifetime, and probably since the introduction of multiagent total cancer therapy ...”

Timothy P. Cripe, MD, PhD
Nationwide Children’s Hospital
Columbus, OH