Novartis CTL019 – JULIET data on DLBCL Investor call

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Progressing our Immuno-Oncology strategy

Focus for today

**Advancing CAR-T**

- Manufacturing optimization
- Filed in pediatric/young adult r/r ALL in US, priority review granted; filing in Europe targeted for H2 2017
- Breakthrough Therapy designation awarded for DLBCL, planned filing in US and EU in H2 2017
- CLL and Multiple Myeloma progressing
- Solid tumors in FIH trials

**PD-1 update**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>PDR001 (PD-1 Antagonist)</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>Phase 3 trial in combination with Tafinlar® + Mekinist®: FPFV achieved for run-in</td>
</tr>
<tr>
<td>NET</td>
<td>Pivotal Phase 2 FPFV achieved</td>
</tr>
<tr>
<td>HCC</td>
<td>Phase 1b in combination with sorafenib FPFV achieved</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Phase 1b FPFV achieved</td>
</tr>
<tr>
<td>CRC</td>
<td>Phase 1b FPFV achieved</td>
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</table>

**Ready for IO 2nd Gen**

18 second generation agents in mono or combination therapies progressing in early studies
CTL019: Genetically Engineered T Cells Directed Against CD19

- **Antigen binding domain**
  - Recognizes CD19 on B cells

- **4-1BB costimulatory domain**
  - Augments antitumor activity
  - Enhances proliferation and persistence of CAR T cells

- **CD3-zeta signaling domain**
  - Initiates T cell activation
  - Mediates antitumor activity

\( V_L \): Light Chain Variable Domain
\( V_H \): Heavy Chain Variable Domain
**CTL019 is a living drug designed to target CD19+ B cells**

In vivo

Ex vivo

Ex vivo

CTLO19 cell

Anti-CD19 CAR construct

Lentiviral vector

Patient’s T cell

Native TCR

Mechanism of action data is based on in vitro/in vivo data
High unmet need for patients with r/r diffuse large B-cell lymphoma (DLBCL)

• Patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) have a **poor prognosis**
  – Patients refractory to chemotherapy or relapsing ≤12 months after auto-SCT have low response rates to subsequent therapy (CR, 8%; PR, 18%)\(^1\)
  – Patients failing second-line salvage therapy have a poor prognosis\(^2\)
    - Median OS, 4.4 months
    - 1-year OS, 23%; 2-year OS, 15.7%
  – Potentially eligible patients for CAR-T therapies based on incidence\(^3\)
    2nd line ~33,000 / ≥3rd line ~16,000

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\(^{3}\) Incidence: Based on 2017 incidence rate in US, EU-14, Israel, Japan and Canada -Surveillance, Epidemiology, and End Results Program (SEER); Decision Resources; Novartis analysis Relapsed/Refractory %: Internal Novartis discussions

auto-SCT: autologous stem cell transplant; CR, complete remission; OS, overall survival; PR, partial remission.
JULIET Study Centers – Global clinical trial

- JULIET is a global clinical trial with centralized manufacturing of CTL019
- 27 sites in 10 countries across North America, Europe, Australia, and Asia
JULIET Study Schema

- JULIET is a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in adult patients with r/r DLBCL (NCT02445248)

Screening
  Apheresis and Cryopreservation

<table>
<thead>
<tr>
<th>Bridging Chemotherapy&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment&lt;sub&gt;a&lt;/sub&gt;</td>
</tr>
<tr>
<td>CTL019 Manufacturing</td>
</tr>
<tr>
<td>Restaging Lymphodepletion&lt;sub&gt;c&lt;/sub&gt;</td>
</tr>
<tr>
<td>CTL019 Infusion&lt;sub&gt;d&lt;/sub&gt;</td>
</tr>
<tr>
<td>Safety and Efficacy Follow-Up&lt;sup&gt;°&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Eligibility criteria confirmed.
<sup>b</sup> To prevent rapid disease progression during CTL019 manufacturing.
<sup>c</sup> To be completed 2 to 14 days prior to CTL019 infusion.
<sup>d</sup> Infusion conducted in- or out-patient at investigator discretion.
<sup>°</sup> Long-term follow-up for 15 years (NCT02445222).
JULIET Patient Disposition

Enrollment began July 2015
Data cutoff, Dec 2016

Enrolled (n = 141)

Discontinued before infusion Total = 43
   Inability to manufacture n = 9
   Patient status related\(^a\) n = 34

Infused (n = 85)

Pending infusion n = 13

- 85 patients evaluated for safety
- 51 patients evaluated for response (completed ≥3 months follow-up or discontinued earlier)
  - Median time of 3.7 months from infusion to data cutoff (20 Dec 2016)
- CTL019 cell dose\(^b\):
  - Median (range), \(3.1 \times 10^8\) (0.1-6.0 \(\times 10^8\)) cells

\(^a\) Progressive disease (n = 28; including 16 deaths); adverse event (n = 2), investigator decision (n = 2), withdrawal (n = 1), protocol deviation (n = 1).

\(^b\) 1 patient received < and 3 patients received > the target dose range.
## JULIET Primary Endpoint Was Met

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Patients (N = 51)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response (CR + PR)</td>
<td>59%</td>
</tr>
<tr>
<td>CR(^1)</td>
<td>43%</td>
</tr>
<tr>
<td>PR(^1)</td>
<td>16%</td>
</tr>
<tr>
<td>SD(^1)</td>
<td>12%</td>
</tr>
<tr>
<td>PD(^1)</td>
<td>24%</td>
</tr>
<tr>
<td>Overall response rate (CR + PR)</td>
<td>45%</td>
</tr>
<tr>
<td>CR(^1)</td>
<td>37%</td>
</tr>
<tr>
<td>PR(^1)</td>
<td>8%</td>
</tr>
</tbody>
</table>

\(^a\) The interim analysis was preplanned to include the first 51 patients treated with CTL019 and followed for at least 3 months or discontinued early.

\(^b\) Null hypothesis of ORR ≤20%; the one-sided p-value threshold to reject the null hypothesis is 0.0047 (O’Brien-Fleming boundary) at the interim analysis and 0.0235 at the primary analysis.

CI, confidence interval; CR, complete remission; ORR, overall remission rate; PD, progressive disease; PR, partial remission; SD, stable disease.
JULIET Duration of Response: 79% Relapse-free at 6 Months

- All responses at 3 months were ongoing at the time of cut-off
  - No responding patients went on to SCT
- Median DOR and OS not reached

DOR, duration of response; OS, overall survival; SCT, stem cell transplant.
JULIET Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>AESIa</th>
<th>All grade %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndromeb</td>
<td>56</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Infections</td>
<td>27</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Cytopenias not resolved by day 28</td>
<td>26</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Neurologic events</td>
<td>21</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>14</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- No cases of cerebral edema
- No deaths attributable to CTL019

a AESI = adverse events of special interest, occurring within 8 weeks of CTL019 infusion.

b Cytokine release syndrome was graded using the Penn scale and managed by a protocol-specific algorithm.
There are differences in cytokine release syndrome grading when using different grading systems

<table>
<thead>
<tr>
<th>Condition</th>
<th>UPenn / CHOP Grading (CTL019)</th>
<th>Lee CRS grading system (others)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hypoxemia requiring $O_2$</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>(if $O_2$ requirement less than 40%)</td>
<td></td>
<td>(if $O_2$ requirement less than 40%)</td>
</tr>
<tr>
<td>Hypotension requiring / responding to IV fluid or low dose vasopressor</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension requiring high-dose or multiple vasopressors</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
### JULIET Management of Cytokine Release Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset, median (range), days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.0 (1-8)</td>
</tr>
<tr>
<td>Duration, median (range), days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.0 (3-34)</td>
</tr>
<tr>
<td>Admitted to ICU</td>
<td>24%</td>
</tr>
<tr>
<td>Hypotension that required intervention</td>
<td>29%</td>
</tr>
<tr>
<td>High dose vasopressors</td>
<td>7%</td>
</tr>
<tr>
<td>Intubated</td>
<td>8%</td>
</tr>
<tr>
<td>Anti-cytokine therapy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18%</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>16%</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>11%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated based only on patients who had cytokine release syndrome (n = 48).

<sup>b</sup> 8 patients received both tocilizumab and corticosteroids.

Novartis CAR-T future directions

**Focus for today**

**Manufacturing improvements**

- Optimization of manufacturing operations, including implementing automation

**Hematologic Malignancies**

- **CAR-T-BCMA**
  - CAR-T therapy for multiple myeloma
  - Early clinical data presented at ASH 2016

- **CTL119** (Humanized CD19 CAR)
  - Early clinical data in CLL presented recently at ASCO 2017

**Solid tumors**

- **CAR-T-EGFRvIII**
  - CAR therapy for GBM
  - Data presented at AACR 2016

- **CAR-T-Meso** (Fully Human Mesothelin CAR)
  - CAR therapy for Ovarian, Mesothelioma
  - FPFV occurred in H1 2017
CTL019 “production” process – from leukapheresis via processing to infusion

1 In patients with relapsed/refractory disease
2 CRS: Cytokine Release Syndrome, a common side effect of CAR-T therapies, which may require hospitalization
Benefits of cryopreservation

• Apheresis **scheduling flexibility** for physicians and patients

• **Durability** in transit in case of unforeseen transport delays

• **Preserved cell quality**
Manufacturing experience:
Consistent T-cell product from variable patient material, Study B2202

- Novartis has accrued significant experience manufacturing patient-specific CAR T cells in global, multi-center trials.
- In JULIET, with proprietary process enhancements, manufacturing success rate improved to 97% for the last 30 patients.
**Conclusions**

- The study met the primary objective at the interim analysis
  - Best ORR, 59% (CR, 43%; PR, 16%); \( P < .0001 \) (\( H_0 = \text{ORR} \leq 20\% \))
  - ORR at 3 months, 45% (CR, 37%)
  - All patients in CR at 3 months remained in CR at the time of data cutoff
  - Median DOR not reached

- JULIET is the first global study of a CAR T-cell therapy in DLBCL with centralized manufacturing, using cryopreserved apheresis products

- AEs were reversible and effectively managed by appropriately trained study site personnel. There were no CTL019-related deaths or cerebral edema events

- This pre-planned interim analysis of CTL019 in adults with r/r DLBCL confirms the high response rates and durable responses observed in the previous single-center trial

- Novartis has developed a highly reproducible manufacturing process for CTL019

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CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ORR, overall remission rate.
Q&A