Durability of Response With Axicabtagene Ciloleucel in Patients With Refractory Large B Cell Lymphoma in the Pivotal Phase 2 Study, ZUMA-1

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Poster O-002
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Background

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy that uses a CD3ζ/CD28-based signaling domain (Figure 1)

- ZUMA-1 is a pivotal Phase 1/2 multicenter study that led to the US Food and Drug Administration approval of axi-cel for the treatment of adult patients with relapsed/refractory large B cell lymphoma after ≥2 lines of systemic therapy.

- Long-term follow-up (median, 15.4 months) of ZUMA-1 (N=108) demonstrated:
  - Objective response rate of 82%; complete response (CR) rate of 58%
    - Ongoing responses in 42% (40% with CR)
  - Median overall survival was not reached

- Grade ≥3 cytokine release syndrome in 12% and Grade ≥3 neurological events in 31%

Figure 1. Structure

Axicabtagene Ciloleucel  
(Axi-Cel)

- scFv (anti-CD19)
- Hinge/Transmembrane
- Signal 2: CD28
- Signal 1: CD3ζ
Over half of the progression events occur by Month 3, leading to the need to define treatment practice for patients at this time point.

- Month 3 is clinically relevant to understand patient outcomes.

Objectives

• To evaluate the time to response for patients with both an objective response and a CR
• To assess the significance of partial response (PR) and CR at Month 3 as a prognostic factor for progression-free survival
Methods

Figure 3. ZUMA-1 Study Design

Phase 1 (N=7)

Refractory DLBCL/PMBCL/TFL (n=7)

Key eligibility criteria
- No response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Conditioning regimen
- Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days
- Axi-cel: 2 × 10^8 CAR+ cells/kg
- 99% enrolled were successfully manufactured
- 91% enrolled were dosed

Phase 2 (N=101)

Cohort 1 Refractory DLBCL (n=77)

Cohort 2 Refractory PMBCL/TFL (n=24)

- Phase 2, N=108
- Data cutoff: August 11, 2017
- Minimum follow-up: 12 months
- Median follow-up: 15.4 months

axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.
Bridging chemotherapy was not allowed per study protocol.

This analysis only includes those patients who achieved a response as assessed by Cheson 2007 criteria per investigator assessment. First response assessment was conducted at Month 1, then every 3 months post-infusion thereafter.
Results

Figure 5. Time to Objective Response and Complete Response

- 41% (18/44) patients with PR converted to CR (Figure 5)
- 1 patient converted from stable disease to CR at >12 months
- Responses deepen and improve over time

Time-to-response was calculated as (date of first observed response – axi-cel infusion date + 1)/(365.25/12).

axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not estimable.
Results

Table 1. Baseline Characteristics by Response at Month 3

<table>
<thead>
<tr>
<th></th>
<th>Response at Mont 3</th>
<th>Overall (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (n=9)</td>
<td>CR (n=42)</td>
</tr>
<tr>
<td>Median age (range), y</td>
<td>62 (53-76)</td>
<td>58 (25-75)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4 (44)</td>
<td>28 (67)</td>
</tr>
<tr>
<td>ECOG 1, n (%)</td>
<td>6 (67)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>Disease stage III/IV, n (%)</td>
<td>7 (78)</td>
<td>32 (76)</td>
</tr>
<tr>
<td>IPI score 3-4, n (%)</td>
<td>2 (22)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>≥3 prior therapies, n (%)</td>
<td>5 (56)</td>
<td>29 (69)</td>
</tr>
<tr>
<td>Median SPD of index lesions (range)(^a), mm(^2)</td>
<td>3335 (1022-16,764)</td>
<td>3579 (171-13,936)</td>
</tr>
</tbody>
</table>

Refractory Subgroup Before Enrollment

<table>
<thead>
<tr>
<th></th>
<th>PR (n=9)</th>
<th>CR (n=42)</th>
<th>Overall (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory to ≥2L therapy, n (%)</td>
<td>8 (89)</td>
<td>29 (69)</td>
<td>77 (76)</td>
</tr>
<tr>
<td>Best response as PD to last prior therapy</td>
<td>8 (89)</td>
<td>25 (60)</td>
<td>67 (66)</td>
</tr>
<tr>
<td>Relapse post-ASCT, n (%)</td>
<td>0</td>
<td>13 (31)</td>
<td>21 (21)</td>
</tr>
</tbody>
</table>

- There were patients in each response group with high tumor burden (Table 1)
- No clinically meaningful differences in baseline characteristics were observed between Month 3 response groups

\(^a\)Index lesion SPD may not represent the totality of a patient’s disease.
2L, second-line; ASCT, autologous stem cell transplantation; CR, complete response; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PD, progressive disease; PR, partial response; SPD, sum of product diameters.
Results

Figure 6. PFS by Response at Month 3

Data represent the response to a single dose of axi-cel, and patients were censored at PD or subsequent anticancer therapy. CR, complete response; NR, not reached; PD, disease progression; PFS, progression-free survival; PR, partial response.
Table 2. Landmark Analysis of PFS Over Time by Response at Month 3

<table>
<thead>
<tr>
<th>Response at Month 3</th>
<th>PR (n=9)</th>
<th>CR (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Month</td>
<td>78 (36-94)</td>
<td>88 (74-95)</td>
</tr>
<tr>
<td>9-Month</td>
<td>78 (36-94)</td>
<td>83 (68-92)</td>
</tr>
<tr>
<td>12-Month</td>
<td>78 (36-94)</td>
<td>79 (63-88)</td>
</tr>
</tbody>
</table>

- Similar progression-free survival was observed in patients who achieved PR or CR by Month 3 (Table 2)
- Patients in response at Month 3 have an 80% likelihood of maintaining response at Month 12

CR, complete response; PFS, progression-free survival; PR, partial response
Results

Table 3. Summary of Safety by Response at Month 3

<table>
<thead>
<tr>
<th></th>
<th>Response at Mont 3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (n=9)</td>
<td>CR (n=42)</td>
</tr>
<tr>
<td>PFS Rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All adverse events</td>
<td>9 (100)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>9 (100)</td>
<td>39 (93)</td>
</tr>
<tr>
<td>CRSa</td>
<td>9 (100)</td>
<td>39 (93)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Neurologic eventsb</td>
<td>7 (78)</td>
<td>28 (67)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3 (33)</td>
<td>15 (36)</td>
</tr>
</tbody>
</table>

Similar rates of cytokine release syndrome and neurologic events were observed across all response groups (Table 3)

aCRS was graded per a modified grading system proposed by Lee DW, et al.5 Neurologic events were graded per CTCAE v 4.03. CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; PR, partial response
Conclusions

- Treatment with axi-cel induces durable, high response rates in patients with refractory large B cell lymphoma
- Rates of objective response and CR increased through the long-term follow-up
  - Patients can achieve CR as late as 1 year post-infusion
- Patients in response at month 3 have an 80% likelihood of maintaining response at Month 12
- Response to axi-cel, either PR or CR, by 3 months may be prognostic for long-term remission
References

3. YESCARTA® (axicabtagene ciloleucel) [Prescribing Information]. Santa Monica, CA, USA: Kite Pharma; 2017.

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