Biomarker Analysis of Tisagenlecleucel Preinfusion Biopsies of Adult Patients With Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)


Introduction
Tisagenlecleucel was recently approved by the US Food and Drug Administration for the treatment of adults with relapsed or primary refractory (r/r) diffuse large B-cell lymphoma (DLBCL) – the safety and efficacy of tisagenlecleucel in adults with r/r DLBCL is being evaluated in the global JULIET trial (NCT02442540).

Tisagenlecleucel is an autologous chimeric antigen receptor (CAR) T-cell therapy that targets and kills CD19-expressing cells.

- The relationship between expression of CD19 on tumor cells and tisagenlecleucel efficacy has not been reported.
- The immunosuppressive tumor microenvironment has been shown to cause T-cell exhaustion and may therefore inhibit the cytotoxic effector mechanisms of CAR T cells.

Methods
- Biomarker analyses were conducted in archival, formalin-fixed, paraffin-embedded tumor and/or biopsy samples collected prior to infusion.
- Images were analyzed using novel algorithms based on AQUA® Technology (NanoLog Biopharma Services Inc., a Novartis subsidiary, Boston, CT) to evaluate relative levels of CD19 expression, the total number of PD-L1+ cells, and the total number of CD3+ T cells.
- Positivity for immune checkpoint molecules (PD-L1, LAG3, TIM3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM3) may impact the tumor’s response to treatment.

- The aim of this study was to explore the potential correlation between tisagenlecleucel efficacy and CD19 and immune checkpoint protein expression in preinfusion biopsies of patients with DLBCL.

Results
- No apparent differences were observed among the best overall response (BOR) groups (CR, PR, SD, PD, unknown) in median or mean levels of PD-L1/PD-1 interaction scores (Figure 2).
- However, the 5 patients with the highest PD-L1/PD-1 interaction scores either did not respond to tisagenlecleucel or were PD (n = 4) or relapsed by month 3 (n = 1).

Figure 1. Best Overall Response and Expression of CD19 (n = 72)

Conclusions
- These preliminary results from the evaluation of biomarkers indicate similar response rates across all CD19 expression levels.
- Furthermore, a small subset of patients with the highest PD-L1/PD-1 interaction scores, highest proportion of PD-1+ cells, and a high proportion of LAG3+ T cells among T cells present seem to not respond to tisagenlecleucel or have early relapse.
- No clear absence of response or early relapse was observed in patients in the low/unknown proportion of T cells because the percentage of T cells that much lower than the percentage of PD-L1+ cells.
- Furthermore, a small subset of patients with the highest PD1/PD/hyphen.capL1 Interaction Score (CR, PR, SD, PD, unknown) in median or mean levels of LAG3+ T cells (Figure 3).

Figure 2. PD-L1/PD-1 Interaction Score in Baseline Biopsies By Best Overall Response, Month 3 Response, and Month 6 Response (n = 74)

Figure 3. Percentage of LAG3+ T Cells in Baseline Biopsies By Best Overall Response, Month 3 Response, and Month 6 Response (n = 69)

Figure 4. Percentage of PD1+ Cells in Baseline Biopsies By Best Overall Response, Month 3 Response, and Month 6 Response (n = 89)

Figure 5. Percentage of PD1+ Cells in the Total Number of Cells and CD3+ T Cells By Best Overall Response and Month 3 Response

Figure 6. Percentage of TIM3+ T Cells in Baseline Biopsies By Best Overall Response, Month 3 Response, and Month 6 Response (n = 69)

Table 1. Overall Response Rates in Patients With CD19-Positive Tumors and in Patients With Low/Negative CD19 Tumor Expression

<table>
<thead>
<tr>
<th>Tumor Expression</th>
<th>Patients #</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>Unknown (%)</th>
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<tbody>
<tr>
<td>CD19 (pos)</td>
<td>49 (24-64)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>11 (22%)</td>
<td>6 (22%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>CD19 (neg)</td>
<td>23 (11-33)</td>
<td>5 (21%)</td>
<td>2 (8%)</td>
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References

Acknowledgments
- Editorial assistance was provided by Liz Gooch, PhD (Articulate Science LLC) and was supported by Novartis Pharmaceuticals Corporation.

Disclosures
- RA – Employment, Novartis Institutes for BioMedical Research; Research and Astellas. PJH – Honoraria, Membership on entity’s BOD/AC, Novartis Pharmaceuticals Corporation, Amgen, and Pfizer; Travel, accommodations or expenses, Novartis Pharmaceuticals Corporation and Jazz Pharmaceuticals.
- SRF – Honoraria, Celgene, Novartis Pharmaceuticals Corporation, and Amgen; Consulting or Advisory role, Seattle Genetics; Speakers bureau; Celgene, Merck, and equity ownership, Novartis Pharmaceuticals Corporation. RA – Employment, Novartis Institutes for BioMedical Research; Membership on an entity’s Board of Directors or advisory committees, Seattle Genetics, Kite Pharma and Zymogen. KvB – Nothing to disclose. DZ – Employment, Novartis Pharmaceuticals Corporation and Oxis, Inc.; Membership on an entity’s Board of Directors or advisory committees, Seattle Genetics, Kite Pharma and Zymogen. Cell, and Pluristem Ltd. SRF – Honoraria, Celgene, Novartis Pharmaceuticals Corporation, and Amgen; Consulting or Advisory role, Seattle Genetics, Kite Pharma and Zymogen. Cell, and Pluristem Ltd. SRF – Honoraria, Celgene, Novartis Pharmaceuticals Corporation, and Amgen; Consulting or Advisory role, Seattle Genetics, Kite Pharma and Zymogen. Cell, and Pluristem Ltd. SRF – Honoraria, Celgene, Novartis Pharmaceuticals Corporation, and Amgen; Consulting or Advisory role, Seattle Genetics, Kite Pharma and Zymogen. Cell, and Pluristem Ltd. SRF – Honoraria, Celgene, Novartis Pharmaceuticals Corporation, and Amgen; Consulting or Advisory role, Seattle Genetics, Kite Pharma and Zymogen. Cell, and Pluristem Ltd.

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No apparent differences were observed among the best overall response (BOR) groups (CR, PR, SD, PD, unknown) in median or mean levels of LAG3+ T cells.

Also, no apparent differences were observed among the BOR groups (CR, PR, SD, PD, unknown) in median or mean levels of PD1+ cells.

Figure 4. Percentage of PD1+ Cells in Baseline Biopsies By Best Overall Response, Month 3 Response, and Month 6 Response (n = 89)

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No apparent differences were observed between BOR groups and the percentage of cells expressing TIM3+ (Figure 6).

No clear absence of response or early relapse was observed in patients with the highest proportions of TIM3+ T cells (among total T cells present).

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