

Cellular Kinetics, Safety, and Efficacy of Zamtocabtagene Autoleucel, a Tandem CD20-CD19 CAR-T Cell Therapy, in Patients with Relapsed/Refractory B-Cell Lymphomas from the DALY 1 and DALY 2-EU Studies

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INTRODUCTION

- Randomized studies in transplant-eligible patients have demonstrated the efficacy of anti-cluster of differentiation (CD)19 chimeric antigen receptor (CAR)-T cell therapies as second-line treatment for relapsed/refractory (r/r) large B-cell lymphoma (LBCL).^{1,2}
 - Additional evidence is needed to further establish the role of CAR-T cell therapies in transplant-ineligible patients.³⁻⁶
- Zamtocabtagene autoleucel (zamto-cel) is an autologous, non-cryopreserved, tandem CD20-CD19 directed CAR-T cell therapy with a fixed 12-day manufacturing window and a vein-to-vein time of approximately 14 to 15 days.^{2,8}

AIMS

- To evaluate the cellular kinetics (CK), efficacy, and safety of zamto-cel from the DALY 1 and DALY 2-EU studies.

METHODS

DALY 1: Study Design and Patient Population⁹

- Prospective, first-in-human, multicenter, open-label, Phase I trial.
- Included 12 patients with r/r CD20- and CD19-positive B-cell non-Hodgkin lymphoma.
- Two dose levels (DL) of zamto-cel were investigated: 1.0×10⁶ cells/kg body weight (BW; DL1) and 2.5×10⁶ cells/kg BW (DL2; n=6 for both).
- Primary endpoint: maximum tolerated dose of zamto-cel.

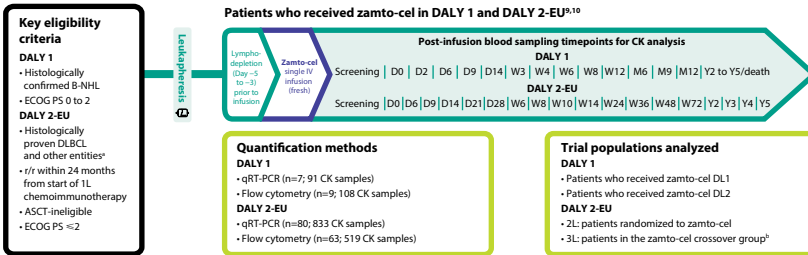
DALY 2-EU: Study Design and Patient Population¹⁰

- Multicenter, randomized, open-label, Phase II trial.
- Included adult patients (aged ≥18 years) with r/r LBCL with Eastern Cooperative Oncology Group performance status ≤2 and one transplant-ineligibility criterion.
- Patients were randomized 1:1 to 2.5×10⁶ cells/kg BW zamto-cel (n=82) or standard of care (SoC; rituximab-gemcitabine-oxaliplatin [R-GemOx; n=78] or polatuzumab vedotin-bendamustine-rituximab [Pola-BR; n=8]).
 - After a protocol amendment, patients in the SoC arm were eligible to cross over to zamto-cel if they relapsed or progressed within ≤1 year of randomization, or failed to achieve a partial response in ≥8 weeks or complete response (CR) at end of treatment.
- Primary endpoint: event-free survival (EFS).

CK Analysis (Figure 1)

- Patients who met the eligibility criteria of DALY 1 and DALY 2-EU and received zamto-cel were included in this analysis.
 - This included patients from DALY 2-EU who had a one-sided crossover from SoC to zamto-cel as third-line treatment.
- CK was assessed via quantitative reverse-transcription polymerase chain reaction (qRT-PCR) and flow cytometry.

Figure 1. DALY 1 and DALY 2-EU: CK Analysis Methods



1/2/3L, first/second/third-line; ASCT, autologous stem-cell transplant; BCL, B-cell lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; CK, cellular kinetics; D, day; DL, dose level; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBL, high-grade B-cell lymphoma; IV, intravenous; M, month; MYC, myelocytomatosis viral oncogene; NOS, not otherwise specified; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; r/r, relapsed/refractory; W, week; Y, year; zamto-cel, zamtocabtagene autoleucel.

*As per the 4th World Health Organization classification (2016), the following entities could be included: DLBCL NOS, HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL/blastoid/intermediate histology or HGBL with MYC and BCL2 and/or BCL6 rearrangements (double hit lymphoma/triple hit lymphoma), high-grade BCL NOS, primary (thymic) large mediastinal BCL, disease transformed from an earlier diagnosis of low-grade lymphoma (e.g., an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with DLBCL disease progression subsequent to DLBCL-directed systemic treatment, and follicular lymphoma Grade 3B; *Patients in the comparator arm of DALY 2-EU could cross over to zamto-cel if they relapsed or progressed within ≤1 year of randomization, or failed to achieve a partial response in ≥8 weeks or complete response at end of treatment.

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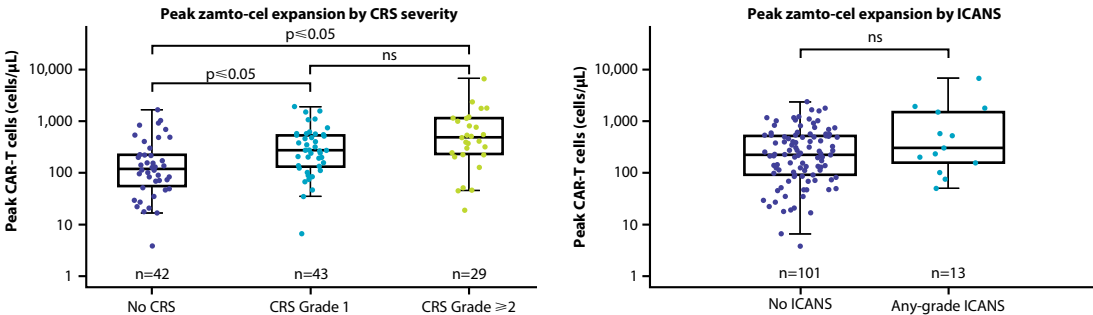
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RESULTS

Summary of Results from DALY 1 and DALY 2-EU (Supplementary Figure 1)

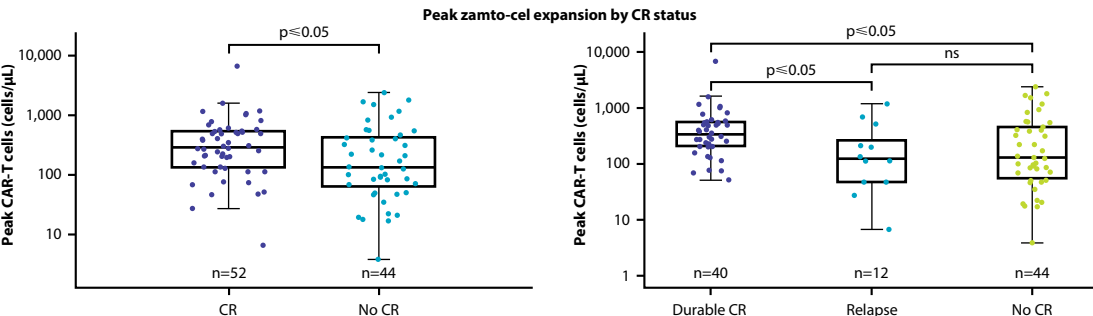
- DALY 1⁹:** Recommended dose of zamto-cel was 2.5×10⁶ CAR-T cells/kg BW.
- DALY 2-EU¹⁰:**
 - Zamto-cel demonstrated superior EFS (median 6.2 vs 2.5 months; hazard ratio 0.39 [95% confidence interval 0.27 to 0.58]; p<0.001) and improved best objective response (72.0 vs 44.9%) vs R-GemOx, as assessed by an independent review committee.
 - Low rates of Grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS; 1.3%) and cytokine release syndrome (CRS; 5.3%) were reported.

Figure 2. Peak Zamto-cel Expansion Stratified by CRS or ICANS



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ns, not significant; zamto-cel, zamtocabtagene autoleucel. Comparison of CAR-T cell concentrations in the first 28 days after infusion in participants who experienced no CRS, CRS Grade 1 or CRS Grade ≥2, and no ICANS or any-grade ICANS. Wilcoxon rank-sum tests were performed to assess statistically significant differences between the two groups.

Figure 3. Peak Expansion of Zamto-cel by CR Status



CAR, chimeric antigen receptor; CR, complete response; ns, not significant; zamto-cel, zamtocabtagene autoleucel. Comparison of peak zamto-cel concentration in the first 28 days after infusion in participants who achieved a durable CR, who subsequently relapsed, or who never achieved a CR in the first 9 months of treatment.

CK Analysis

- Strong congruence was observed between qRT-PCR and flow cytometry for all key pooled DALY 1 and DALY 2-EU CK analyses (Supplementary Figure 2 and Supplementary Table 1).

Safety

- Higher peak zamto-cel expansion was associated with developing CRS; no statistically significant differences were observed for ICANS (Figure 2).
- Patients with Grade ≥2 CRS had higher baseline inflammatory biomarkers (Supplementary Figure 3).

Efficacy

- Patients achieving a durable CR showed higher peak zamto-cel expansion than patients who subsequently relapsed and those who never achieved CR (Figure 3).
 - Additionally, the patients with durable CR had prolonged persistence of zamto-cel (Figure 4).
- Significantly lower baseline lactate dehydrogenase (LDH) was reported in patients who achieved durable CR vs those who did not; no significant difference in C-reactive protein and ferritin was observed (Figure 5).
- Durable CRs were observed across baseline tumor burden levels, but were more frequent in patients with peak zamto-cel expansion at or above the median (Figure 6).

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Zamtocabtagene autoleucel (zamto-cel) is an investigational product and is not approved for therapeutic use in any country.

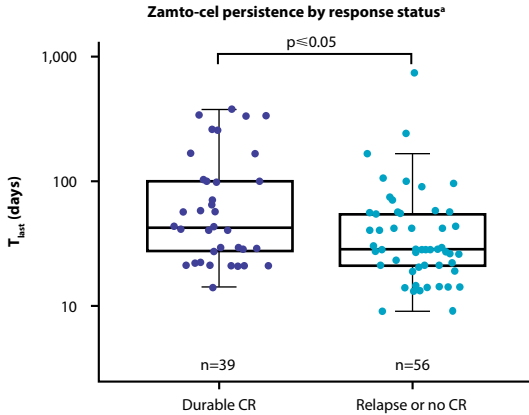
Disclosures

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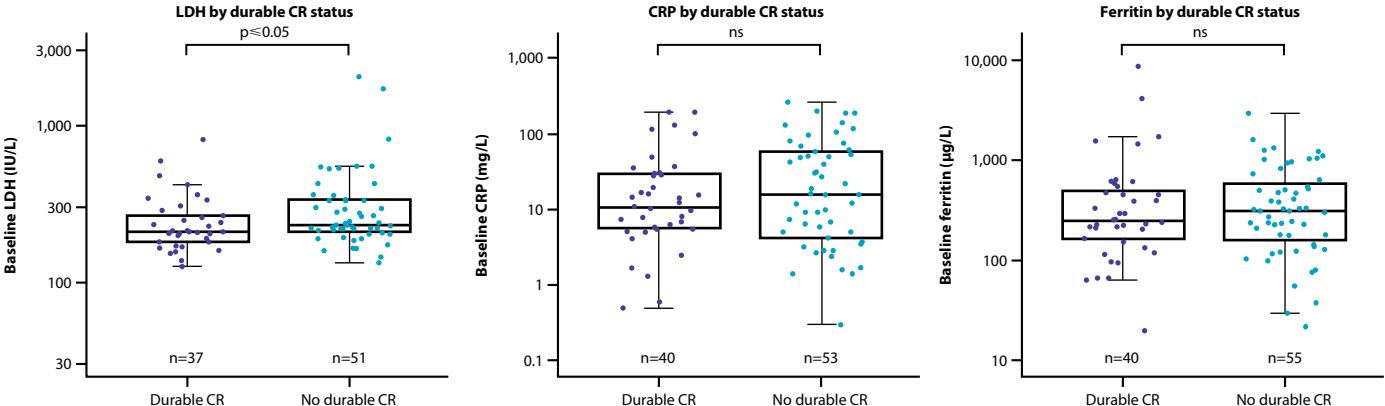
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Figure 4. Persistence and Blood Levels of Zamto-cel Stratified by Response Status



CAR, chimeric antigen receptor; CR, complete response; T_{max}, time of last quantifiable CAR-T cell concentration in peripheral blood; zamto-cel, zamtocabtagene autoleucel. *Durable CR status vs time of last quantifiable CAR-T cell concentration in peripheral blood (T_{max}) based on flow cytometry in the first 9 months after infusion; the p value was calculated using a Wilcoxon rank-sum test.

Figure 5. Durable CRs and Baseline Inflammatory Biomarkers



CR, complete response; CRP, C-reactive protein; LDH, lactate dehydrogenase; ns, not significant. Comparison of LDH, CRP, or ferritin concentrations at baseline in participants with or without a durable CR in the first 9 months after infusion. Wilcoxon rank-sum tests were performed to assess statistically significant differences between the two groups.

CONCLUSIONS

- Zamto-cel expansion was associated with an increased risk of CRS.**
- Durable CR was associated with longer persistence of CAR-T cells.**
- Lower baseline LDH was correlated with higher rate of durable CR.**
- Durable CR was observed across baseline tumor burden levels, and was more frequent in patients with a peak zamto-cel expansion at or above the median, supporting expansion as a key driver of long-term clinical benefit.**