Poster IBCL-195

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Primary Analysis of the Phase 2 ELARA Trial: Tisagenlecleucel Efficacy and Safety in Adult Patients With Relapsed/Refractory Follicular Lymphoma

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CONCLUSIONS

- As of September 28, 2020, tisagenlecleucel demonstrated high rates of durable responses with an ORR of 86% and CRR of 66%
- Data from the ELARA study suggest that tisagenlecleucel is effective in patients with r/r FL (including the high-risk subgroup)
- Safety data are consistent with the established favorable safety profile of tisagenlecleucel
  - No cases of high-grade CRS were reported
  - One case (1%) of high-grade neurotoxicity was reported
  - No treatment-related mortalities were observed
- The cellular kinetic analyses showed no apparent impact of dose on probability of CRS or NEs
- Tisagenlecleucel merits continued exploration as a therapy for the treatment of adult patients with r/r FL following ≥2 lines of therapy

INTRODUCTION

- Despite recent advancements, follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma in the Western world and remains incurable[1]
  - Approximately 20% of patients with FL experience disease recurrence within 2 years after first-line therapies[2,3]
  - Patients with relapsed or refractory (r/r) FL typically have worsening treatment outcomes with increasing lines of therapy, emphasizing an unmet need for new therapies
- Tisagenlecleucel is an autologous anti-CD19 chimeric antigen receptor (CAR)-T cell therapy
  - Approved for use in r/r pediatric and young adult acute lymphoblastic leukemia and r/r adult diffuse large B-cell lymphoma populations[4,5]
- The ELARA trial of tisagenlecleucel in adults with r/r FL met the primary endpoint (complete response rate) at the interim analysis[6]
- Here we report the primary analysis of the ELARA trial with a median follow-up of 10.9 months for efficacy and 10.6 months for safety

METHODS

Study Design

- ELARA is an international, multicenter study conducted at 32 sites in 12 countries across the United States, Europe, Japan, and Australia (ClinicalTrials.gov: NCT03568461; **Figure 1**)
- Central histologic confirmation of the diagnosis was performed at study entry
- All patients underwent leukapheresis; enrollment was complete when the cryopreserved material was received by the manufacturing facility and clinical eligibility was confirmed
- Bridging therapy was allowed at the investigator's discretion and disease status was reassessed prior to tisagenlecleucel infusion in all patients to establish a new baseline
- Before infusion, all patients received 1 cycle of lymphodepleting chemotherapy with either fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) daily for 3 days or bendamustine (90 mg/m^2) daily for 2 days
- Tisagenlecleucel was administered as a single intravenous (IV) infusion at the protocol-specified dose of 0.6-6×10^8 CAR-positive viable T cells on Day 1

Figure 1. ELARA Study Schema



[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IRC, Independent Review Committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Statistical Analysis

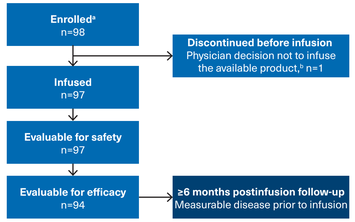
- Based on the null hypothesis of complete response rate (CRR) of 15% or less and assuming an underlying CRR of 30% for tisagenlecleucel, 90 patients in the primary analysis were required to provide at least 90% cumulative power to demonstrate statistical significance, using a 2-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact CI at 1-sided cumulative 0.025 level of significance
- The primary analysis occurred after 90 patients had reached 6 months follow-up post infusion or had discontinued early
- Duration of response (DOR), progression-free survival (PFS), and overall survival were estimated using the Kaplan-Meier method
- Cellular kinetics were measured in the peripheral blood of evaluable patients by quantitative polymerase chain reaction

RESULTS

Patients

- As of September 28, 2020, 98 patients were enrolled and 97 patients with r/r FL received tisagenlecleucel (**Figure 2**)
- Median follow-up for infused set (n=97): 10.6 months (4.3-19.7 months)
- Median follow-up for efficacy set (n=94): 10.9 months (4.3-19.7 months)

Figure 2. Patient Disposition



[a]The median time from enrollment to infusion was 45 days (range, 22-126 days). [b]CR before infusion.
CR, complete response.

- Patient demographic and baseline disease characteristics are summarized in **Table 1**
  - 18% of patients received tisagenlecleucel infusion in an outpatient setting
  - Bridging therapy was administered for stabilization in 44% of patients
  - Median infused dose of tisagenlecleucel was 2.06×10^8 CAR+ viable T cells

Table 1. Demographics and Baseline Disease Characteristics

	All Patients (N=97)
Median age (range), y	57.0 (29-73)
≥65 y, n (%)	24 (24.7)
ECOG PS, n (%)	
0	56 (57.7)
1	37 (38.1)
2	4 (4.1)
Bulky disease at study entry,[a] n (%)	63 (64.9)
Stage at study entry III-IV, n (%)	82 (84.5)
FLIPI ≥3 at study entry, n (%)	58 (59.8)
Median no. of prior therapies (range)	4 (2-13)
≥5, n (%)	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy,[b] n (%)	58 (59.8)
Refractory to last line of therapy,[c] n (%)	76 (78.4)
Prior autologous HSCT, n (%)	35 (36.1)
Refractory to ≥2 regimens,[d] n (%)	74 (76.3)
Double refractory,[e] n (%)	67 (69.1)
Prior therapy	
Anti-CD20 mAb and alkylating agents,[f] n (%)	63 (64.9)
PI3K inhibitors, n (%)	20 (20.6)
Lenalidomide and rituximab, n (%)	16 (16.5)

[a]Disease burden, as defined by GELF criteria and includes a single nodal site ≥7 cm or 3 distinct nodal sites ≥3 cm. [b]Disease progression <24 months from initiation of first-line therapy, including primary refractory patients. [c]Refractory: Failure to respond to previous treatment or progression within 6 months of prior therapy completion. [d]Same regimen or different regimens. [e]Subjects who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen. [f]Treatment density was also measured and is defined as the time from initial diagnosis to study entry (y) over the number of prior therapies (median treatment density was 1.4 y).
ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplant; mAb, monoclonal antibody; PI3K, phosphatidylinositol 3-kinase; POD24, progression of disease within 24 months.

Efficacy

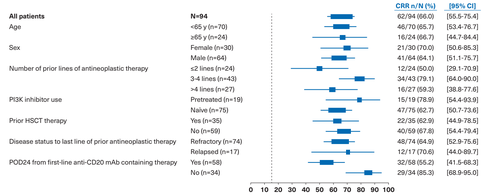
- CRR by Independent Review Committee was 66%; overall response rate (ORR) was 86% (**Table 2**)
  - Investigator-assessed CRR was 69.1% (95% CI, 58.8-78.3); ORR was 90.4%
  - CRR was consistent across subgroups (**Figure 3**)
    - CRRs/ORRs were comparable among key high-risk subgroups

Table 2. Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[a] (n=94)
CR	66.0
PR	20.2
ORR (CR+PR)	86.2

First efficacy assessment conducted at Month 3 (all but 1 responded at Month 3 assessment); probability of remaining in CR > Month 6. [a]P<0.0001; indicates statistical significance (1-sided) at the 0.0025 level so that the null hypothesis CRR ≤0.15 is rejected.
CI, confidence interval; CR, complete response; CRR, complete response rate; NE, not estimable; PR, partial response.

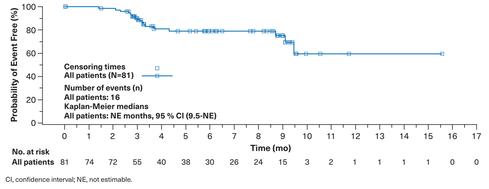
Figure 3. Complete Response Rate for Subgroups



CI, confidence interval; CRR, complete response rate; HSCT, hematopoietic stem cell transplant; ORR, overall response rate; PI3K, phosphatidylinositol 3-kinase; POD24, progression of disease within 24 months.

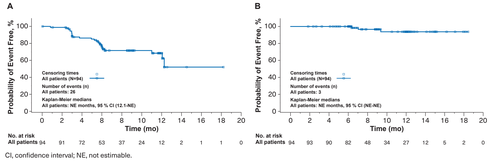
- Median DOR was not reached at 11-month median follow-up (**Figure 4**)
  - Median follow-up for efficacy (n=94): 10.9 months (4.3-19.7 months)
- Probability for a responding patient to remain in response ≥6 months was 79% (95% CI, 66-87)
- 12 of 31 partial responses (38.7%) converted to complete responses; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached

Figure 4. Duration of Response



CI, confidence interval; NE, not estimable.

Figure 5. Progression-Free Survival (A) and Overall Survival (B)



CI, confidence interval; NE, not estimable.

- Median PFS (95% CI, 12.1-NE) and overall survival (95% CI, NE-NE) were not reached (**Figure 5**)
- 6-month PFS was 76% (95% CI, 65-84)

Cellular Kinetics

- Cellular kinetic parameters for tisagenlecleucel were estimated using transgene levels in peripheral blood (n=94; **Table 3**)
- The persistence of CAR transgene was observed for up to 370 days in responding patients and 187 days in nonresponding patients, and is expected to increase with additional follow-up
- Probability of achieving response was comparable across dose quartiles
- No apparent impact of dose was observed on probability of cytokine release syndrome (CRS) or neurological events (NEs)

Table 3. Cellular Kinetic Parameters

Parameter	Responders CR/PR (N=81)[a]	Nonresponders SD/PD (N=12)
T_{max}, n	74	9
Median, d	167	126
T_{max}, n	71	9
Median, d	10	12.9
C_{max}, n	71	9
Geo-Mean (copies/µg),	5190	3000
Geo-CV%	447	1190
AUC_{0-28d}, n	68	5
Geo-Mean (copies/µg*d)	53,700	86,800
Geo-CV%	276	417

[a]One patient with an unknown response is excluded.
AUC_{0-28d}, area under the curve from Day 0-28; C_{max}, geometric mean estimate for expansion; CR, complete response; CRS, cytokine release syndrome; Geo-CV, geometric coefficient of variation; Geo-Mean, geometric mean; PR, partial response; PD, progressive disease; SD, stable disease; T_{max}, transgene persistence; T_{max}, time to maximal transgene expansion.

Safety

- Among 97 patients evaluable for safety, 99% experienced any-grade adverse events (AEs), and 76.3% experienced at least 1 grade 3 or higher AE during the study (**Table 4**)

Table 4. Overall Safety

Adverse Events, n (%)	Treated Patients (N=97)
Any AE (all grade)	96 (99.0)
AEs suspected to be drug-related	75 (77.3)
Any SAE	40 (41.2)
Suspected to be drug-related	28 (28.9)
Any grade 3/4 AE	74 (76.3)
Suspected to be drug-related	44 (45.4)
Death	3 (3.1)
Deaths due to study indication	3 (3.1)
Deaths within 30 days post infusion	0

AEs as per CTCAE v4.03. Median follow-up for safety (n=97): 10.6 months (4.3-19.7 months).
AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

- AEs of special interest that occurred within 8 weeks of tisagenlecleucel infusion are reported in **Table 5**
- 74.5% of the CRS events and 100% of immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in patients with bulky disease
- All neurological and CRS events resolved with appropriate management

Table 5. Adverse Events of Special Interest

AESI (within 8 weeks of infusion)	Treated Patients (N=97) All grades, %	Grade ≥3, %
Cytokine release syndrome[1,6]	48.5	0
Neurological adverse reactions	9.3	1
Infections	18.6	5.2
Tumor lysis syndrome	1	1
Prolonged depletion of B cells and/or agammaglobulinemia[b]	10.3	0
Hematologic disorders including cytopenias		
Neutropenia[c,d]	30.9	27.8
Anemia[c]	24.7	13.4
Thrombocytopenia[c]	16.5	9.3

[a]CRS was graded using the Lee scale 2014. [b]Prolonged depletion is defined as lasting >28 days. Agammaglobulinemia is defined as IgG <4 g/L. Patients were counted here if they had either B-cell depletion or agammaglobulinemia or both. [c]One of multiple preferred terms evaluated under the AESI. [d]Hematologic disorders including cytopenias. [e]Median duration of grade 3/4 neutropenia was 52 days (based on laboratory data).
AESI, adverse event of special interest; CRS, cytokine release syndrome.

- Any-grade CRS (Lee scale) occurred in 49% of patients (**Table 6**)
- Among patients with CRS, 34% of patients received tocilizumab and 6.4% received corticosteroids

Table 6. Cytokine Release Syndrome

Events,[a] n (%)	Treated Patients (N=97)
Patients with CRS[5,6]	47 (48.5)
Grade 1	27 (27.8)
Grade 2	20 (20.6)
Grade ≥3	0 (0)
CRS management	
Tocilizumab	16 (34)
Corticosteroids	3 (6.4)
Median time to onset, d (range)	4 (1-14)
Admitted to ICU, n (%)	4 (8.5)
Median total duration of ICU stay during CRS, d (range)	4 (2-5)
Patients with resolved events, n (%)	47 (100)

[a]Occurring within 8 weeks of tisagenlecleucel infusion. [b]CRS was graded using the Lee scale 2014.
CRS, cytokine release syndrome; ICU, intensive care unit.

- NEs occurred in 9 patients (**Table 7**)
- Median onset was 8.5 days (4-190 days[b])
- All NEs resolved for all patients; median time to resolution was 2 days
- Only 1 case of serious ICANS within the first 8 weeks

Table 7. Neurological Events

Events, n (%)	Treated Patients (N=97) All Grades	Grade 3	Grade 4
Number of patients with at least 1 event	9 (9.3)	0	1 (1.0)[a]
Encephalopathy	3 (3.1)	0	0
Immune effector cell-associated neurotoxicity syndrome	3 (3.1)	0	1 (1.0)
Tremor	2 (2.1)	0	0
Dyskinesia	1 (1.0)	0	0
Dysphagia	1 (1.0)	0	0
Muscular weakness	1 (1.0)	0	0
Neurotoxicity	1 (1.0)	0	0

[a]Grade 4 ICANS: Onset Day 10, recovered – Related to tisagenlecleucel. Patient presenting with tremors, then seizures, with concomitant HHV-6 positivity on CSF. The event fully recovered after high-dose MPD and GCV. [b]Grade 3 Delirium: Onset Day 190, recovered – Not related to tisagenlecleucel. Patient was in PD at the time of the event, with new anticancer therapy started.
CSF, cerebrospinal fluid; GCV, ganciclovir; HHV-6, human herpesvirus 6; MPD, methylprednisolone; PD, progressive disease.

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