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Four-Year Update of Phase 2 ELARA Trial: Clinical Outcomes of Tisagenlecleucel in Patients With High-Risk Relapsed/ Refractory Follicular Lymphoma

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KEY FINDINGS & CONCLUSIONS

- Updated long-term follow-up from the ELARA trial continues to demonstrate robust durable responses >4 years post infusion, alongside a favorable safety profile
- Subgroup analyses suggest that most baseline high-risk disease characteristics (double-refractory disease, bulky disease, POD24, and high FLIPI) are not associated with inferior CRR, 48-month PFS, or 48-month OS
  - Although lower CRR, 48-month PFS, and 48-month OS rates were reported for patients with high tumor burden, it is important to remember high-risk subgroup analyses were exploratory and some subgroups (ie, high tumor burden) had very limited patient numbers
- High frequencies of MRD-negative status were achieved among MRD-evaluable patients, showing that tisagenlecleucel therapy can achieve deep response in treated patients

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INTRODUCTION

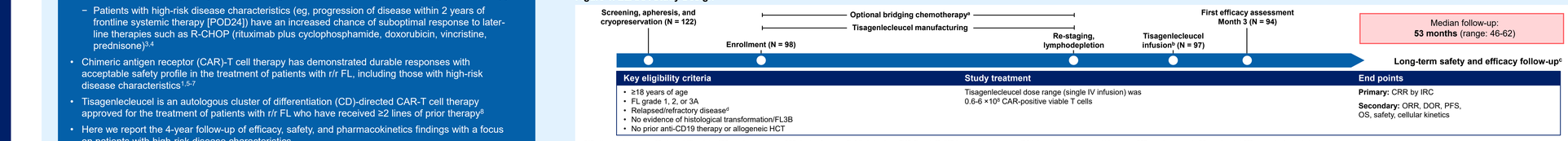
- Treatment strategies for patients with relapsed/refractory follicular lymphoma (r/r FL) require consideration of prior therapies and patient-related factors[1]
  - Patients with r/r FL typically have worsening treatment outcomes with increasing lines of therapy[2]
  - Patients with high-risk disease characteristics (eg, progression of disease within 2 years of frontline systemic therapy [POD24]) have an increased chance of suboptimal response to later-line therapies such as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone)[3,4]
- Chimeric antigen receptor (CAR)-T cell therapy has demonstrated durable responses with acceptable safety profile in the treatment of patients with r/r FL, including those with high-risk disease characteristics[1,5-7]
- Tisagenlecleucel is an autologous cluster of differentiation (CD)-directed CAR-T cell therapy approved for the treatment of patients with r/r FL who have received ≥2 lines of prior therapy[8]
- Here we report the 4-year follow-up of efficacy, safety, and pharmacokinetics findings with a focus on patients with high-risk disease characteristics

METHODS

Study design

- ELARA study design, including eligibility criteria and key end points, can be found in **Figure 1**

Figure 1. ELARA Study Design



CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; FL3B, FL grade 3B; HCT, hematopoietic cell transplant; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[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]Every 3 months until month 12, and every 6 months until end of study. [d]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.

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- Cellular kinetics were determined by measurement of transgene levels by quantitative polymerase chain reaction
- Minimal residual disease (MRD) levels were determined via clonoSEQ® next-generation sequencing assay performed at Adaptive Biotechnologies (Seattle, WA, USA)

RESULTS

Baseline Characteristics

- As of March 27, 2024, 97 patients were infused; 94 patients were evaluable for efficacy with a median follow-up of 53 months (range: 46-62)
  - The last patient in the ELARA trial was infused May 22, 2020
- Baseline and primary disease characteristics of the infused set can be found in **Table 1**
  - Median age was 57 years (range: 29-73), with 25% of infused patients ≥65 years of age
  - Median number of prior therapies was 4 (range: 2-13)
  - Thirty-six percent of patients received a prior autologous hematopoietic cell transplant (HCT)
  - Seventy-eight percent of patients were refractory to the last line of therapy
- Key patient subgroups at high risk among efficacy-evaluable patients (N = 94):
  - Disease refractory to ≥2 prior regimens: 72%
  - Bulky disease (>7 cm or at least 3 lesions >3 cm): 66%
  - POD24 from first anti-CD20 monoclonal antibody (mAb)-containing therapy: 65%
  - High Follicular Lymphoma International Prognostic Index (FLIPI; ≥3): 61%
  - High tumor burden (total metabolic tumor volume >510 mL[b]): 21%

Table 1. Disease History and Baseline Patient Characteristics

	Infused set (N = 97), n (%)
Median age (range), years	57.0 (29-73)
18 to <65 years	73 (75)
≥65 years	24 (25)
ECOG PS ≥1 prior to infusion	42 (43)
Stage at study entry III-IV	83 (86)
Bone marrow involvement	37 (38)
Bulky disease[a]	63 (65)
FLIPI high at study entry (≥3)	58 (60)
Median no. of prior therapies (range)	4 (2-13)
POD24[b]	61 (63)
Refractory disease to last line of therapy	76 (78)
Refractory to ≥2 regimens	69 (71)
Double refractory: anti-CD20 mAb + alkylating agent	66 (68)
Refractory to PI3K inhibitors	14 (14)
Prior autologous HCT	35 (36)

CD, cluster of differentiation; ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; HCT, hematopoietic cell transplant; mAb, monoclonal antibody; PI3K, phosphatidylinositol-3-kinase; POD24, progression of disease within 2 years of frontline systemic therapy.
[a]Bulky disease defined as 1 lesion >7 cm or at least 3 lesions >3 cm.
[b]POD24 from first anti-CD20 mAb-containing therapy or rituximab monotherapy.

Safety

- No new safety signals were reported since the last data cut. Adverse events (AEs) of special interest can be found summarized by timing post infusion in **Table 2**
  - Among the 47 patients who experienced cytokine release syndrome (CRS), all first events occurred within 8 weeks after infusion. Two patients experienced a second late onset CRS event; one in the context of a new anticancer therapy
  - Most cytopenias had their onset in the first-year post infusion
  - Rates of infections (including grade 3) increased over time

Table 2. AEs of Special Interest by Timing After Tisagenlecleucel Infusion

	Infused set (N = 97), n (%)					
	Within 8 weeks of infusion		>8 weeks to 1 year post infusion		>1 year post infusion	
Preferred term	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients with at least one AE	88 (90.7)	68 (70.1)	70 (72.9)	42 (43.8)	38 (45.2)	24 (28.6)
Patients with at least one infection[a]	20 (20.6)	6 (6.2)	37 (38.5)	12 (12.5)	31 (36.9)	16 (19.0)
Cytokine release syndrome	47 (48.5)	0	1 (1.0)	0	1 (1.2)	1 (1.2)
Cytopenias						
Neutropenia	33 (34.0)	32 (33.0)	21 (21.9)	18 (18.8)	5 (6.0)	5 (6.0)
Neutrophil count decreased	15 (15.5)	15 (15.5)	7 (7.3)	7 (7.3)	2 (2.4)	1 (1.2)
Anemia	23 (23.7)	13 (13.4)	7 (7.3)	5 (5.2)	4 (4.8)	3 (3.6)
Thrombocytopenia	15 (15.5)	9 (9.3)	8 (8.3)	5 (5.2)	3 (3.6)	2 (2.4)
Platelet count decreased	7 (7.2)	4 (4.1)	4 (4.2)	2 (2.1)	0	0
White blood cell count decreased	18 (18.6)	13 (13.4)	12 (12.5)	7 (7.3)	2 (2.4)	0
Leukopenia	7 (7.2)	7 (7.2)	3 (3.1)	3 (3.1)	1 (1.2)	0
Febrile neutropenia	10 (10.3)	10 (10.3)	2 (2.1)	2 (2.1)	2 (2.4)	2 (2.4)
Lymphocyte count decreased	10 (10.3)	8 (8.2)	2 (2.1)	0	0	0
Lymphopenia	6 (6.2)	6 (6.2)	4 (4.2)	4 (4.2)	1 (1.2)	1 (1.2)
Hypogammaglobulinemia	9 (9.3)	0	7 (7.3)	1 (1.0)	2 (2.4)	0
Patients with at least one serious neurological AE	10 (10.3)	1 (1.0)	2 (2.1)	2 (2.1)	2 (2.4)	1 (1.2)

AE, adverse event.
[a]Grade ≥3 infections reported within 8 weeks of infusion included bacteremia, *Campylobacter* infection, *Escherichia* sepsis, human herpesvirus 6 encephalitis, neutropenic sepsis, pseudomonal sepsis, and staphylococcal sepsis. Grade ≥3 infections reported >8 weeks to 1 year post infusion included pneumonia, COVID-19, lower respiratory tract infection, tooth infection, coronavirus pneumonia, diverticulitis, pneumonia influenza, progressive multifocal leukoencephalopathy, pseudomonal bacteremia, and sepsis. Grade ≥3 infections reported >1 year post infusion included COVID-19, pneumonia, sinusitis, COVID-19 pneumonia, encephalitis, infection, pneumonia respiratory syncytial viral, rhinovirus infection, sepsis, skin infection, and varicella zoster virus infection.

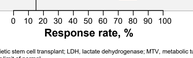
- Second primary malignancies (defined as any new cancer occurring post infusion regardless of tisagenlecleucel relationship) were reported in 6 patients (6.2%) and included basal cell carcinoma (N = 2), squamous cell carcinoma (N = 2), acute myeloid leukemia (N = 1), bladder transitional cell carcinoma (N = 1), Bowen's disease (N = 1), malignant melanoma (N = 1), metastatic squamous cell carcinoma (N = 1), and myelodysplastic syndrome (N = 1)
- As of data cutoff, 19 patients have died during the study: 8 due to progressive disease, 10 due to AEs (1 patient each; acute myeloid leukemia, bladder transitional cell carcinoma, cardiac arrest, CRS, encephalitis, gastrointestinal hemorrhage, infection, metastatic squamous cell carcinoma, pneumonia, and sepsis), and 1 from euthanasia

Efficacy

- Subgroup analyses suggest that most baseline high-risk disease characteristics (double-refractory disease, bulky disease, POD24, and high FLIPI) were not associated with inferior overall or complete response following tisagenlecleucel infusion in patients with r/r FL (**Figure 2**)

Figure 2. Complete Response Rate by Subgroups

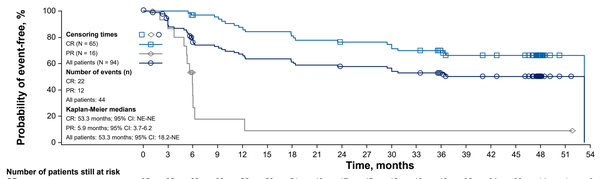
		CRR, n/N (%)	[95% CI]
All patients	All patients (N = 94)	65/94 (69.1)	[58.8-78.3]
Age	<65 years (N = 70)	46/70 (65.7)	[53.4-76.7]
	≥65 years (N = 24)	19/24 (79.2)	[57.8-92.9]
Sex	Female (N = 30)	22/30 (73.3)	[54.1-87.7]
	Male (N = 64)	43/64 (67.2)	[54.3-78.4]
Race	Asian (N = 11)	9/11 (81.8)	[8.2-97.7]
	White (N = 79)	54/79 (68.4)	[56.9-78.4]
Ethnicity	Not Hispanic or Latino (N = 87)	60/87 (69.0)	[58.1-78.5]
FLIPI at study entry	Low/Intermediate (N = 37)	29/37 (78.4)	[61.8-90.2]
	High (N = 57)	36/57 (63.2)	[49.3-75.6]
Histological grade	1-2 (N = 85)	59/85 (69.4)	[58.5-79.0]
	3A (N = 9)	6/9 (66.7)	[29.9-92.5]
Number of prior lines	≤2 lines (N = 24)	14/24 (58.3)	[36.6-77.9]
	3-4 lines (N = 43)	35/43 (81.4)	[66.6-91.6]
	>4 lines (N = 27)	16/27 (59.3)	[38.8-77.6]
PI3K inhibitor use	Pre-treated (N = 19)	15/19 (78.9)	[54.4-93.9]
	Naive (N = 75)	50/75 (66.7)	[54.8-77.1]
Prior HSCT therapy	Yes (N = 35)	22/35 (62.9)	[44.9-78.5]
	Relapsed ≤12 months (N = 14)	10/14 (71.4)	[41.9-91.6]
	Relapsed >12 months (N = 21)	12/21 (57.1)	[34.0-78.2]
	No (N = 59)	43/59 (72.9)	[59.7-83.6]
Disease status to last line	Refractory (N = 74)	52/74 (70.3)	[58.5-80.3]
	Relapsed (N = 17)	11/17 (64.7)	[38.3-85.8]
POD24	Yes (N = 61)	37/61 (60.7)	[47.3-72.9]
	No (N = 33)	28/33 (84.8)	[68.1-94.9]
Bulky disease at baseline	Yes (N = 62)	41/62 (66.1)	[53.0-77.7]
	No (N = 32)	24/32 (75.0)	[56.6-88.5]
Bridging therapy	Yes (N = 44)	29/44 (65.9)	[50.1-79.5]
	No (N = 50)	36/50 (72.0)	[57.5-83.8]
LDH at study entry	≤ULN (N = 53)	39/53 (73.6)	[59.7-84.7]
	>ULN (N = 41)	26/41 (63.4)	[46.9-77.9]
Prior R2 use	Pre-treated (N = 16)	12/16 (75.0)	[47.6-92.7]
	Naive (N = 78)	53/78 (67.9)	[56.4-78.1]
US sites	Yes (N = 26)	17/26 (65.4)	[44.3-82.8]
	No (N = 68)	48/68 (70.6)	[58.3-81.0]
Double refractory	Yes (N = 65)	44/65 (67.7)	[54.9-78.8]
	No (N = 29)	21/29 (72.4)	[52.8-87.3]
MTV at baseline	High tumor burden (N = 20)	8/20 (40.0)	[19.1-63.9]
	Low tumor burden (N = 72)	55/72 (76.4)	[64.9-85.6]



CRR, complete response rate; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; MTV, metabolic tumor volume; PI3K, phosphatidylinositol-3-kinase; POD24, progression of disease within 2 years of frontline systemic therapy; R2, lenalidomide + rituximab; ULN, upper limit of normal.

- The estimated 48-month progression-free survival (PFS) was 50.2% as assessed by independent review committee (IRC) (**Figure 3**)
  - Patients who had a best overall response of complete response had a 48-month probability of PFS of 66.1%
  - Among patient subgroups at high risk, 48-month PFS by IRC was 45.5% (POD24), 45.5% (high FLIPI), 45.2% (bulky disease), 52.8% (double-refractory), and 23.2% (high tumor burden)

Figure 3. Progression-Free Survival



CR, complete response; NE, not estimable; PR, partial response.

- Median overall survival (OS) was not reached as assessed by IRC (**Figure 4**); 48-month OS was 79.3% in efficacy-evaluable patients
  - Among patient subgroups at high risk, 48-month OS by IRC was 80.8% (POD24), 73.2% (high FLIPI), 73.0% (bulky disease), 83.7% (double-refractory), and 65.5% (high tumor burden)

Figure 4. Overall Survival

CR, complete response; NE, not estimable; PR, partial response.

- Median time to next treatment among all patients and patients with a best overall response of complete response was not reached (**Figure 5**)

Figure 5. Time to Next Treatment

CR, complete response; NE, not estimable; PR, partial response.

- MRD data were available for 31 of 94 patients (33.0%)
  - 90.3% of evaluable patients (28/31) achieved MRD negativity at any time point (**Table 3**)
  - 63.6% of patients with MRD-negative status at month 6 (7/11) are ongoing without relapse
  - All 5 patients with MRD-positive status at month 6 relapsed

Table 3. MRD-Negative Rate by Timing After Tisagenlecleucel Infusion

	MRD-negative (N = 31[a]), % (n/N)
Day 28	82.0 (22/27)
Month 3	75.0 (12/16)
Month 6	69.0 (11/16)
Month 12	76.0 (13/17)
Any time	90.0 (28/31)

MRD, minimal residual disease.
[a]Patients evaluated for MRD response.

- CAR transgene persistence was observed for up to 1680 days; median Tlast (time to last measurable concentration) was 210 days (range: 13-1680)

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