UPDATED CLINICAL RESULTS FROM THE ALLELE TRIAL: A MULTICENTER, OPEN-LABEL, PHASE 3 STUDY OF TABELECLEUCEL FOR SOLID ORGAN OR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS WITH EPSTEIN–BARR VIRUS-DRIVEN POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE AFTER FAILURE OF RITUXIMAB OR RITUXIMAB PLUS CHEMOTHERAPY

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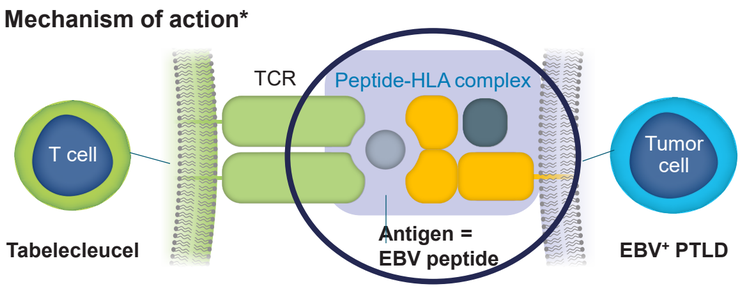
INTRODUCTION

- Patients undergoing allogeneic hematopoietic cell transplant (HCT) or solid organ transplant (SOT) are at risk of developing Epstein–Barr virus-positive (EBV⁺) posttransplant lymphoproliferative disease (PTLD)[1-3]
- Currently, initial treatments for EBV⁺ PTLD include reduction in immunosuppression and anti-CD20 antibody (rituximab [RTX]) ± chemotherapy (CT),[1,4] but response rates are variable
- The reported median overall survival (OS) rates—0.7 months for allogeneic HCT and 4.1 months for SOT—in patients with EBV⁺ PTLD who did not respond to RTX ± CT highlight a critical and urgent unmet need in this patient population[5-7]

Tabelecleucel Is a Novel Treatment for EBV⁺ PTLD After Failure of RTX ± CT[8]

- Tabelecleucel is an off-the-shelf, non–genetically modified, allogeneic, EBV-specific, T-cell immunotherapy that targets and eliminates EBV-infected cells in a human leukocyte antigen (HLA)-restricted manner
- Tabelecleucel has been investigated in multiple EBV-associated malignancies[9]

Mechanism of action*



Manufacturing
Derived from unrelated third-party healthy donors and cryopreserved in a biobank adapted to cover multiple HLA profiles

Product selection
Based on the characterization of HLA restriction and donor:recipient compatibility

Administration
No lymphodepletion or premedication needed; 1-hour postinjection monitoring; can be administered in both inpatient and outpatient settings

*Tabelecleucel is a polyclonal T-cell population enriched for the recognition of EBV antigens, with a variable CD8+/CD4+ ratio.
CD, cluster of differentiation; EBV, Epstein-Barr virus; EBV⁺, Epstein–Barr virus-positive; HLA, human leukocyte antigen; PTLD, posttransplant lymphoproliferative disease; TCR, T-cell receptor.

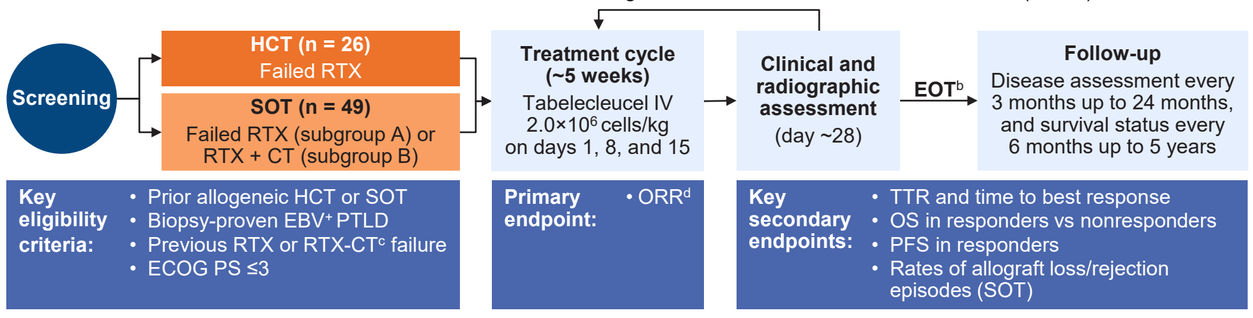
- The ALLELE study is an ongoing, phase 3 study investigating the efficacy and safety of tabelecleucel after failure of RTX ± CT in patients with EBV⁺ PTLD following HCT or SOT[10]
  - Results were previously reported in 43 patients (14 HCT; 29 SOT) with EBV⁺ PTLD[10]
    - The objective response rate (ORR) was 50% in the HCT group and 52% in the SOT group
    - Tabelecleucel had a well-tolerated safety profile
- Based on interim data from ALLELE, tabelecleucel was approved in Europe in December 2022[8]

Objective: To provide updated efficacy and safety data from the ALLELE study in a larger EBV⁺ PTLD patient population (N = 75; 26 HCT; 49 SOT)

METHODS

- The ALLELE study (NCT03394365) is an ongoing, global, multicenter, open-label, phase 3 study of tabelecleucel after failure of RTX ± CT in patients with EBV⁺ PTLD following HCT or SOT[10]
  - Patients received tabelecleucel at 2×10⁶ cells/kg on days 1, 8, and 15 in 35-day cycles
  - Responses were evaluated by independent oncologic response adjudication (IORA; primary assessment) using Lugano Classification with Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification
  - Patients were assessed up to 5 years
  - Data cutoff date: October 9, 2023

Patients receive additional treatment cycles until best response is achieved. In cases of nonresponse, patients may be administered tabelecleucel using a T-cell line with different HLA restrictions (switch)[a]



[a]Patients may receive up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions. [b]Defined as any of the following: maximal response achieved; unacceptable toxicity; initiation of nonprotocol therapy; or failure of up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions. [c]Including R-CHOP. [d]Evaluated by independent review.
CT, chemotherapy; EBV⁺, Epstein–Barr virus-positive; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PTLD, posttransplant lymphoproliferative disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RTX, rituximab; SOT, solid organ transplant; TTR, time to response.

RESULTS

Baseline Demographics and Disease Characteristics

Demographics	HCT (n = 26)	SOT (n = 49)	All (N = 75)
Age, median (range), years	49.3 (3.2–73.2)	42.8 (2.7–81.5)	44.4 (2.7–81.5)
Male sex, n (%)	15 (57.7)	29 (59.2)	44 (58.7)
ECOG PS score, median (range)[a]	1 (0–3)	1 (0–3)	1 (0–3)
ECOG PS score ≥2, n (%)[b]	6 (24)	12 (27.9)	18 (26.5)
Disease characteristics			
Extranodal disease at screening, n (%)	16 (61.5)	40 (81.6)	56 (74.7)
PTLD-adapted prognostic index, n (%)[c]	n = 25	n = 43	N = 68
High risk	12 (48.0)	17 (39.5)	29 (42.6)
Intermediate risk	13 (52.0)	21 (48.8)	34 (50.0)
Low risk	0	4 (9.3)	4 (5.9)
Unknown	0	1 (2.3)	1 (1.5)
PTLD morphology, n (%)	n = 26	n = 49	N = 75
Diffuse large B-cell lymphoma	18 (69.2)	34 (69.4)	52 (69.3)
Plasmablastic lymphoma	1 (3.8)	2 (4.1)	3 (4.0)
Other[d]	7 (26.9)	12 (24.5)	19 (25.3)
Median (range) time, months			
From transplant to EBV⁺ PTLD diagnosis	3.9 (0.6–66.0)	10.8 (2.4–314.4)	–
From EBV⁺ PTLD diagnosis to first tabelecleucel administration	2.1 (0.6–28.1)	6.9 (1.3–190.5)	4.6 (0.6–190.5)

[a]Data are shown for patients aged ≥16 years and having a baseline ECOG measurement (n = 67; n = 25 for HCT and n = 42 for SOT). [b]Data are shown for patients aged ≥16 years (n = 68; n = 25 for HCT and n = 43 for SOT). [c]PTLD-adapted prognostic index at study entry: low risk (no high-risk factors among age, ECOG, and LDH) vs intermediate risk (1 high-risk factor) vs high risk (2 or 3 high-risk factors); data are shown for patients aged ≥16 years. [d]Morphologies not clearly diffuse large B-cell lymphoma or plasmablastic lymphoma were categorized as "Other."
EBV⁺, Epstein–Barr virus-positive; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; LDH, lactate dehydrogenase; PTLD, posttransplant lymphoproliferative disease; SOT, solid organ transplant.

Prior Therapies and Transplant Type

Treatment and prior therapies	HCT (n = 26)	SOT (n = 49)	All (N = 75)
Median number of lines of prior systemic treatment, n (range)	1 (1–4)	1 (1–5)	1 (1–5)
Prior RTX monotherapy, n (%)	26 (100.0)	39 (79.6)	65 (86.7)
Prior CT, n (%)	4 (15.4)	31 (63.3)	35 (46.7)
Prior CT in combination with RTX, n (%)	0	28 (57.1)	28 (37.3)
Prior immunotherapy, n (%)	1 (3.8)	2 (4.1)	3 (4.0)
Transplant type, n (%)			
Kidney	–	14 (28.6)	–
Heart	–	12 (24.5)	–
Lung	–	9 (18.4)	–
Liver	–	4 (8.2)	–
Multivisceral	–	10 (20.4)	–

CT, chemotherapy; HCT, hematopoietic cell transplant; RTX, rituximab; SOT, solid organ transplant.

RESULTS (CONT'D)

Tabelecleucel Exposure

Tabelecleucel exposure	HCT (n = 26)	SOT (n = 49)	All (N = 75)
Number of tabelecleucel cycles, median (range)	2 (1–5)	2 (1–6)	2 (1–6)
Number of tabelecleucel infusions, median (range)	6 (2–15)	6 (1–18)	6 (1–18)
Tabelecleucel treatment duration, median (range), months	2.0 (0.2–5.8)	1.8 (0.03–6.5)	1.9 (0.03–6.5)
Location of infusion administration, n (%)[a]			
Inpatient, number of infusions (%)	72 (36.0)	103 (31.4)	175 (33.1)
Outpatient, number of infusions (%)	128 (64.0)	225 (68.6)	353 (66.9)
Number of unique lots received, n (%)			
1	15 (57.7)	34 (69.4)	49 (65.3)
2	8 (30.8)	15 (30.6)	23 (30.7)
3	3 (11.5)	0	3 (4.0)

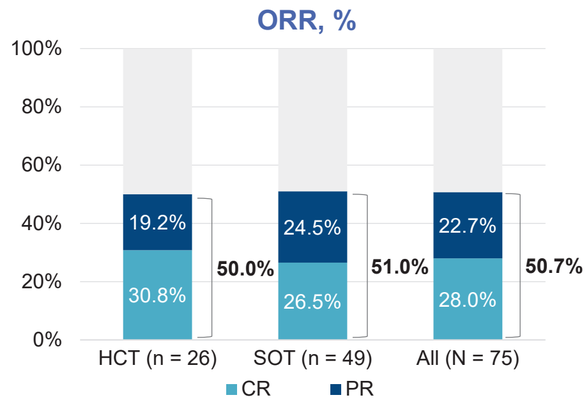
[a]Denominator is total number of tabelecleucel infusions.
HCT, hematopoietic cell transplant; SOT, solid organ transplant.

- Regarding the change of lot with different HLA restrictions, 65% of patients received only 1 lot, 31% received 2, and 4% received 3 different lots
- Patients received a median (range) of 2 (1–6) cycles of tabelecleucel

Primary Endpoint: ORR

- The ORR (complete response [CR] + partial response [PR]) in all patients was **50.7%** (n = 38/75), with a best overall response of CR in 21 patients (**28.0%**) or PR in 17 (**22.7%**)
- Median time to response in all patients was **1.1 months**
- Estimated median duration of response (DOR) was **23 months**

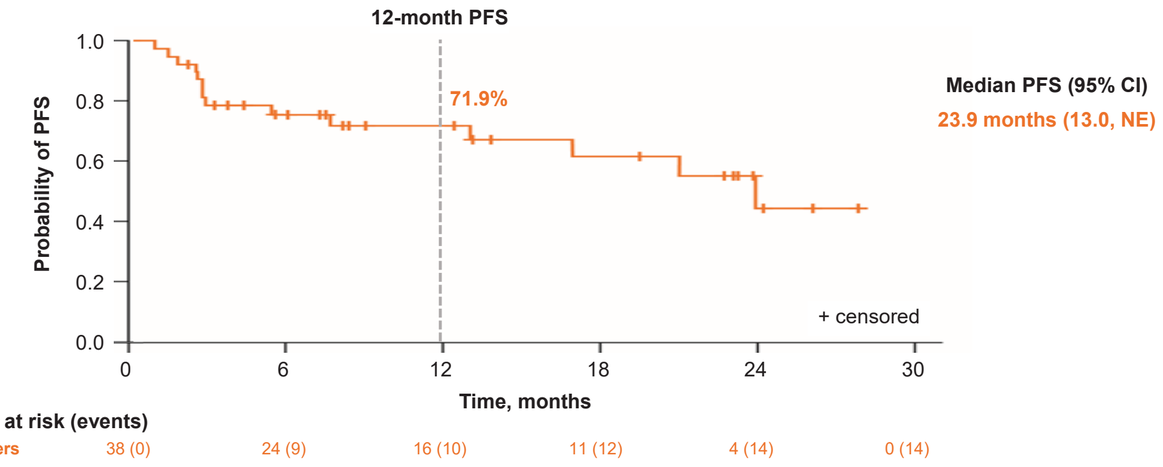
	HCT (n = 26)	SOT (n = 49)	All (N = 75)
Responders, n (%)[a]	13 (50.0)	25 (51.0)	38 (50.7)
[95% CI]	[29.9, 70.1]	[36.3, 65.6]	[38.9, 62.4]
Before first restriction switch	12 (46.2)	20 (40.8)	32 (42.7)
[95% CI]	[26.6, 66.6]	[27.0, 55.8]	[31.3, 54.6]
Median (range) time, months	n = 13	n = 25	n = 38
TTR	1.0 (0.6–9.0)	2.0 (0.7–4.7)	1.1 (0.6–9.0)
Time to best response	1.0 (0.6–9.0)	2.1 (0.7–7.3)	1.6 (0.6–9.0)
Estimated DOR, median (95% CI), months[b]	19.0 (1.5, NE)	NE (6.8, NE)	23.0 (12.1, NE)



[a]Response assessed per Lugano classification with LYRIC modification by IORA. [b]Estimated by the Kaplan–Meier method.
CI, confidence interval; CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplant; IORA, independent oncologic response adjudication; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; NE, not estimable; ORR, objective response rate; PR, partial response; SOT, solid organ transplant; TTR, time to response.

Progression-Free Survival (PFS) in Responders

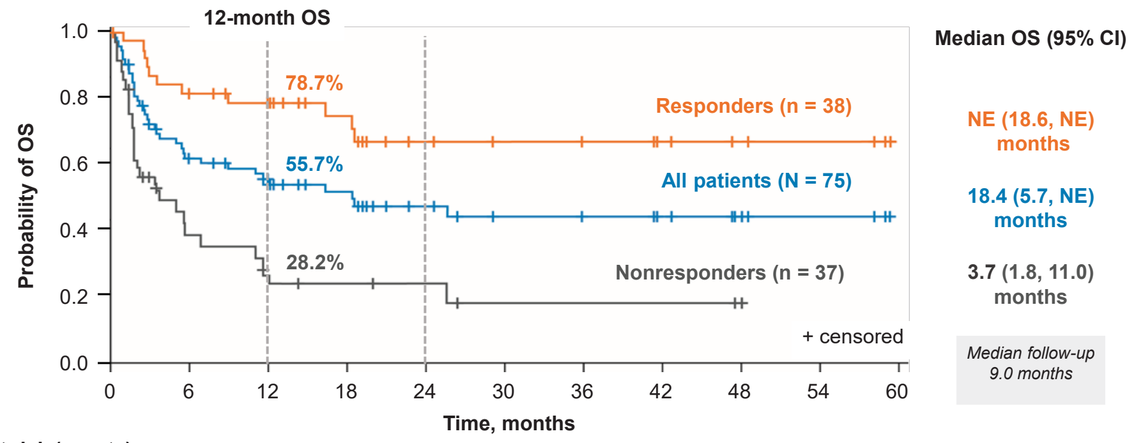
- Responders to tabelecleucel had a 12-month PFS rate[a] of 71.9%



[a]PFS was estimated by the Kaplan–Meier method.
CI, confidence interval; NE, not estimable; PFS, progression-free survival.

One-Year OS

- Responders had a 1-year OS rate[a] of 78.7% compared to nonresponders (28.2%)



[a]OS was estimated by the Kaplan–Meier method.
CI, confidence interval; NE, not estimable; OS, overall survival.

Safety Outcomes

	HCT (n = 26)	SOT (n = 49)	All (N = 75)
TESAEs, n (%)			
Any	17 (65.4)	30 (61.2)	47 (62.7)
Treatment-related[a]	2 (7.7)	4 (8.2)	6 (8.0)
Treatment-related fatal	0	0	0
Treatment-emergent identified and potential risks including AESI by SOC, n (%)			
Tumor flare reaction	0	0	0
Infusion-related reaction	0	0	0
Cytokine release syndrome	0	0	0
Transmission of infectious disease	0	0	0
Graft-vs-host disease	3 (11.5)	0	3 (4.0)
Bone marrow/organ rejection	0	3 (6.1)	3 (4.0)
ICANS	0	0	0
Immunogenicity[b]	0	0	0

Fatal TESAEs were disease progression (n = 7), multiple organ dysfunction syndrome (n = 2), respiratory failure (n = 1), COVID-19 (n = 1), acute respiratory distress (n = 1), pneumococcal sepsis (n = 1), and shock (n = 1). [a]Treatment-related TESAEs were pyrexia, diarrhea, hypoxia, hypotension, rash, rash erythematous, and tachycardia. [b]47 participants had pan–anti-HLA antibody testing completed, 18 of which were evaluable (18 in target population) for anti-HLA antibody assessment.
AESI, adverse event of special interest; HCT, hematopoietic cell transplant; ICANS, immune effector cell–associated neurotoxicity syndrome; SOC, system organ class; SOT, solid organ transplant; TESAE, treatment-emergent serious adverse event.

- Most treatment-emergent serious adverse events (TESAEs) were not treatment-related
- None of the fatal TESAEs were related to tabelecleucel
- No reports of tumor flare reactions, cytokine release syndrome, or immune effector cell–associated neurotoxicity syndrome (ICANS)
- No cases of tabelecleucel-related graft-vs-host disease or organ rejection were reported

CONCLUSIONS

- ALLELE study data from this larger cohort (75 patients) confirm the previously reported benefit-risk profile of tabelecleucel in EBV⁺ PTLD after RTX failure
- Tabelecleucel had a promising ORR and OS in this difficult-to-treat patient population
  - **ORR was 50.7%** in all patients (best overall response: CR in 28.0%; PR in 22.7%)
  - **Estimated median DOR was 23.0 months**
  - **OS rate at 1 year** was better in **responders (78.7%)** vs **nonresponders (28.2%)**
  - **Median OS was 18.4 months** in all patients
- Tabelecleucel was **well tolerated**

Tabelecleucel represents a transformative treatment for patients with EBV⁺ PTLD after RTX failure

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