Clinical Experience of Tabelecleucel in Epstein–Barr Virus-Positive Post-transplant Lymphoproliferative Disease (EBV⁺ PTLD) Involving the Central Nervous System

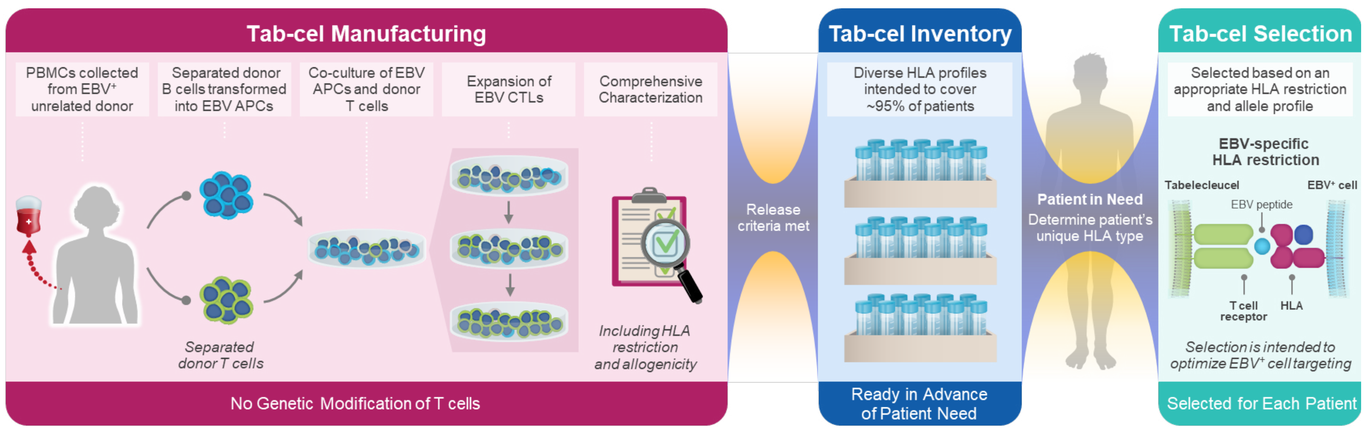
Daan Dierickx,[1] Robert Baiocchi,[2] Sylvain Choquet,[3] Monalisa Ghosh,[4] Enrico Orciuolo,[5] Rajani Dinavahi,[6] Justin Wahlstrom,[6] Xiaoli You,[6] Sue Zhang,[6] Susan Prockop[7]

[1] University Hospitals Leuven, Leuven, Belgium; [2] James Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA; [3] Centre Hospitalier Universitaire Pitié Salpétrière, Paris, France; [4] University of Michigan, Ann Arbor, MI, USA; [5] Haematology Unit, Department of Clinical and Experimental Medicine, University of Pisa/AOUP, Pisa, Italy; [6] Atara Biotherapeutics, Thousand Oaks, CA, USA; [7] Department of Pediatrics, Boston Children's Hospital/Dana Farber Cancer Institute, Boston, MA, USA

There is an Unmet Need for Effective and Well-tolerated Therapies in Patients With EBV⁺ PTLD with CNS Involvement

- Tabelecleucel is an investigational, off-the-shelf, allogeneic EBV-specific T-cell immunotherapy being studied in patients with EBV⁺ diseases, including EBV⁺ PTLD with CNS involvement following HCT or SOT
- With recent EU marketing authorization, tabelecleucel is the first off-the-shelf, allogeneic EBV-specific T-cell immunotherapy to receive approval for treatment of R/R EBV⁺ PTLD
- PTLD with CNS involvement is an uncommon presentation of PTLD that occurs following HCT and SOT and has been shown to be associated with a poor prognosis especially for patients with R/R disease[1-4]
- Standard initial treatment includes reduction of immunosuppression, along with CNS-penetrating chemotherapeutic agents in combination with rituximab but is limited by the fact that patients are already significantly immunosuppressed with tenuous graft function[5,6]
- We previously reported an overall response rate of 82% in 11 patients with R/R CNS EBV⁺ PTLD treated within two single-center studies[7]
- We report here a combined analysis including multicenter, global experience in front-line and R/R patients with CNS EBV⁺ PTLD

Figure 1: Tabelecleucel is an Investigational, Off-the-shelf, Allogeneic EBV-specific T-cell Immunotherapy Being Studied in Patients With Serious EBV⁺ Diseases



Study design

- Safety and efficacy were evaluated using data from four single-arm, open-label studies:
  - Two single-center, phase 2 trials (NCT00002663, n=10; NCT01498484, n=2)
  - A multicenter, expanded-access protocol (EAP-201 [2016–2020]; NCT02822495, n=2)
  - The multicenter, global, phase 2 EBVision (ATA129-EBV-205) multicohort study (NCT04554914, n=4)
- Patients with R/R or treatment-naïve CNS EBV⁺ PTLD received 3-weekly infusions of tabelecleucel at ~2x10^6 cells/kg per 35-day cycle. Participants received additional treatment cycles until they met end-of-treatment criteria, including: maximal response achieved, unacceptable toxicity, initiation of non-protocol therapy, failure of up to four tabelecleucel with different HLA restrictions (HCT) or two tabelecleucel with different HLA restrictions (SOT)
- Response was assessed by study investigator
- Key endpoints were ORR, OS, and safety parameters

Table 1: Baseline demographics and disease characteristics

Characteristics	All (N=18)
Median age, years (range)	22.0 (8–77)
Male, n (%)	8 (44.4)
Race, white, n (%)	13 (72.2)
PTLD-adapted prognostic index* (age ≥16 years†), n (%)	High: 4 (30.8) Int: 6 (46.1) Low: 1 (7.7) Unknown: 2 (15.4)
Bone marrow transplant, n (%)	8 (44.4)
Solid organ transplant, n (%)	10 (55.6)
Transplant organ type, n (%)	
Heart	1 (10.0)
Intestine	1 (10.0)
Kidney	5 (50.0)
Lung	1 (10.0)
Liver	1 (10.0)
Multivisceral‡	1 (10.0)

*PTLD-adapted prognostic index at study entry: low risk (no high-risk factors among age, ECOG, and LDH vs intermediate risk (one high risk factor) vs high risk (two or three high risk factors)[8]; data are shown in the 13 patients aged ≥16 years. Data were not collected for the 1 patient ≥16 years inthe 95-024 study. † Age <16, n=4. ‡ Includes heart/liver.

Table 2: Summary of prior therapy

Characteristics	All (N=18)
Median number of lines of prior systemic treatment, n (range)	1.0 (0–5)
Patients reporting any prior therapy, n (%)	17 (94.4)
Rituximab as a monotherapy, n (%)	12 (66.7%)
Chemotherapy-containing regimen, n (%)	11 (61.1)
Immunotherapy other than rituximab, n (%)	1 (5.6)
Radiation therapy, n (%)	4 (22.2)
Other therapy, n (%)	6 (33.3)

17 patients with R/R CNS EBV⁺ PTLD and 1 CNS EBV⁺ PTLD patient with no prior treatment were included in this pooled analysis

Table 3: Tabelecleucel exposure

Median time from transplant to EBV⁺ PTLD diagnosis was 6.9 months (range 3.1–14.8) for the 8 patients in the HCT cohort and 1.5 years (range 0.5–11.7) for the 10 patients in the SOT cohort

	All (N=18)
Median time from initial EBV⁺ PTLD diagnosis to first administration of tabelecleucel, months (range)	2.3 (0.1–135.8)
Median cycles of tabelecleucel (range)	3.0 (1–5)
Median dosage of tabelecleucel (range)	2.0 (1.0–2.4)
Median number of doses administered (range)	9.0 (1–15)
Median treatment duration, months (range)	2.8 (0.03–7.9)

Patients received a median (range) of 3.0 (1–5) cycles of tabelecleucel

Table 4: Primary endpoint: objective response rate

	All (N=18)
ORR, n (%)	14 (77.8)
95% CI	52.4, 93.6
Best overall response, n (%)	
CR	7 (38.9)
PR	7 (38.9)
SD	1 (5.6)
PD	3 (16.7)
Median time to response, months (range)	1.8 (0.7–6.4)
Median follow-up in response, months (range)	2.5 (0.03–14.1)
Estimated median duration of response, months (95% CI)	NE (0.5, NE)

The ORR (best overall response of PR+CR) was 77.8% (14/18), with a best overall response of CR (38.9%; n=7) or PR (38.9%; n=7) Median time to response was 1.8 months (range 0.7–6.4)

Response assessed per investigator. Median duration of response was estimated by the Kaplan–Meier method.

Table 5: Tabelecleucel was well tolerated in these treatment refractory and immunocompromised patients

Event type*	All (N=18)
Treatment-related TEAEs, n (%)	1† (5.6%)
Treatment-related fatal TEAEs, n (%)	0 (0)
Any TESAEs, n (%)	13 (72.2)
Treatment-related TESAEs, n (%)	0 (0)
Grade ≥3 TESAEs, n (%)	11 (61.1)
Grade ≥3 treatment-related TESAEs, n (%)	0 (0)
Grade 5 TESAEs, n (%)	3‡ (16.7%)

No treatment-related fatal or life-threatening TEAEs were reported

*Non-serious AEs were not collected for 12 patients in studies NCT00002663 and NCT01498484. † Grade 2 brain edema that resolved. ‡ 2 patients died due to disease progression; 1 patient died due to multi-organ failure.

TEAEs are events that occurred from start of tabelecleucel to 30 days after the last dose or treatment-related events that occurred on or after the first dose of tabelecleucel. Table presents the number (%) of patients with events in each category.

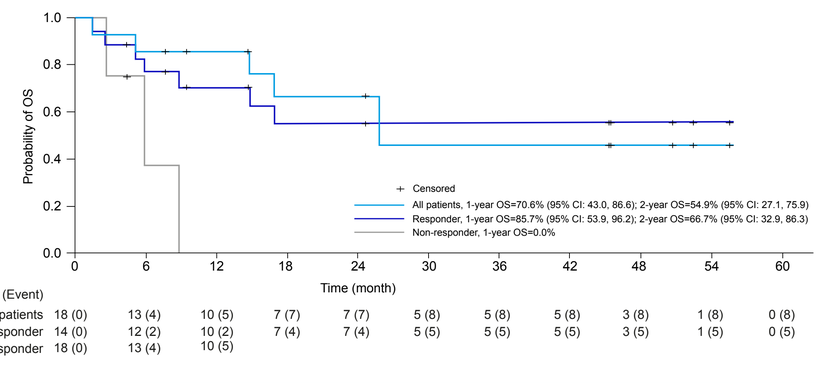
Table 6: No reports of serious treatment-emergent adverse events of identified risks or potential risks related to tabelecleucel

Event type	All (N=18)
Tumor flare reaction, n (%)	0
Neurotoxicity, including ICANS, n (%)	0
Graft vs host disease, n (%)	0
Marrow/organ rejection, n (%)	0
Transmission of infectious disease, n (%)	0
Cytokine release syndrome, n (%)	0
Infusion-related reaction, n (%)	0

There were no reports of serious treatment-related TEAEs of neurotoxicity, organ rejection, graft vs host disease, or tumor flare reaction of any grade

Table presents the number (%) of patients with events in each category. There were 2 reports of TEAEs (one case of GvHD in GI tract and one case of infusion-related reaction [pyrexia]), neither of which were related to tabelecleucel.

Figure 2: Patients responding to tabelecleucel had longer 1- and 2-year overall survival



Number at Risk (Event)

All patients	18 (0)	13 (4)	10 (5)	7 (7)	7 (7)	5 (8)	5 (8)	5 (8)	3 (8)	1 (8)	0 (8)
Responder	14 (0)	12 (2)	10 (2)	7 (4)	7 (4)	5 (5)	5 (5)	5 (5)	3 (5)	1 (5)	0 (5)
Non-responder	18 (0)	13 (4)	10 (5)								

Patients had a median (range) follow-up time of 14.8 months (1.4–55.4) and an overall estimated median (95% CI) OS of 25.7 months (5.8–NE). Patients responding to tabelecleucel had longer OS compared with non-responders.

Conclusions

- **Consistent with previous single-center experience, this combined analysis that includes the first reported data from the EBVision (ATA129-EBV-205) multicohort trial showed a high response rate of ~78% in patients with CNS EBV⁺ PTLD:**
  - **No prior treatment: 1/1 (100%; CR, n=1)**
  - **R/R: 13/17 (76.5%; CR, n=6, PR, n=7)**
- **Patients with CNS EBV⁺ PTLD treated with tabelecleucel demonstrated promising survival consistent with previous single-center experience in CNS EBV⁺ PTLD patients and in PTLD patients without CNS involvement**
  - **1-year and 2-year OS rates were 70.6% and 54.9% for all patients**
  - **1-year and 2-year OS rates were higher in responders (85.7% and 66.7%, respectively) vs non-responders (0% and 0%, respectively)**
- **Additionally, tabelecleucel was well tolerated, with no reports of serious treatment-related fatal or life-threatening TEAEs, and no reports of serious treatment-related TEAEs of neurotoxicity, organ rejection, graft vs host disease, or tumor flare reaction of any grade**
- **Based on the efficacy and safety profile demonstrated here, tabelecleucel may represent a favorable alternative therapy in CNS EBV⁺ PTLD, where available treatment options are more limited**

The phase 2 EBVision (ATA129-EBV-205) multicohort trial is ongoing to further investigate the clinical benefit of tabelecleucel in patients with EBV⁺ diseases, including frontline EBV⁺ PTLD and frontline CNS EBV⁺ PTLD

Acknowledgments
Thank you to the patients and their families who participated in these studies. Thank you to the investigators and study staff at the study sites in the United States, France, and Italy.

References
1.Balaguer-Rosello A *et al.* Transplant Cell Ther. 2021;27:261.e1-261.e7. **2.**Gifford G *et al.* Intern Med J. 2015;45:583-6. **3.**Evens AM *et al.* J Clin Oncol. 2010;28:1038-46. **4.**Leblond V *et al.* J Clin Oncol. 2001;19:772-8. **5.**Mendez JS, Grommes C. Am Soc Clin Oncol Educ Book. 2018;38:604-15. **6.**Rubenstein JL *et al.* J Clin Oncol. 2013;31:3061-8. **7.**Prockop S *et al.* J Clin Invest. 2020;130:733-47. **8.**Choquet S, *et al. Ann Hematol.* 2007;86(8):599-607.

Abbreviations
AE = adverse event; APC = antigen-presenting cell; CI = confidence interval; CNS = central nervous system; CR = complete response; CTL = cytotoxic T-lymphocyte; EBV = Epstein-Barr virus; EBV+ = EBV-positive; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; GvHD = graft-versus-host disease; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; ICANS = immune effector cell-associated neurotoxicity syndrome; LDH = lactate dehydrogenase; NE = not estimable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PBMC = peripheral blood mononuclear cell; PR = partial response; PTLD = post-transplant lymphoproliferative disease; R/R = relapsed/refractory; SD = stable disease; SOT = solid organ transplant; Tab-cel = tabelecleucel; TEAE = treatment-emergency adverse event; TESAE = treatment-emergent serious adverse event.

Disclosures
This clinical study is funded by Atara Biotherapeutics
Medical writing assistance was provided by Lee Blackburn, MSc from AMICULUM Ltd, funded by Atara Biotherapeutics