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

Robert Baiocchi MD, PHD[1], Sylvain Choquet MD[2], Monalisa Ghosh MD[3], Enrico Orciuolo MD[4], Rajani Dinavahi MD[5], Justin Wahlstrom MD[5], Xiaoli You MD[5], Sue Zhang[5], **David Schonberg PhD**[6], Susan Prockop MD[7]

[1] James Comprehensive Cancer Center, The Ohio State University, Columbus, USA. [2] Centre Hospitalier Pitié Salpêtrière, Paris, France. [3] University of Michigan, Ann Arbor, USA. [4] University of Pisa/AOUP, Pisa, Italy. [5] ATARA Biotherapeutics, Thousand Oaks, USA. [6] Pierre Fabre Pharmaceuticals, Parsippany, USA. [7] Boston Children's Hospital/Dana Farber Cancer Institute, Boston, USA.

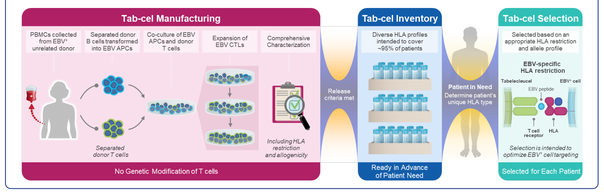
There is an Unmet Need for Effective and Well-tolerated Therapies in Patients With EBV+ PTLD with CNS Involvement

- 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

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

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



Results

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)"; data are shown in the 13 patients aged ≥16 years. Data were not collected for the 1 patient ≥16 years in the 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 10^6 cells/kg (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.

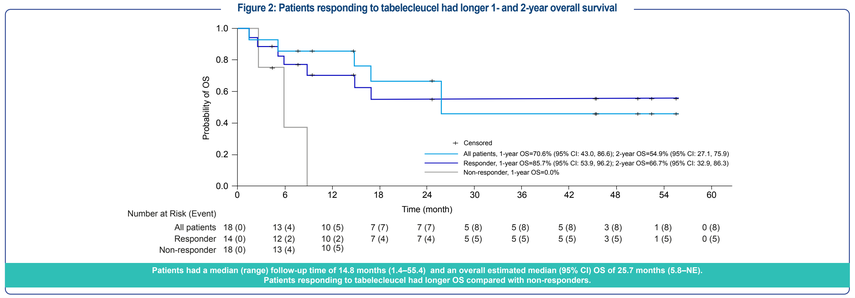
Table 6: No reports of serious treatment-emergent adverse events of identified risks or potential risks related to tabelecleucel

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



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)
- 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
- 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)

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

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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

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