Clinical Experience of Tabelecleucel in Patients with EBV+ Primary (PID) or Acquired Immunodeficiency (AID)-Associated Lymphoproliferative Disease

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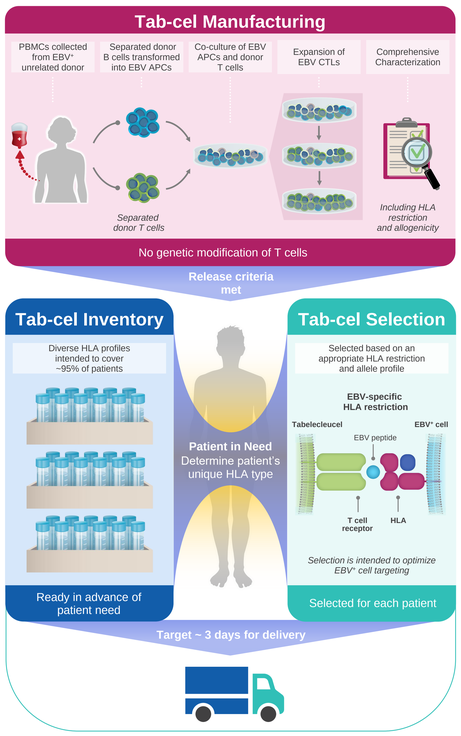
BACKGROUND

- PID is a result of inherited or congenital deficiencies affecting immune system development or maturation; there are over 350 types of PID.[1] Unlike PID, AID is a result of immune system impairment by causes other than a genetic defect, such as an HIV infection, a consequence of malnutrition or other metabolic disorders such as diabetes mellitus.[2]
- Patients with PID or AID are at higher risk of developing EBV+ LPD.[3,4]
- Although there are no approved therapies, initial treatment of EBV+ PID and AID LPDs includes chemotherapy +/- rituximab. Patients with PID LPDs are less able to tolerate standard doses of chemotherapy, and HCT remains the only long-term curative option.[5]
- However, HCT is not suitable for all patients with PID LPD and is associated with high rates of treatment-related mortality.[3] Patients with PID and AID LPD who do not respond to standard therapies usually have a poor prognosis and limited treatment options, representing an area of significant unmet need.[5,6]
- Tabelecleucel, an investigational off-the-shelf, allogeneic EBV-specific T-cell immunotherapy, has previously shown clinical activity in patients with EBV+ PTLD.[7,8]
- **Here, we report initial data in patients with EBV+ PID and AID LPDs treated with tabelecleucel, after failure of standard therapies, as part of an expanded access program (NCT02822495) with two non-overlapping protocols (EAP-201 [2016–20] and EAP-901 [2018–present; ongoing]).**
- After December 2018, patients requiring expanded access to tabelecleucel were enrolled in an updated protocol EAP-901 under the same study number.
- Tabelecleucel manufacturing process (Figure 1) involves collecting PBMCs from unrelated donors and separating the B and T cells. Donor B cells are then transformed to generate EBV APC and then co-cultured with donor T cells, along with cytokine stimulation. After EBV CTL expansion, the product is comprehensively characterized and stored as inventory.

Figure 1: Tab-cel Manufacturing, Inventory and Selection



Tabelecleucel is selected for individual patients from an existing inventory based on an appropriate HLA restriction and allele profile

METHODS

Expanded Access Study

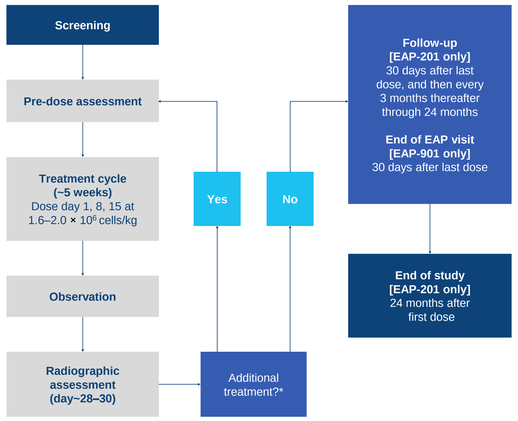
- Patients with diverse EBV+ diseases were treated with tabelecleucel in this EAP, including EBV+ post-transplant lymphoproliferative disease following HCT or solid organ transplant, EBV+ PID and AID LPD, EBV+ LPD not associated with immunodeficiency, EBV+ nasopharyngeal carcinoma, leiomyosarcoma, other EBV+ solid tumors, and EBV viremia.
- Key inclusion and exclusion criteria for patients with EBV+ PID or AID LPD are shown in Table 1.

Table 1: Key Inclusion and Exclusion Criteria for Patients with EBV+ PID and AID LPD, Across Protocols EAP-201 and EAP-901

Key Inclusion Criteria	Key Exclusion Criteria
• Presence of EBV+ disease • Relapsed or refractory disease, defined as failure to achieve response (CR or PR) or recurrent disease following first-line therapy for which there are no appropriate therapies (applicable in EAP-901) • No other approved alternative therapies • Not eligible for any other Atara clinical development study • Adequate organ function – Absolute neutrophil count ≥500/μL ± cytokine support; platelets ≥20,000/μL ± transfusion support – Alanine aminotransferase, aspartate aminotransferase, total bilirubin<3 × ULN; creatinine <3 × ULN (applicable in EAP-201) • ECOG performance status ≤4 or Lansky performance status ≥20 and lack of approved alternative therapies (applicable in EAP-201) • Availability of appropriate HLA partially-matched and restricted tabelecleucel (applicable in EAP-201)	• Any investigational therapy received ≤4 weeks prior to cycle 1, day 1 – Or within five half lives from the most recent dose (applicable in EAP-901) • Vasopressor or ventilatory support that is not a result of the EBV disease • Ongoing need for methotrexate or extracorporeal photopheresis; steroid doses >0.5 mg/kg prednisone require discussion with the medical monitor – Steroid doses >1 mg/kg/day of prednisone (applicable in EAP-901) • Ongoing need for antithymocyte globulin, alemtuzumab, or similar anti-T-cell antibody therapy, or T-cell therapy (donor lymphocyte infusion, other CTLs) ≤4 weeks prior to cycle 1, day 1

METHODS CONT'D

Figure 2: Expanded Access Program Schema



*EAP-901 assessed response only to determine whether additional treatment or a restriction switch was required

- Eligible patients received tabelecleucel at 1.6–2.0 × 10^6 cells/kg/dose on days 1, 8 and 15, with investigator-assessed response per Lugano classification response criteria on day ~28–30 of each 5-week cycle (Figure 2).
  - Patients who did not respond could switch to tabelecleucel with a different HLA restriction (restriction switch).
- As EAP-901 is intended to provide expanded access to tabelecleucel, limited patient data are collected compared with EAP-201; however, response is assessed by the investigators based on Lugano classification response criteria to determine whether an HLA restriction switch is needed.
- Patients continued treatment until unacceptable toxicity, maximal response (two consecutive CR or three PRs), or up to four different HLA restrictions.
- Both protocols collected TESAEs.

RESULTS

Baseline Characteristics

- As of 28 January 2020, 17 patients with EBV+ PID (N=8) or AID (N=9) LPD have been enrolled and received treatment with tabelecleucel. Patient characteristics and treatment exposure are shown in Table 2.

Table 2: Baseline Characteristics of Patients with EBV+ PID or AID LPD Across EAP-201 and EAP-901

	EBV+ PID LPD (N=8)	EBV+ AID LPD (N=9)
Median age, yrs (range)	25.0 (1–91)	64.0 (34–69)
Sex (m) – n (%)	4 (50.0)	7 (77.8)
Median no. of tabelecleucel treatment cycles (range)	2.0 (1–3)	2.0 (1–4)

Data as of 28 Jan 2020. Three patients in EAP-201 with EBV+ AID LPD were recorded as having HIV infection. HIV status was not recorded in EAP-901. Across EAP-201 and EAP-901, eight patients with EBV+ AID LPD received prior EBV disease therapies, including chemotherapy and/or rituximab (n=7) or immunotherapy (n=1). Eight patients with EBV+ PID LPD received prior EBV disease therapies, including chemotherapy and/or rituximab (n=7) or surgical treatments (n=1)

Efficacy

- Efficacy data are shown in Table 3. ORRs were 37.5% in the EBV+ PID (3/8) and 33.3% in the AID (3/9) LPD cohorts. Median time to response was 0.9 and 2.1 months for EBV+ PID and EBV+ AID LPD cohorts, respectively.

Table 3: Efficacy for Patients with EBV+ PID or AID LPD Treated with Tabelecleucel Across EAP-201 and EAP-901

	EBV+ PID LPD (N=8)	EBV+ AID LPD (N=9)
Objective response rate (CR + PR) – n (%)	**3 (37.5)**	**3 (33.3)**
Best overall response – n (%)		
CR	1 (12.5)	1 (11.1)
PR	2 (25.0)	2 (22.2)
SD	2 (25.0)	0 (0.0)
PD	3 (37.5)	3 (33.3)
NE	0	3 (33.3)
Median time to response – months (min, max)	0.9 (0.8–1.6)	2.1 (1.0–2.6)

Data as of 28 Jan 2020. NE = no post-baseline assessments available

RESULTS CONT'D

- The OS rate at 1 year in patients treated per EAP-201 (Table 4) was:
  - 80% (95% CI 20.4, 96.9) in patients with EBV+ PID LPD (n=5) for a median follow-up of 17.9 months (min 0.8, max 24.4)
  - 71.4% (95% CI 25.8, 92.0) in patients with EBV+ AID LPD (n=7) for a median follow-up of 2.0 months (min 0.2, max 21.0).

Table 4: Overall Survival EBV+ PID or AID LPD Treated with Tabelecleucel in EAP-201*

	EBV+ PID LPD (N=5)	EBV+ AID LPD (N=7)
Median follow-up time – months (min, max)	**17.9** (0.8, 24.4)	**2.0** (0.2, 21.0)
OS rate (95% CI)		
At 6 months	**80.0** (20.4, 96.9)	**71.4** (25.8, 92.0)
At 12 months	**80.0** (20.4, 96.9)	**71.4** (25.8, 92.0)

*OS is not presented from EAP-901 due to shorter follow-up as defined per study protocol. EAP-201 had a 2-year defined follow-up period, whereas EAP-901 only required follow-up related to response assessment needed to drive restriction switch, if needed. Data as of 28 Jan 2020

SAFETY

- There were five patients with treatment-related TESAEs in the EBV+ PID (n=3) and AID (n=2) LPD cohorts (Table 5). No fatal events were reported as treatment related.

Table 5: Summary of the Safety Profile of Tabelecleucel in Patients with EBV+ PID or AID LPD

	EBV+ PID LPD (N=8)	EBV+ AID LPD (N=9)
Patients with any TESAEs – n (%)	6 (75.0)	5 (55.6)
Patients with fatal TESAEs – n (%)	1 (12.5)	1 (11.1)
Patients with treatment-related TESAEs* – n (%)	3 (37.5)	2 (22.2)
Patients with treatment-related fatal TESAEs – n (%)	0 (0.0)	0 (0.0)
Patients with treatment-related TESAEs leading to treatment discontinuation – n (%)	0 (0.0)	1 (11.1)

*Depressed level of consciousness (grade 2, led to treatment discontinuation), hypoxia (grade 3), pyrexia (grade 1), skin ulcer and tumor flare (both grade 3, same patient), GvHD in skin (grade 1, patient with ongoing chronic skin condition; no biopsy performed to confirm GvHD). Data as of 28 Jan 2020

TESAEs were defined as SAEs occurring from the start of tabelecleucel to 30 days after the last dose, or treatment-related SAEs occurring after the start of tabelecleucel

CONCLUSIONS

- **Tabelecleucel was well tolerated and showed 33.3% ORR in AID and 37.5% in PID LPD, with an estimated OS at 1 year in EAP-201 patients of 71.4% in AID (~2 months median follow-up) and 80% in PID (~18 months median follow-up).**
- **Based on these results, further clinical investigation of tabelecleucel in EBV+ PID and AID LPDs is planned within an upcoming study (ATA129-EBV-205; NCT04554914).**

DISCLOSURES

- This study was funded by Atara Bio.
- S Nikiforow receives consultancy fees from Kite/Gilead, Novartis and Nkarta.
- R Baiocchi receives consultancy fees from Viracta, Prelude Tx and Atara.
- S Nasta receives research funding from Genentech/Roche, Millenium/Takeda, Rafael, Debiopharm and Pharmacyclics.
- KM Mahadeo receives support for the conduct of sponsored clinical trials from Atara Bio.
- J Whangbo receives consultancy fees from Orchard Therapeutics.
- S Prockop is a co-inventor on intellectual property licensed to Atara Bio. S Prockop has waived her rights to this intellectual property to MSK and has no personal financial interests in Atara Bio. S Prockop receives support for the conduct of sponsored clinical trials through MSK from Atara Bio. MSK has financial interests in Atara and intellectual property interests relevant to the work that is related to this poster. S Prockop also receives funding from Mesoblast, Jasper Pharmaceuticals and consultancy fees from Mesoblast.
- W Navarro, R Dinavahi, L Gamelin, Y Sun and N Guzman-Becerra are employees and shareholders of Atara Bio. P Phuong is a former employee of Atara Bio.
- WK Weng and D Loeb have nothing to disclose.
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ABBREVIATIONS

AID = acquired immunodeficiency; APC = antigen-presenting cells; CI = confidence interval; CR = complete response; CTL = cytotoxic T-lymphocyte; EAP = expanded access program; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; GvHD = graft vs host disease; HCT = hematopoietic stem cell transplant; HLA = human leukocyte antigen; LPD = lymphoproliferative disease; NE = not evaluable; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PID = primary immunodeficiency disease; PR = partial response; PTLD = post-transplant lymphoproliferative disease; SAE = serious adverse event; SD = stable disease; TESAE = treatment-emergent serious adverse event; ULN = upper limit of normal