Long Term Outcomes of Tabelecleucel (Third-Party, Allogeneic EBV-Targeted Cytotoxic T-lymphocytes) for Rituximab-Refractory Post-Transplant EBV+ Lymphomas: A Single Center Experience

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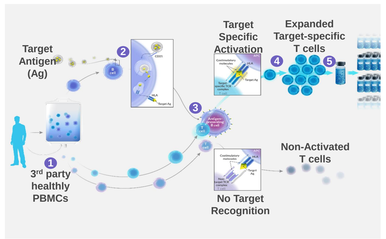
INTRODUCTION

Epstein-Barr Virus (EBV+) post-transplant lymphoproliferative disorder (PTLD) represents a life-threatening challenge for patients following solid organ transplant (SOT) or allogeneic hematopoietic cell transplant (HCT). Patients who fail rituximab-based therapy have limited treatment options. Rituximab failure in EBV+ PTLD following HCT often portends a dismal prognosis with a median overall survival (OS) in the range of 16-56 days (1-3). In SOT, patients failing rituximab experience increased treatment-related mortality from anthracycline-based chemotherapy more frequently than their non-immunocompromised lymphoma counterparts (4). High-risk SOT patients failing upfront rituximab have an OS of approximately 36% at 1 year and 0% at 2 years (5). Effective, less toxic therapies are required to fulfill the substantial unmet medical need for these patients. We have previously shown that treatment with tabelecleucel (tab-cel™, previously known as ATA129) results in durable responses and a response rate of 54-65% in rituximab-refractory EBV+ PTLD patients after SOT or HCT (6). Here, we report long-term study results of tabelecleucel in EBV+ PTLD after failure of rituximab with a median follow-up of 23.3 months and 21.3 months in HCT and SOT subjects, respectively.

Tabelecleucel is an off-the-shelf, allogeneic, T-cell immunotherapy that targets EBV viral antigens. The tabelecleucel manufacturing process is illustrated below. Normal, healthy volunteer donors undergo peripheral blood mononuclear cell (PBMC) collection; B and T cells are separated. B cells are then transformed and co-cultured as antigen-presenting cells with T cells, along with cytokine stimulation. After EBV specific T-cell expansion, the product is characterized, cryopreserved, and stored for off-the-shelf use.

EBV-targeted T cells that comprise tabelecleucel act via their specific HLA restriction(s), the HLA allele(s) required by the T cells to activate the T cell receptor and initiate cytotoxicity against EBV-expressing tumor cells. In addition, the T-cells proliferate in response to the antigen to drive sustained responses.

Figure 1. Tabelecleucel Manufacturing Process



Note: Technology licensed from Memorial Sloan Kettering Cancer Center (MSK) by Atara Biotherapeutics

METHODS

This poster presents updated data, including long term follow-up, from two single center, open-label studies, 95-024 (NCT00002663) (phase I/II) and 11-130 (NCT01498484) (phase II) that were conducted at MSK. These trials evaluate the safety and efficacy of tabelecleucel in the treatment of EBV+ PTLD or other EBV-associated malignancies in severely immunocompromised individuals and organ allograft recipients who are at high risk for these complications. Long term follow-up data for subjects treated on these protocols were collected by MSK via an IRB-approved retrospective research protocol.

Following signed informed consent, subjects were treated with tabelecleucel sharing ≥2/10 HLA alleles with the disease, including ≥1 HLA allele through which tabelecleucel exerts cytotoxicity (HLA restriction). Tabelecleucel was given at 2 x 10^6 cells/kg/dose (Protocol 11-130) or 1-2 x 10^6 cells/kg/dose (Protocol 95-024) on days 1, 8, and 15 of every 4-6 week cycle, which included PET/CT or MRI imaging, at approximately day 35 of each cycle. Subjects could receive multiple cycles of tabelecleucel.

Studies 11-130 and 95-024 are ongoing. The analyses presented include data as of 16th May, 2018 from subjects with EBV+ PTLD following HCT (n=35) or SOT (n=14) who failed to respond or relapsed after prior therapy with rituximab and received at least one dose of tabelecleucel.

Summaries are provided for baseline characteristics, efficacy and safety endpoints. The overall response rate (ORR) was defined as the percentage of subjects who achieved a best overall response of complete response (CR) or partial response (PR) during the study. CR was defined as complete resolution of all clinical and radiologic evidence of lymphoma, confirmed by biopsy of affected tissues when indicated, and PR was defined as a > 50% reduction in the size of all lymphomatous lesions as determined by CT or MRI measurements of tumor volume. OS was estimated using the Kaplan-Meier approach. In these studies, grade 3 serious adverse events (SAEs) identified as related or potentially related to the product, as well as all grade 4 and 5 SAEs were reported per protocol. Treatment-emergent serious adverse events (TESAEs) are defined as any SAEs that occurred after first dose of tabelecleucel, or any SAE that occurred prior to first dose but worsened after initiation of the first dose of tabelecleucel, through 30 days after the last administration of tabelecleucel or any related SAE regardless of date of onset after first dose of tabelecleucel. The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 was used to code serious adverse events (SAEs). Relatedness to treatment was determined by investigators. Severity of SAEs was based on the Common Toxicity Criteria for Adverse Events (CTCAE) version 2.0 and 4.03.

RESULTS

Table 1. Baseline Characteristic and Demographics

	EBV+ PTLD following HCT after failure of rituximab N=35	EBV+ PTLD following SOT after failure of rituximab N=14
Age in years, n (%)		
Age ≥ 16	28 (80)	9 (64.3)
Age < 16	7 (20)	5 (35.7)
Age in years, median (range)	28 (5, 74)	18 (6.4, 77.2)
Sex, n (%)		
Male	17 (48.6)	6 (42.9)
Female	18 (51.4)	8 (57.1)
Race, n (%)		
Asian	3 (8.6)	1 (7.1)
Black or African American	4 (11.4)	2 (14.3)
White	23 (65.7)	10 (71.4)
Unknown	5 (14.3)	1 (7.1)
Karnofsky score (Age > 16 only), n (%)		
> 80 (low risk)	2 (7.1)	1 (11.1)
≤ 80 (high risk)	21 (75)	6 (66.7)
Missing	5 (17.9)	2 (22.2)
Karnofsky score, median (range)	70 (30, 100), n=23*	60 (40, 90), n=7*

*Performance scores were collected only on trial 11-130

Subjects enrolled in these studies were mostly white and adult, although 20% of HCT and 36% of SOT were children. In HCT and SOT, median Karnofsky performance scores score for adults > 16 years of age was 70 and 60, respectively, with a majority of the subjects (75% and 67%) having a score of < 80).

Table 2. Summary of Responses as Assessed by Investigator

	EBV+ PTLD following HCT after failure of rituximab N=35	EBV+ PTLD following SOT after failure of rituximab N=14
ORR, % (95% CI)	68.6 (50.7, 83.1)	50 (23, 77)
Best overall response per investigator, n (%)		
CR	20 (57.1)	2 (14.3)
PR	4 (11.4)	5 (35.7)
SD	1 (2.9)	1 (7.1)
PD	9 (25.7)	6 (42.9)

*One subject in HCT was not evaluable due to relapse of the primary disease for which the subject was transplanted.

The overall response rate in subjects with EBV+ PTLD following HCT or SOT who fail rituximab is 69% and 50%, respectively.

EFFICACY RESULTS

FIGURE 2. Kaplan-Meier Estimate of OS, EBV+ PTLD Following HCT After Failure of Rituximab

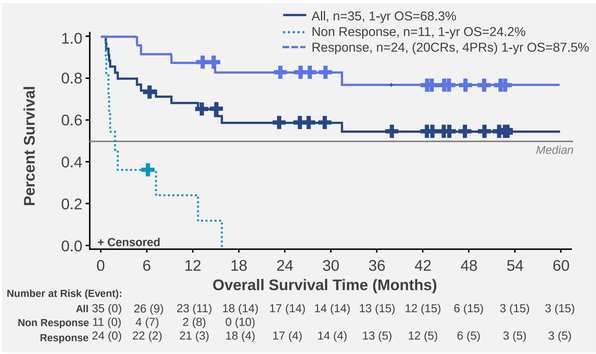
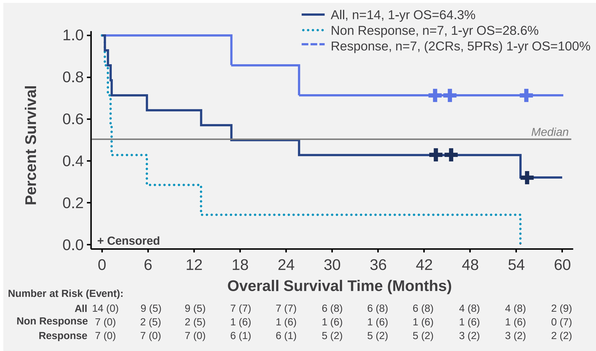


FIGURE 3. Kaplan-Meier Estimate of OS, EBV+ PTLD Following SOT After Failure of Rituximab



The median follow-up time is 23.3 months with a range of 0.5 – 88.9 months for HCT and 21.3 months with a range of 0.4 – 115 months for SOT, respectively. In HCT the 1-yr OS rate is 68% and the 3-yr OS rate is 55%. In SOT, the 1-yr OS rate is 64% and the 3-yr OS rate is 43%. The median OS was not reached in HCT; in SOT, the median OS is 21.3 months.

Responder (CR or PR) analyses reveal that for subjects who responded to tabelecleucel, the 2-yr OS is 83% in HCT (n=24); and 86% in SOT, (n=7). None of the subjects responding to tabelecleucel died of EBV+ PTLD. Subjects who do not achieve CR or PR in response to tabelecleucel have a short overall survival: median OS is 1.7 months in HCT and 1.2 months in SOT.

SAFETY RESULTS

In HCT and SOT, 28.6% and 50% of subjects, respectively, experienced at least one SAE regardless of attribution to study treatment. Two subjects experienced SAEs considered to be possibly related to treatment; one HCT subject with an SAE of lymphocyte count decreased, grade 4, and one SOT subject with an SAE of acidosis, grade 4. No SAEs were considered definitely related to tabelecleucel.

Among the subjects responding to tabelecleucel (n=24, HCT and n=7, SOT), the majority were alive as of the data snapshot of 16th May 2018. Of the responders who died (n=5, HCT and n=3, SOT), none died of progression or relapse of PTLD, and all deaths occurred after 30 days following the last dose. Causes of death during long-term follow-up of the HCT responders were as follows: relapse of the primary disease for which subjects had initially undergone HCT (n=2), viral infection (n=1), and neurologic disorder (n=1). For SOT responders, one subject died of acute my`ocardial infarction and another subject, who had received a liver transplant, died of liver failure 433 days after last dose of tabelecleucel. The cause of death in two responders, one in HCT and one in SOT, was unknown.

Among the subjects who did not achieve CR or PR in response to tabelecleucel (n=11, HCT; n=7, SOT), most died of PTLD progression (n=8, HCT; n=5, SOT).

CONCLUSIONS

- Tabelecleucel elicits high overall response rates (69% in HCT and 50% in SOT) in subjects with difficult to treat EBV+ PTLD following HCT or SOT who have failed rituximab treatment.
- Median survival has not been reached in HCT; median survival is 21.3 months in SOT, though with small numbers of subjects.
- Tabelecleucel elicits durable responses in subjects with EBV+ PTLD following HCT and SOT who have failed rituximab treatment, (1 yr OS of 68% in HCT and 64% in SOT).
- For subjects who responded to tabelecleucel, the 2-yr OS is 83% and 86% in the HCT and SOT, respectively. None of the subjects responding (CR or PR) to tabelecleucel died of PTLD.
- Tabelecleucel has been well tolerated in this population that comprised quite ill, immunosuppressed patients with multiple comorbidities. No treatment-emergent adverse events have been definitively related to tabelecleucel.

These studies, albeit small and single center in nature, demonstrate the safety and efficacy of tabelecleucel in EBV+ PTLD, following HCT and SOT after failure of rituximab, with durable remissions after substantial follow-up time. Atara Biotherapeutics is currently studying tabelecleucel in two phase 3 trials for PTLD following HCT (NCT03392142) and SOT (NCT03394365).

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