Correlation of Circulating Epstein-Barr Virus-targeted Cytotoxic T Lymphocyte Precursors (EBV-CTLp) and Clinical Response Following Tabelecleucel (tab-cel®) Infusion in Patients With EBV-driven Disease

Abstract # 2532

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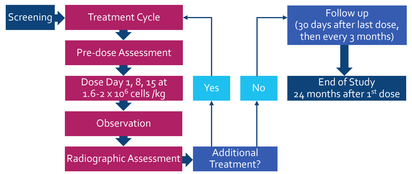
INTRODUCTION

- Epstein Barr Virus (EBV) is implicated in the pathogenesis of a variety of diseases including lymphomas, solid tumors and autoimmune diseases.
- EBV-CTL-201 is a multicenter expanded access protocol of tab-cel® for subjects with Epstein Barr Virus-associated viremia or malignancies for whom there are no appropriate alternative therapies (NCT02822495).
- Tab-cel® is an investigational off-the-shelf, allogeneic T-cell immunotherapy utilizing endogenous T-cell receptors targeting EBV antigens.
- It is hypothesized that the clinical activity of tab-cel® is mediated by expansion and persistence of EBV-specific T-cells.

METHODS

- Samples from 10 patients with EBV+ post-transplant lymphoproliferative disease (PTLD) and other EBV-driven diseases (table 2) enrolled in EBV-CTL-201 were collected and analyzed as described in schema 2.
- Patient response to tab-cel® was assessed via radiographic assessment ~15 days after the last dose (~day 34 of cycle) of tab-cel® to determine the need for additional treatment. Best overall response to initial tab-cel® HLA restriction was used in this analysis.
- For CTLp Frequency and Cytokine Analysis, whole blood was collected and separated into viable PBMC and plasma fractions prior to cryopreservation and analysis at a central laboratory. Paired PBMC and plasma samples were analyzed in parallel. PBMC samples were subject to a limiting dilution CTL culture assay to determine the frequency of CTLp that were cytoreactive to EBV+ BLCLs. Plasma fractions were quantified using immuno-assays for levels of IL-6, IL-2, TNF-α, and IL1-β.
- Correlation between frequency of circulating EBV-specific CTLp at ~day 34 with best overall response to initial tab-cel® HLA restriction (as of April 1st, 2019) was tested using the two-tailed Mann-Whitney test.

Schema 1: EBV-CTL-201 Study Schema



Key Inclusion Criteria

1. EBV-associated disease:
   - PTLD following allo-HCT
   - PTLD following SOT
   - EBV-associated LPD associated with congenital or acquired immunodeficiency
   - EBV-associated lymphomas and LPDs not associated with immunodeficiency
   - Other EBV-associated malignancies (biopsy required) including nasopharyngeal carcinoma, EBV+ gastric cancer, EBV+ leiomyosarcoma
   - EBV+ HLH
   - Persistent EBV viremia
2. Evidence of EBV positivity
3. ECOG < 4; Lansky score > 20

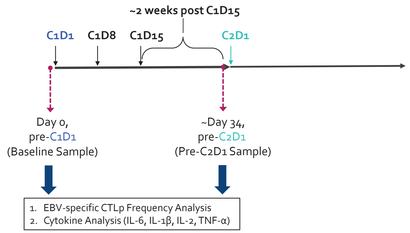
Key Exclusion Criteria

1. Ongoing methotrexate or extracorporeal photopheresis; steroid doses > 0.5 mg/kg as prednisone equivalent required discussion with medical monitor
2. Anti-T cell therapy or T-cell therapy < 4 weeks prior to 1st dose

Restriction Switch

1. Subjects not responding to initial tab-cel® could receive tab-cel® with different restrictions from up to 3 other donors, if available
2. Per the treatment algorithm, subjects switched tab-cel® for:
   - Progressive disease (PD)
   - Stable disease (SD) x 2
3. Subjects ended treatment if:
   - Maximal response was attained
     - Partial response (PR) x 3
     - Complete response (CR) x 2
   - Subject received tab-cel® with different HLA restrictions, from up to 4 donors
   - Unacceptable toxicity

Schema 2: EBV-CTL-201 Sample Collection Schema



C1D1 = treatment cycle 1, day 1; C1D8 = treatment cycle 1, day 8; C1D15 = treatment cycle 1, day 15; C2D1 = treatment cycle 2, day 1.
Subjects included in this analyses were sampled at baseline pre-C1D1 of tab-cel® on day 0. Following three weekly administrations of tab-cel® (C1D1, C1D8, C1D15) and a period of approximately two weeks after last dose (C1D15), patients were subject to a follow-up sample pre-C2D1 on ~day 34.

Table 1. Subject Baseline Demographics

	N = 10
Age in years, median (range)	36.5 (19, 74)
Sex, n(%)	
Male	6 (60)
Female	4 (40)
Race, n (%)	
Black or African American	1 (10)
White	8 (80)
Missing	1 (10)
ECOG, n (%)	
< 2	5 (50)
≥ 2	5 (50)

RESULTS

Table 2. Subject Indication and Best Overall Response (BOR) to Initial Tab-cel® HLA Restriction

Subject ID	Indication	BOR to Initial Tab-cel® HLA Restriction
201-1	PTLD-SOT	CR
201-2	PTLD-SOT	CR
201-3	PTLD-SOT	PD
201-4	EBV-LPD (T-cell)	PR
201-5	PTLD-SOT	PR
201-6	EBV-viremia	SD†
201-7	EBV-LMS	SD
201-8	EBV-viremia	CR
201-9*	PTLD-HCT	SD
201-10**	PTLD-HCT	CR

CR = complete response; HCT = hematopoietic cell transplant; LMS = leiomyosarcoma; LPD = lymphoproliferative disorder; PD = progressive disease; PR = partial response; PTLD = post-transplant lymphoproliferative disorder; SD = stable disease; SOT = solid-organ transplant.
*Subject 201-9 achieved a BOR to first tab-cel® HLA restriction of SD but received concomitant chemotherapy with romidepsin. BOR with tab-cel® alone is PD.
**Subject 201-10 achieved a BOR of CR but received concomitant therapy with rituximab. BOR with tab-cel® alone is not evaluable.
†Subject 201-6 achieved BOR in relation to initial tab-cel® HLA restriction. Subject later received HLA restriction switch of tab-cel® and achieved BOR of PR. CTLp and cytokines were measured in relation to initial tab-cel® HLA restriction.

Figure 1. CTLp Fold Change vs. Best Overall Response

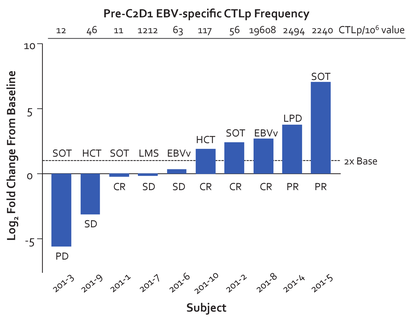


Figure 1. Fold change in frequency of circulating EBV-specific CTLp between baseline and pre-C2D1 samples is shown from lowest to highest for each subject in the cohort (blue bars, n = 10). Corresponding EBV-driven disease and best overall response to initial tab-cel® HLA restriction are annotated above and below the bar for each subject, respectively. Responders annotated in bold. Absolute frequency of CTLp measured in pre-C2D1 samples is also enumerated along the top of the plot corresponding to each subject.

Figure 2. CTLp Fold Change and CTLp Frequencies

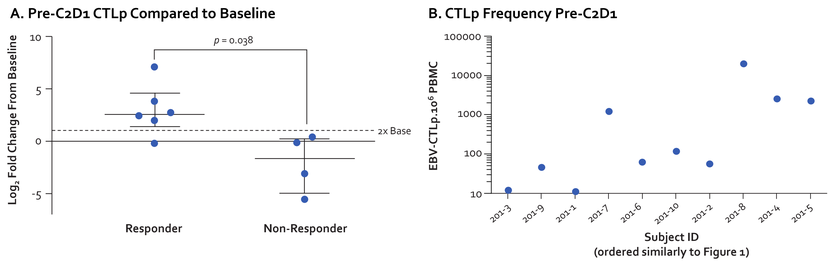


Figure 2A. Fold change in circulating EBV-specific CTLp in subjects designated as responders (PR or CR) or non-responders (SD or PD). Result of unpaired, non-parametric Mann-Whitney T test comparing the distribution of fold change in CTLp frequency between each responder group is shown. A 2-fold change in CTLp frequency is depicted by the dotted line. 2B. Measured CTLp frequency at pre-C2D1 for subjects included in this analysis are shown in order to which they appear in Figure 1.

Figure 3. Cytokine Analysis

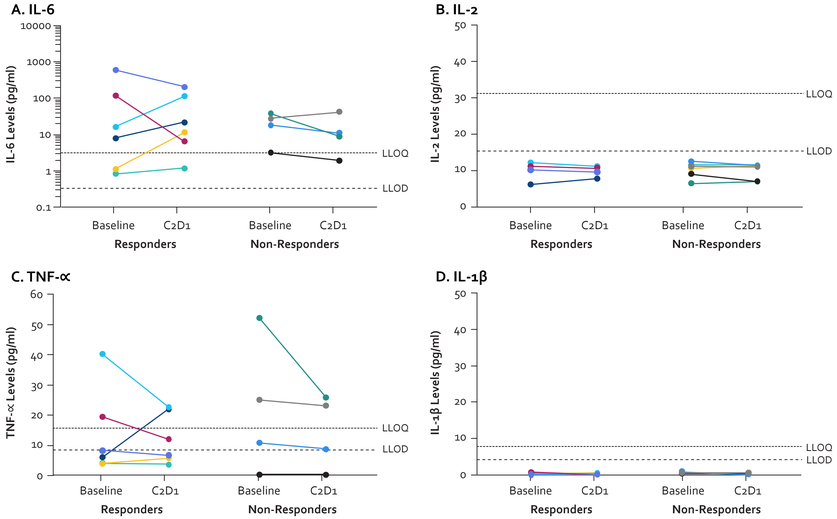


Figure 3. No induction of circulating cytokines commonly associated with cytokine release syndrome were observed. Concentrations of circulating cytokines for A. IL-6, B. IL-2, C. TNF-α, D. IL-1β are shown. For each plot, concentrations for paired baseline (pre-C1D1) and pre-C2D1 samples for each subject is shown, with relative change denoted by a connecting line. Subjects are further grouped into responder and non-responder categories as in Figures 1 and 2. Lower limits of detection (LLOD) and quantification (LLOQ) are depicted by horizontal dashes.

CONCLUSIONS

- From these analyses, ex-vivo measurement of the fold change in frequency of circulating EBV-specific CTLp following administration of tab-cel® significantly correlated (p = 0.038) with clinical response in a cohort of subjects with a variety of EBV-driven conditions (Figure 2A).
- Additionally, subjects exhibiting a 2-fold expansion in frequency of EBV-specific CTLp from baseline (pre-C1D1) to pre-C2D1 therapy appear to correlate with favorable response (figure 2A).
- Although absolute EBV-specific CTLp frequency at C2D1 trended similarly to subject response, fold change from baseline was more predictive (figure 2B).
- Despite measurement and presence of EBV-reactive CTLp in circulation pre-C2D1, concurrent induction of inflammatory cytokines commonly associated with cytokine release syndrome was not evident (figure 3A-D).
- These data further support the clinical activity of tab-cel® in a broad range of EBV-driven diseases including EBV+PTLD following HCT and SOT.
- The safety profile of tab-cel® in these subjects is consistent with previously reported data.[1]

REFERENCES

1. Prockop S, Li A, Baiocchi RA, Bunin N, Mahadeo KM, Nemecek ER, Nikiforow S, Reshef R, Tsai DE, Navarro WH, O'Reilly RJ. Efficacy and Safety of ATA129, Partially Matched Allogeneic Third-Party Epstein-Barr Virus-Targeted Cytotoxic T Lymphocytes in a Multicenter Study for Post-Transplant Lymphoproliferative Disorder. *Blood.* 2017;130: 4520.

DISCLOSURES

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Blake T. Aftab: Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics; Patents, Royalties, Other Intellectual Property - Atara Biotherapeutics **Daniel Munson:** Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics; Research Funding - Atara Biotherapeutics; Patents, Royalties, Other Intellectual Property - Atara Biotherapeutics **Kevin Rasor:** Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics **Philippe Foubert:** Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics **Donald Edward Tsai:** Employment - Loxo; Stock and Other Ownership Interests - Loxo; Honoraria - Atara Biotherapeutics; Consulting or Advisory Role - Brystol-Myers-Squibb, Novartis **Wen-Kai Weng:** No Relationships to Disclose **Armin Ghobadi:** No Relationships to Disclose **Koen Van Besien:** Stock and Other Ownership Interests - HemOgenyx; Consulting or Advisory Role - Actinium Medical Advisory Board, HemOgenyx, Juno Therapeutics, Tessa Therapeutics; Research Funding - Atara Biotherapeutics, Fate Therapeutics, Juno Therapeutics, Miltenyi Biotec, Novartis **Yan Sun:** Employment - Amgen, Atara Biotherapeutics; Stock and Other Ownership Interests - Amgen, Atara Biotherapeutics **Minoti Hiremath:** Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics **Willis H. Navarro:** Employment - Atara Biotherapeutics; Stock and Other Ownership Interests - Atara Biotherapeutics, GE Healthcare, Kite Pharma, Pfizer; Patents, Royalties, Other Intellectual Property - Patent pending for a use of cytotoxic T lymphocytes (Inst) **Susan Prockop:** No Relationships to Disclose

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