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Administration of Tabelecleucel

ICD-10-PCS Coordination & Maintenance Meeting
March 8, 2022

Agenda

- Tabelecleucel Overview
- Epstein-Bar Virus Positive Post-transplant Lymphoproliferative Diseases (EBV+ PTLD)
- Review of Manufacturing and Clinical Data
- Request for ICD-10-PCS Code

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Tabelecleucel is an Investigational, Allogeneic T-cell Immunotherapy

EBV-specific T cell Immunotherapy

- Being developed to target and eliminate EBV expressing cells in a human leukocyte antigen (HLA) restricted manner
- Derived from 3rd party donor cells that have had further processing/ manufacturing
- Product selected for patient on a minimum of 2 common HLA alleles
- Kills EBV infected cells with limited off target activity

Administration:

- Ability to be administered in the inpatient or outpatient setting, depending on patient's condition at time of administration.
- **According to the Allele Study:**
  - 51% of patients received at least one dose in the inpatient setting
  - 33% of patients received all doses in the inpatient setting
- Dose is weight based
- Administered in doses or cycles; not a one time infusion
- Patient receives administrations on days 1, 8 and 15
- Cycles are determined based on clinical response
- Product must be thawed, diluted, and dosed properly
- No pre treatment required before therapy
- 5 10 minute IV with 1 hour monitoring
- Information regarding tabelecleucel, and its associated administration procedure, will be documented in the medical record and identifiable from multiple perspectives (e.g., physician orders, pharmacy notes, treatment summary)

FDA Status

- Atara has on going interactions with the FDA and plans to complete the Biologics License Application (BLA) submission for tabelecleucel in Q2 2022
- FDA Breakthrough Therapy Designation

There is an Unmet Need for Effective and Well-tolerated Therapies in Patients With EBV+ PTLD as Patients Who Do Not Respond to Initial Treatment Have Few Treatment Options

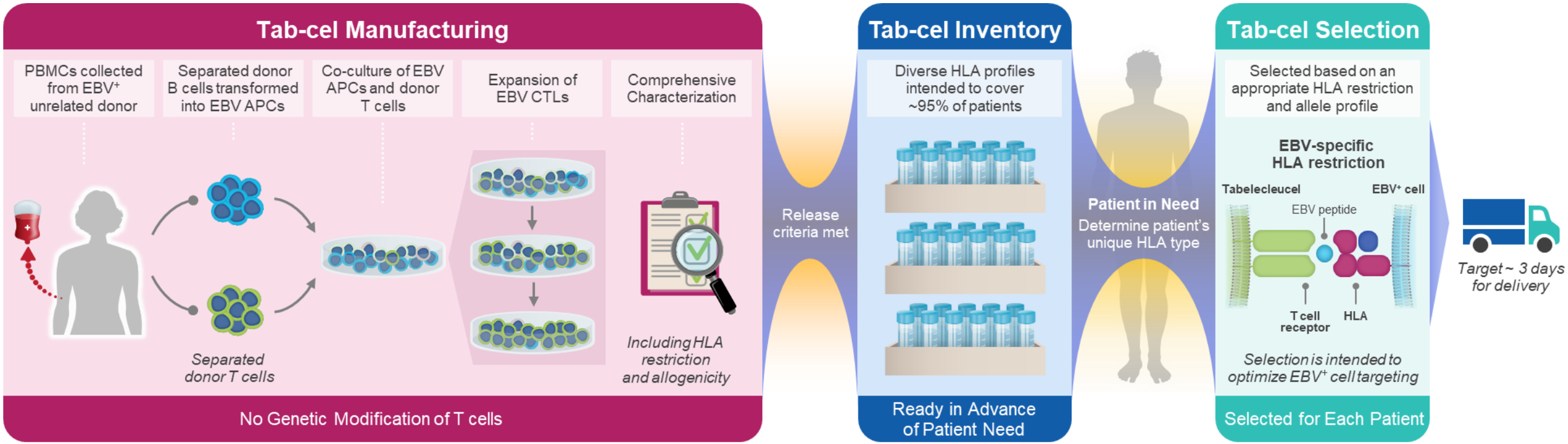
- Patients undergoing allogeneic hematopoietic cell transplant (HCT) or solid organ transplant (SOT) are at risk of developing Epstein–Barr virus driven post-transplant lymphoproliferative disorder (EBV+ PTLD), an ultra-rare, aggressive, and potentially deadly hematologic malignancy[1–3]
- There are no approved treatments for EBV+ PTLD[4]
  - Rituximab is the recommended therapy for EBV+ PTLD following HCT
  - Rituximab ± chemotherapy is the suggested therapeutic approach for EBV+ PTLD following SOT[5]

The poor median survival (0.7 months for HCT, 4.1 months for SOT) reported in patients with EBV+ PTLD for whom rituximab + CT failed demonstrates an urgent unmet need in this patient population

HCT = hematopoietic cell transplant; SOT = solid organ transplant.

1. Ocheni S, et al. *Bone Marrow Transplant.* 2008;42:181–6. 2. Uhlin M, et al. *Haematologica*. 2014;99:346–52. 3. Nijland ML, et al. *Transplant Direct*. 2015;15;2:e48. 4. Al Hamed R et al. *Bone Marrow Transplant* 2020;55:25–39. 5. Trappe R et al. *Lancet Oncol* 2012;13:196–206.

Overview from Manufacturing to Selection of Tabelecleucel for a Specific Patient



APC, antigen-presenting cells; CTL, cytotoxic T lymphocyte; EBV, Epstein Barr Virus; PBMC, peripheral blood mononuclear cell; HLA, human leukocyte antigen; tab-cel, tabelecleucel.

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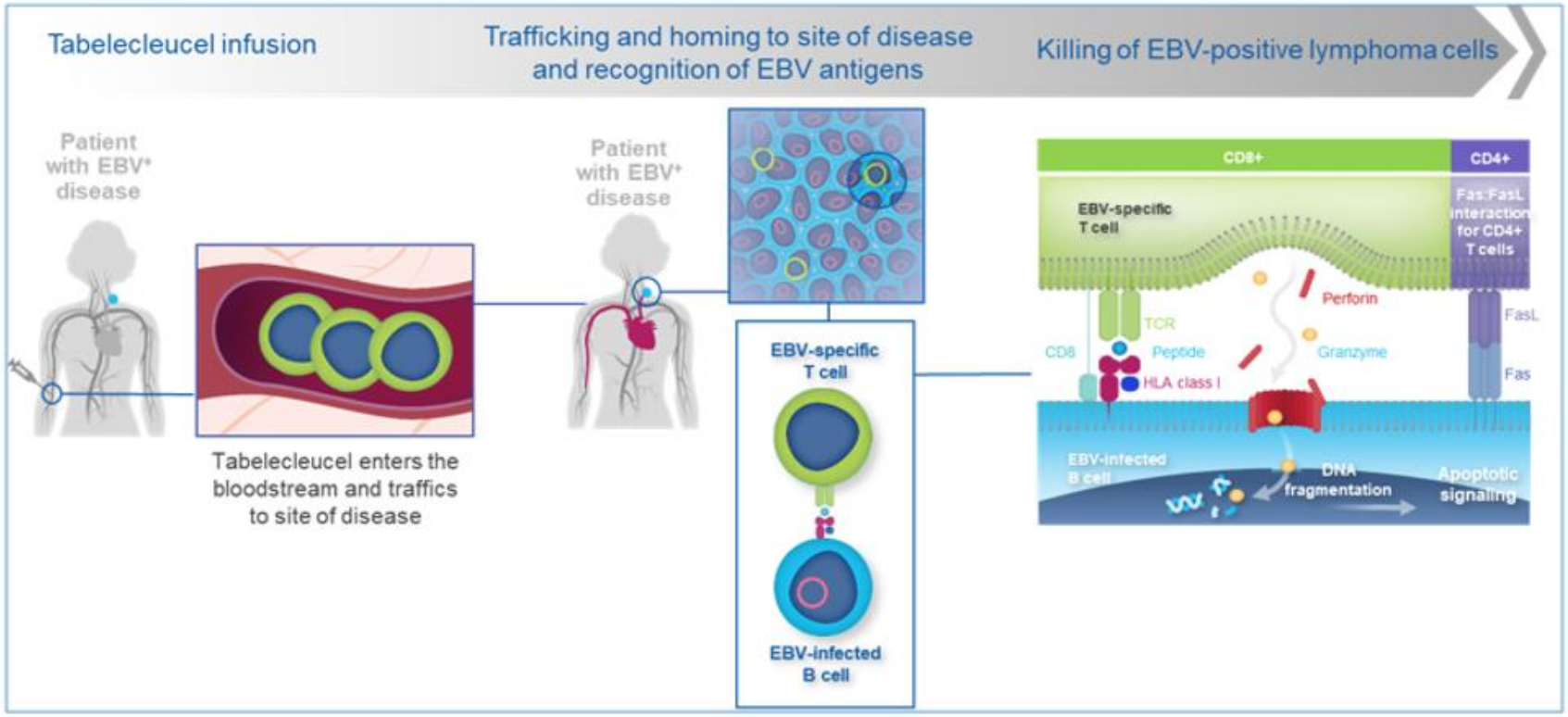
Tabelecleucel is administered intravenously (peripheral vein)

Figure 1. Tabelecleucel mechanism of action



- The T-cell receptor of each clonal population within tabelecleucel recognizes an EBV peptide in complex with a specific HLA molecule on the surface of target cells (the restricting HLA allele) and allows tabelecleucel to exert cytotoxic activity against the EBV-infected cell.

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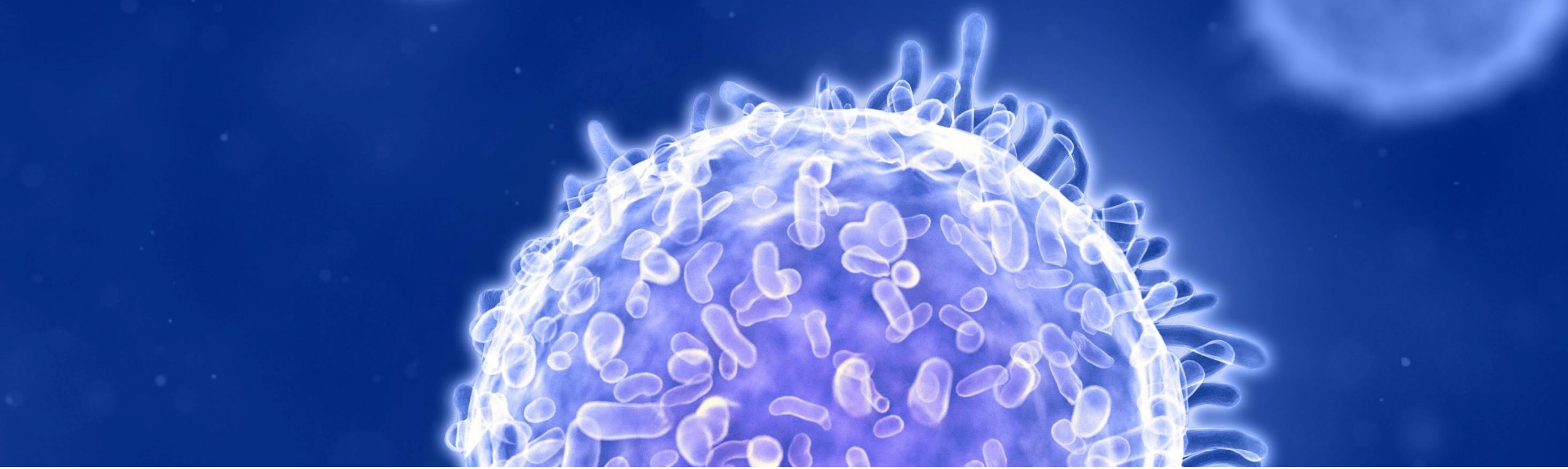

Clinical Study Data & Adverse Events

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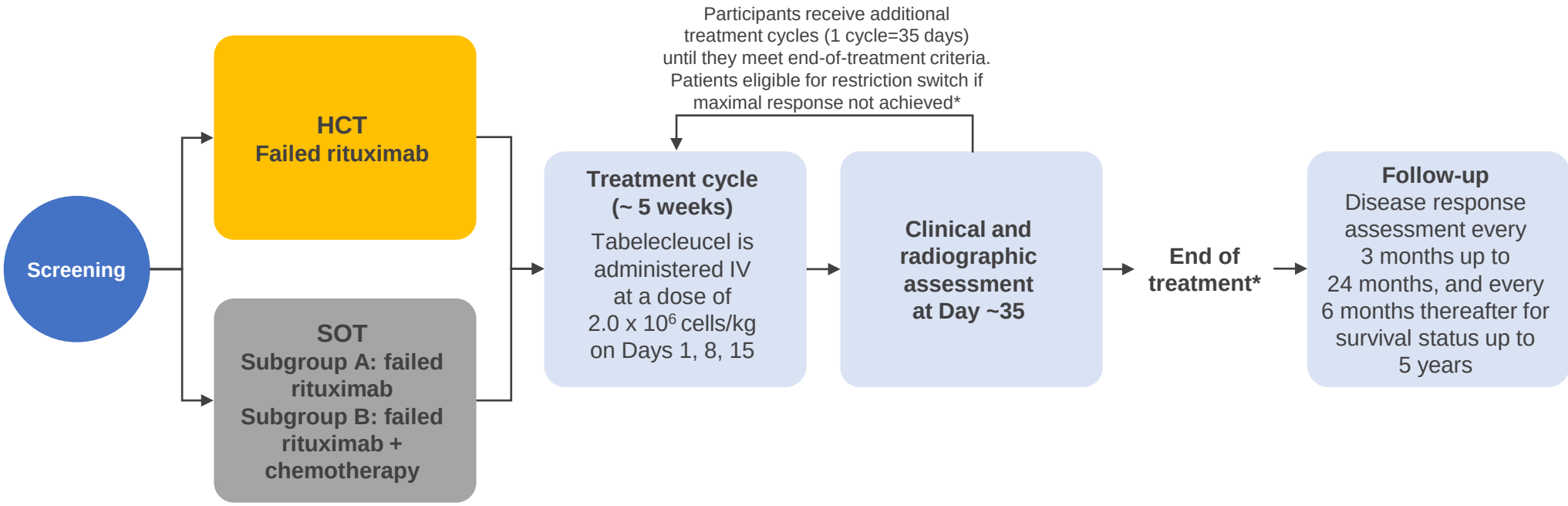
ALLELE: Multicenter, Open-Label, Phase 3 Study of Tabelecleucel after Failure of Rituximab ± Chemotherapy in Patients with EBV+ PTLD Following HCT or SOT



- **Key eligibility criteria:**
  - **Prior allogeneic HCT or SOT**
  - **Biopsy proven EBV+ PTLD**
  - **Previous rituximab or rituximab chemo failure**
  - **ECOG ≤ 3**

- **Primary endpoint: ORR†**
- **Key secondary endpoints:**
  - **OS**
  - **DOR**
  - **TTR and time to best response**
  - **Rates of allograft loss/ rejection episodes (SOT)**

*Treatment ends with any of the following: maximal response achieved, unacceptable toxicity, initiation of non-protocol therapy, failure of up to 4 tabelecleucel with different HLA restrictions (HCT) or 2 tabelecleucel with different HLA restrictions (SOT).
†Evaluated by independent review (independent oncologic response adjudication, IORA).
DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; HCT = hematopoietic stem cell transplant; HLA = human leukocyte antigen; IV = intravenously; ORR = objective response rate; OS = overall survival; SOT = solid organ transplant; TTR = time to response.

Baseline Demographics

Characteristics	HCT (n 14)	SOT (n 24)	All (N 38)
Median age, years (range)	51.9 (3.2–73.2)	52.9 (15.4–81.5)	52.9 (3.2–81.5)
Male, n (%)	8 (57.1)	13 (54.2)	21 (55.3)
Race, White, n (%)	12 (85.7)	21 (87.5)	33 (86.8)
Median ECOG score (range)*	1 (0–3)	1 (0–3)	1 (0–3)
ECOG score ≥2 (age ≥16 years), n (%)†	3 (23.1)	8 (34.8)	11 (30.6)
Median number of lines of prior systemic treatment, n (range)	1 (1–4)	1 (1–5)	1 (1–5)
Prior rituximab monotherapy, n (%)	14 (100)	21 (87.5)	35 (92.1)
Prior chemotherapy, n (%)‡	3 (21.4)	13 (54.2)	16 (42.1)
Prior immunotherapy, n (%)§	1 (7.1)	1 (4.2)	2 (5.3)

Thirty eight patients (14 HCT, 24 SOT) with EBV+ PTLD R/R to rituximab ± chemotherapy were treated with tabelecleucel and had the opportunity for 6 months follow up

Data cutoff date: May 7, 2021.

*Data are shown in patients aged ≥16 years and having baseline ECOG measurement (n=35; n=13 for HCT and n=22 for SOT). †Data are shown in patients aged ≥16 years (n=36; n=13 for HCT and n=23 for SOT). ‡Including combined therapy with rituximab. §Any immunotherapy other than rituximab.

ECOG = Eastern Cooperative Oncology Group; HCT = hematopoietic cell transplant; LDH = lactate dehydrogenase; R/R = relapsed/refractory; SOT = solid organ transplant.

Disease Characteristics

Characteristics	HCT (n=14)	SOT (n=24)	All (N 38)
PTLD-adapted prognostic index (age ≥16 years), n (%)*	High: 6 (46.2) Int: 6 (46.2) Low: 1 (7.7) Unknown: 0	High: 10 (43.5) Int: 11 (47.8) Low: 1 (4.3) Unknown: 1 (4.3)	High: 16 (44.4) Int: 17 (47.2) Low: 2 (5.6) Unknown: 1 (2.8)
Extranodal disease at screening, n (%)	9 (64.3)	19 (79.2)	28 (73.7)
PTLD morphology, n (%)			
Diffuse large B-cell lymphoma	10 (71.4)	17 (70.8)	27 (71.1)
Plasmablastic lymphoma	1 (7.1)	1 (4.2)	2 (5.3)
Other†	3 (21.4)	6 (25.0)	9 (23.7)
Transplant organ type, n (%)			
Heart	N/A	6 (25.0)	N/A
Kidney	N/A	6 (25.0)	N/A
Lung	N/A	5 (20.8)	N/A
Liver	N/A	1 (4.2)	N/A
Multivisceral	N/A	6 (25.0)	N/A

Thirty eight patients (14 HCT, 24 SOT) with EBV+ PTLD R/R to rituximab ± chemotherapy were treated with tabelecleucel and had the opportunity for 6 months follow up

Data cutoff date: May 7, 2021.

*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 is shown in patients aged ≥16 years (n=36; n=13 for HCT and n=23 for SOT). Choquet S, *et al*. *Ann Hematol*. 2007;86(8):599-607. †Morphologies not clearly diffuse large B-cell lymphoma or plasmablastic lymphoma were categorized as Other.
ECOG = Eastern Cooperative Oncology Group; HCT = hematopoietic cell transplant; LDH = lactate dehydrogenase; R/R = relapsed/refractory; SOT = solid organ transplant.

Primary Endpoint: Objective Response Rate by Independent Review (IORA)*

	HCT (n=14)	SOT (n=24)	All (N 38)
Responders, n (%)	7 (50.0)	12 (50.0)	19 (50.0)
95% CI	23.0, 77.0	29.1, 70.9	33.4, 66.6
Best overall response, n (%)			
CR	5 (35.7)	5 (20.8)	10 (26.3)
PR	2 (14.3)	7 (29.2)	9 (23.7)
SD	3 (21.4)	2 (8.3)	5 (13.2)
PD	2 (14.3)	7 (29.2)	9 (23.7)
NE	2 (14.3)	3 (12.5)	5 (13.2)
Median time to response, months (range)	1.0 (1.0–4.7)	1.6 (0.7–4.1)	1.1 (0.7–4.7)
Median follow-up in response, months (range)	10.2 (1.3–23.3)	4.7 (0.6–21.0)	7.1 (0.6–23.3)
Estimated median duration of response, months (95% CI)†	NE	NE (0.8, NE)	NE (6.8, NE)

The objective response rate (PR+CR) in all patients was 50.0% (19/38), with a best overall response of CR (26.3%; n=10) or PR (23.7%; n=9)

Median time to response in all patients was 1.1 month (range: 0.7–4.7)

Data cutoff date: May 7, 2021.

*Response assessed per Lugano Classification with LYRIC modification by IORA. †Median duration of response was estimated by the KM method.
CI = confidence interval; CR = complete response; IORA = independent oncologic response adjudication; KM = Kaplan Meier; NE = not evaluable (best overall response)/not estimable (median DOR); PD = progressive disease; PR = partial response; SD = stable disease.

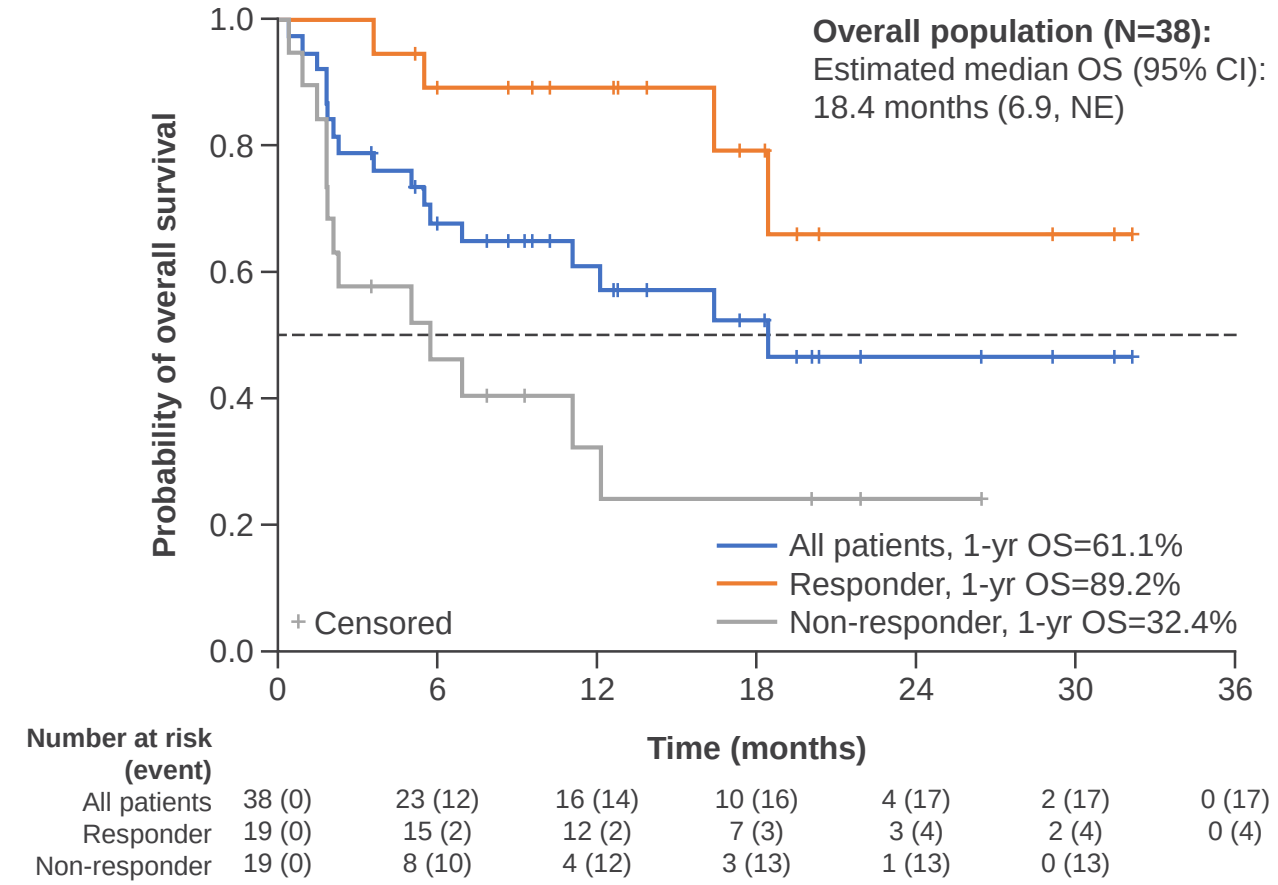
Tabelecleucel Exposure

	HCT (n 14)	SOT (n 24)	All (N 38)
Median time from transplant to EBV⁺ PTLD diagnosis (range)	4.3 months (0.6–66.0)	1.2 years (0.3–26.2)	---
Median time from initial EBV⁺ PTLD diagnosis to first administration of tabelecleucel (range)	1.2 months (0.6–28.1)	6.6 months (2.0–190.5)	3.6 months (0.6–190.5)
Median cycles of tabelecleucel (range)	3.0 (1–5)	2.0 (1–6)	2.5 (1–6)
Median dosage of tabelecleucel (range)	2 x 10^6 cells/kg/dose (2–2)	2 x 10^6 cells/kg/dose (2–2)	2 x 10^6 cells/kg/dose (2–2)
Median number of doses administered (range)	9 (2–15)	6 (2–18)	7.5 (2–18)
Median treatment duration (range)	2.8 months (0.2–5.7)	2.0 months (0.3–6.5)	2.4 months (0.2–6.5)

Patients received a median (range) of 2.5 (1 6) cycles of tabelecleucel

Patients Responding to Tabelecleucel had Longer Overall Survival

	HCT (n=14)	SOT (n=24)	All (N 38)
Median follow-up, months (range)	10.6 (2.0–31.4)	8.0 (0.4–32.1)	9.4 (0.4–32.1)
Estimated median OS, months (95% CI)	NE (5.7, NE)	16.4 (3.5, NE)	18.4 (6.9, NE)
Estimated 1-year OS rate % (95% CI)	66.8 (32.4, 86.6)	57.4 (35.2, 74.5)	61.1 (42.9, 75.0)
Responders, n	7	12	19
Estimated median OS, months (95% CI)	NE	NE (5.5, NE)	NE (16.4, NE)
Estimated 1-year OS rate % (95% CI)	100	82.5 (46.1, 95.3)	89.2 (63.1, 97.2)
Non-responders, n	7	12	19
Estimated median OS, months (95% CI)	11.0 (2.0, NE)	3.4 (0.9, 12.1)	5.7 (1.8, 12.1)
Estimated 1-year OS rate % (95% CI)	26.8 (1.3, 67.0)	33.3 (10.3, 58.8)	32.4 (12.1, 54.9)

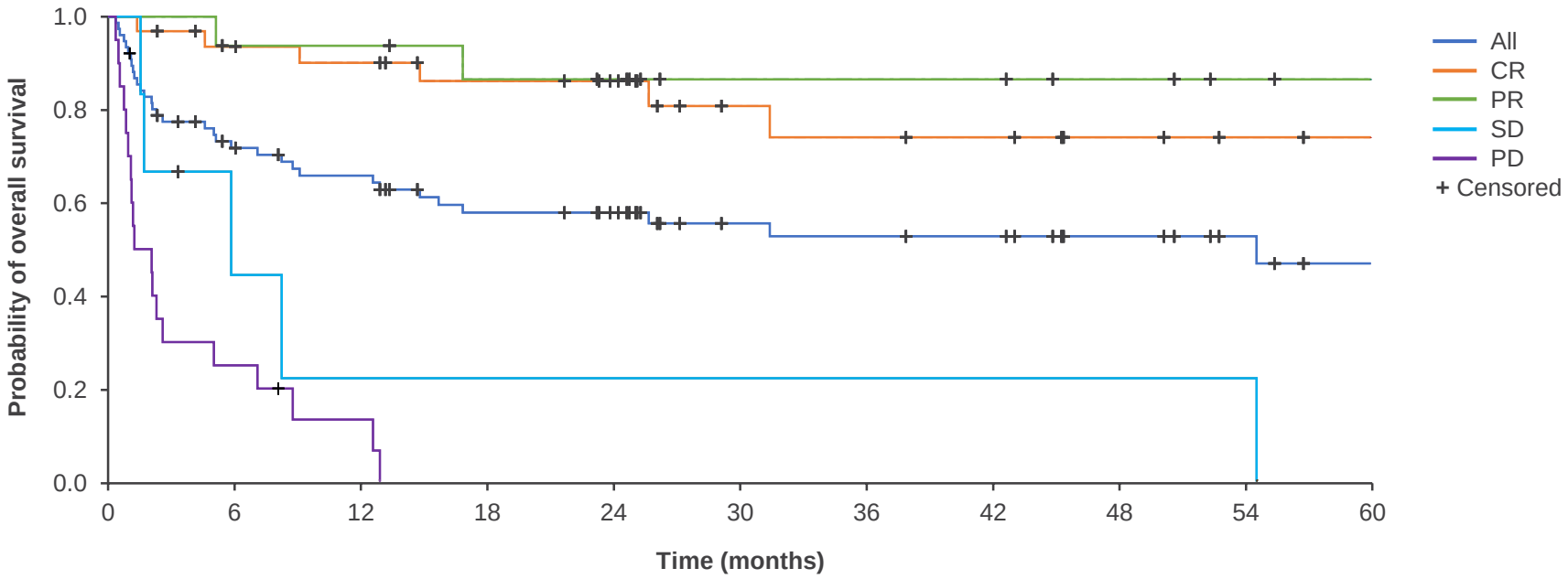


Patients responding to tabelecleucel had higher 1 year overall survival rate compared with non responders (89.2% vs 32.4%)

Data cutoff: May 7, 2021.
OS was estimated by the KM method.

CI = confidence interval; HCT = hematopoietic cell transplant; KM = Kaplan Meier; NE = not estimable; OS = overall survival; SOT = solid organ transplant.

Estimated Overall Survival by Best Overall Response Per Investigator in All Patients from the Legacy and 201 Clinical Trials



Number at risk (event)

All	76 (0)	50 (21)	44 (25)	35 (30)	31 (30)	20 (31)	19 (32)	18 (32)	13 (32)	9 (32)	6 (33)
CR	32 (0)	28 (2)	26 (3)	22 (4)	19 (4)	12 (5)	11 (6)	10 (6)	7 (6)	5 (6)	4 (6)
PR	16 (0)	14 (1)	14 (1)	12 (2)	11 (2)	7 (2)	7 (2)	7 (2)	5 (2)	3 (2)	2 (2)
SD	6 (0)	2 (3)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	0 (5)
PD	20 (0)	5 (15)	2 (17)	0 (19)							

Estimated overall survival was greater in responders (vs non-responders) and was similar across patients with CR or PR

*Two out of 76 patients did not have post-baseline assessments per investigator

CR = complete response; mOS = median overall survival; PD = progressive disease; PR = partial response; SD = stable disease

Tabelecleucel was Well Tolerated in These Treatment Refractory and Immunocompromised Patients

Event type	HCT (n 14)	SOT (n 24)	All (N 38)
Any TESAEs – n (%)	8 (57.1)	15 (62.5)	23 (60.5)
Grade ≥3 TESAEs – n (%)	8 (57.1)	15 (62.5)	23 (60.5)
Fatal TESAEs – n (%)*	1 (7.1)	4 (16.7)	5 (13.2)
Treatment-related TESAEs – n (%)†	0	4 (16.7)	4 (10.5)
Grade ≥3 treatment-related TESAEs – n (%)‡	0	2 (8.3)	2 (5.3)
Treatment-related fatal TESAEs – n (%)	0	0	0

None of the fatal TESAEs were related to tabelecleucel

There was no trend in treatment related TESAEs, as all except for pyrexia were reported in single patients

Data cutoff date: May 7, 2021.

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.
*Fatal TESAEs were disease progression (n=3), respiratory failure (n=1), multiple organ dysfunction syndrome (n=1). †Treatment-related TESAEs were diarrhoea, hypoxia, pyrexia (1 patient each, with hypoxia grade 3), and hypotension, pyrexia, rash, rash erythematous, and tachycardia (same patient, with hypotension grade 3 and rash erythematous grade 4). ‡One patient (SOT) had grade 3 hypotension and grade 4 rash erythematous and one patient (SOT) had grade 3 hypoxia.
AE = adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

No Evidence for Identified or Potential Risks in Relation to Tabelecleucel

Event type	HCT (n 14)	SOT (n 24)	All (N 38)
Tumor flare reaction, n (%)	0	0	0
Infusion-related reaction, n (%)	0	0	0
Cytokine release syndrome, n (%)	0	0	0
Transmission of infectious diseases, n (%)	0	0	0
Graft vs host disease, n (%)	0	0	0
Marrow/organ rejection, n (%)	0	0	0

There were no reports of tumor flare reaction, infusion related reaction, cytokine release syndrome, marrow rejection, or transmission of infectious diseases, including cytomegalovirus

There were no events of graft vs host disease or organ rejection reported as related to tabelecleucel

Data cutoff date: May 7, 2021.

Table presents the number (%) of patients with events in each category.

Tabelecleucel Has Demonstrated Clinical Benefit in the Treatment of EBV+ PTLD After Failure of Rituximab ± Chemotherapy

- Single-center study experience demonstrates promising outcomes in EBV+ PTLD after failure of rituximab ± chemotherapy and/or radiation[1]
  - **ORR* of 64% in all patients;** 83% estimated 2-year OS rates in those patients who responded with either CR or PR to EBV+ CTLs[1]
- Data from the single-center study experience as well as a multi-center study, demonstrates potential clinical benefit in patients with relapsed/refractory EBV+ PTLD after HCT or SOT
  - **ORR* of >60% in all patients**, >80% estimated 2-year OS rates in those patients who responded with either a CR or PR to tabelecleucel[2,3]
- To date, safety data have been assessed in >180 patients with EBV+ PTLD treated with tabelecleucel, with tumor flare reaction as the only identified risk[4]
- We report efficacy and safety results from an interim analysis of the pivotal phase 3 clinical trial ALLELE (NCT03394365) – a multicenter, open-label study of tabelecleucel after failure of rituximab ± chemotherapy in patients (N=38†) with EBV+ PTLD following HCT or SOT

*ORR was investigator-assessed. †Evaluable analysis set, consisting of all subjects who received ≥1 dose of tabelecleucel and ≥1 evaluable post-baseline disease assessment, or discontinued study or received non-protocol anti-PTLD therapy.

CR = complete response; CTL = cytotoxic T lymphocyte;; HCT = hematopoietic stem cell transplant; ORR = objective response rate; OS = overall survival; PR = partial response; SOT = solid organ transplant.

1. Prockop S, *et al*. *J Clin Invest*. 2020;130:733-747. 2. Prockop S, *et al*. *Bone Marrow Transpl*. 2021;55:21-183. Presented at EBMT 2021. 3. Prockop S *et al*. *Am J Transplant*. 2021; 21 (suppl 3). Presented at ATC 2021. Abstract #5503.
4. Data on File. Atara Biotherapeutics. May 7, 2021.

There are currently no ICD-10-PCS codes that uniquely describe the administration of tabelecleucel

1

A unique ICD-10-PCS Section X code is needed for tabelecleucel:

- To facilitate research and reporting purposes
- To identify and track the use of tabelecleucel for related outcomes data if NTAP is granted, for claims processing of qualifying cases of tabelecleucel

2

Information regarding tabelecleucel and its associated administration procedure, will be documented in the medical record and identifiable from multiple perspectives (e.g., physician orders, pharmacy notes, treatment summary)