GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

FAD SINCRONA
4 dicembre 2024

con il patrocinio di: S·I·T·O· SOCIETÀ ITALIANA DEI TRAPIANTI D'ORGANO E DI TESSUTI

Come migliorare l'outcome con l'immunoterapia a cellule T EBV-specifica nel trapianto di organo solido dell'adulto

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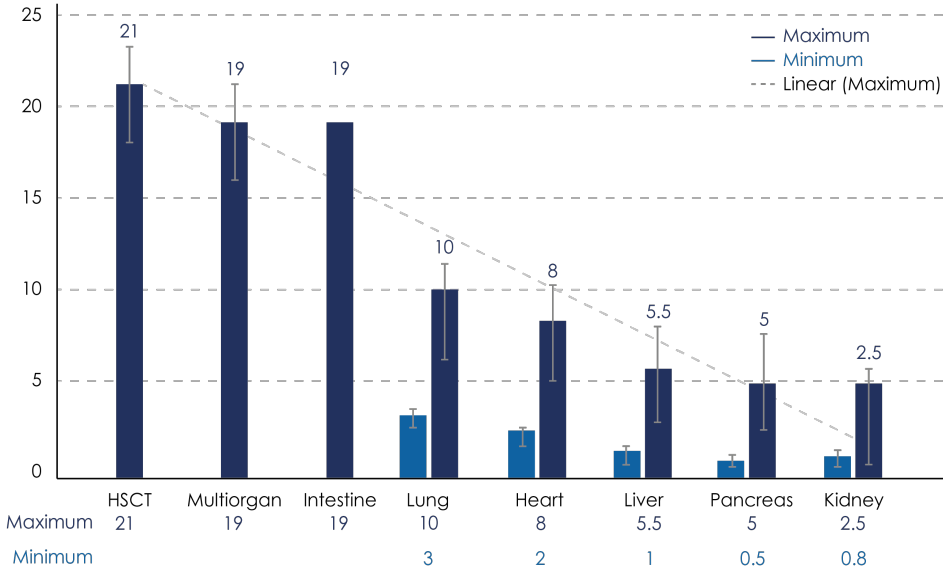
Disclosures

Advisory Board: Incyte, Roche, Astra Zeneca

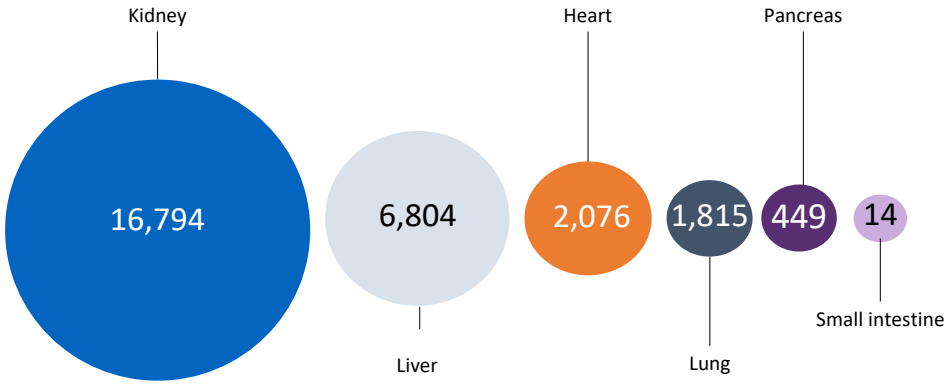
Speakers Bureau: Novartis, Incyte, Lilly, Astra Zeneca, Gilead, Pierre Fabre, Beigene, Sobi

Incidence of PTLD post-SOT varies by organ transplant site

Incidence of PTLDs in various transplants[1]*



Number of SOT performed in Europe in 2022[2]

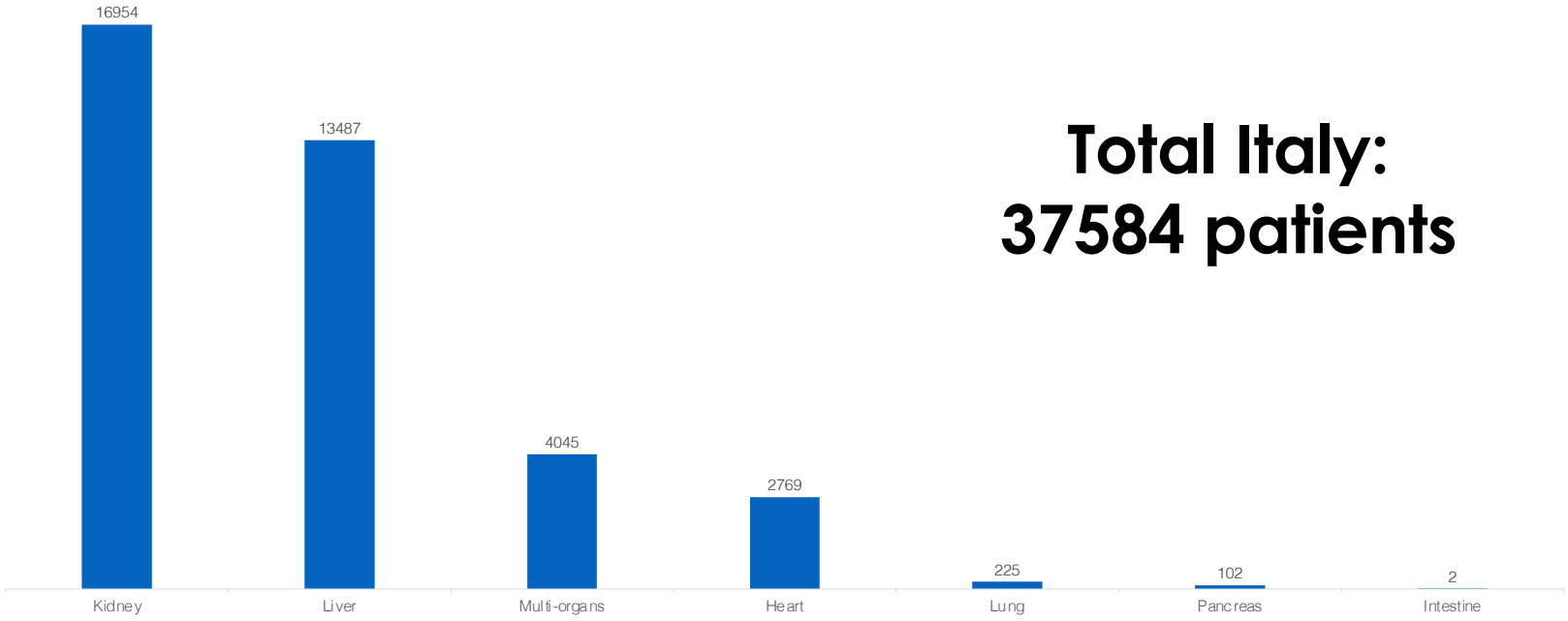


Total transplanted organs: 27,952

*Note: Minimum values were not given for multiorgan or intestinal.
HSCT: Haplo-identical allogeneic haematopoietic stem-cell transplant; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant.

1. Abbas F, et al. World J Transplant 2020;10(2):29–46; 2. Statista. Number of organ transplants carried out in the European Union in 2022. Available at: https://www.statista.com/statistics/1204326/organ-transplantation-activity-in-the-eu/. Accessed June 2024.

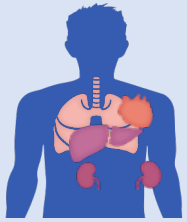
Patients transplanted for Solid Organs in Italy between 2013 and 2023.



Total Italy:
37584 patients

Source: CNT (Centro Nazionale Trapianti)

EBV+ PTLD: a rare disease in SOT patients



27,952[1]
SOT patients in the EU in 2022[1]

- Incidence of PTLD : 1–33%[2]
- ~50% of PTLD cases are associated with EBV[3]
- >50% cases arise after >1 year after transplant[4]

The incidence of EBV reactivation post-SOT ranges from 13–48%[5]

Patients with relapsed or refractory EBV+ PTLD that have received at least one previous treatment are considered ultra-rare haemopathies[6]

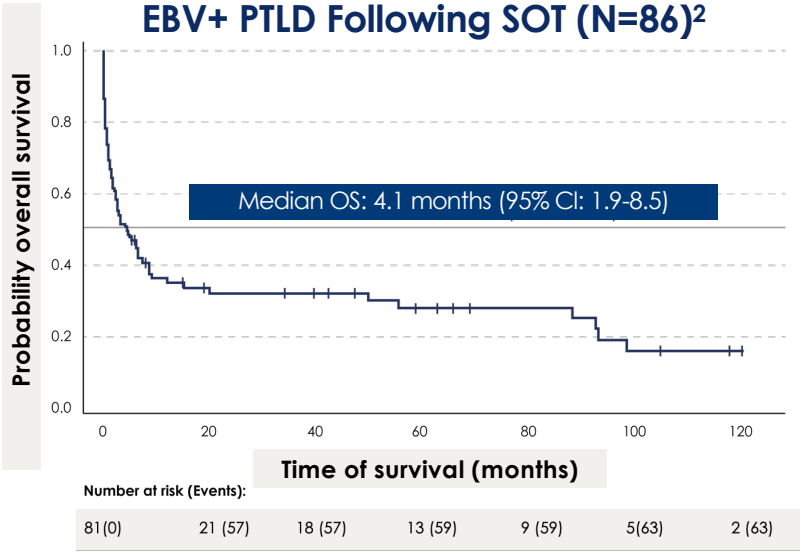
EBV, Epstein Barr virus; HCT, haematopoietic cell transplant; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplant.

1.La Moncla. Available at: https://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2023/20230830_eu-donors. Accessed June 2024 ; 2.Fujimoto A, et al. Cancers (Basel). 2020;12:328; 3. Vergote VKJ. et al. Transpl Int 2022;35:10707; 4 Dierickx D et al. Curr Opin Oncol 2022;34(5):413–421; 5.Blazquez-Navarro A, et al. Transpl Int. 2021;341680–1688; 6. DeStephano CB. et al. British Journal of Haematology 2018;182:330–343.

Outcomes of SOT recipients with relapsed/refractory EBV+ PTLD

A large multinational, multicenter* retrospective chart review study of EBV+ PTLD patients following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000–December 2018 and were refractory or relapsed at any point after such therapy[1,2]

Overall survival in Patients with R/R EBV+ PTLD Following SOT (N=86)[2]



Adapted from Dhamidharka V, et al. 2022.

Unmet clinical need for relapsed/refractory patients

* Data were collected from 29 centers across North America (United States and Canada) and the European Union.[1,2]

EBV+, Epstein-Barr virus positive, GvHD, graft vs host disease; HCT, haematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplantation.

2. Dharnidharka V, et al. HemaSphere 2022;6(Abstract):997–998.

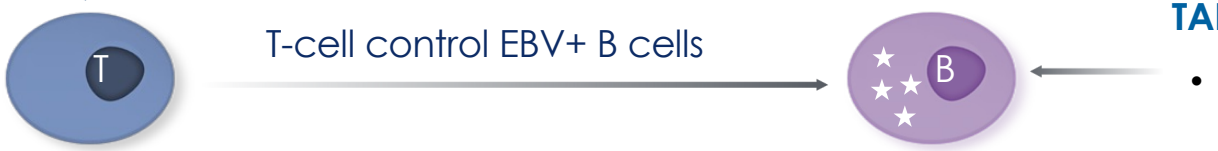
Therapeutic strategies for treatment of EBV+ PTLD

RESTORING T-CELL FUNCTION[1]

- Reduction of immunosuppression
- Donor lymphocyte Infusion
- EBV+ CTLs
- Checkpoint inhibitors
- CAR-T

REDUCTION OF B-CELL MASS[1]

- Anti-CD20 antibodies
- Chemotherapy
- Surgery/radiation
- Anti-CD30 antibodies
- Bruton kinase inhibitors



TARGETING EBV

- Antivirals / HDAC inhibitors

CAR-T, chimeric antigen receptor T-cell therapy; CD20/30, cluster of differentiation 20/30; CTL, cytotoxic T lymphocyte; EBV+, Epstein–Barr virus positive; HDAC, histone deacetylase; PTLD, post-transplant lymphoproliferative disorder.

1. Styczynski J, et al. Anti cancer Research. 2022;42(11):5181–5186.

Tabelecleucel is an allogeneic T-cell immunotherapy licensed for the treatment of relapsed/refractory EBV+ PTLD[1]

Tabelecleucel is indicated:[1]

As monotherapy for the treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received at least one prior therapy

For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

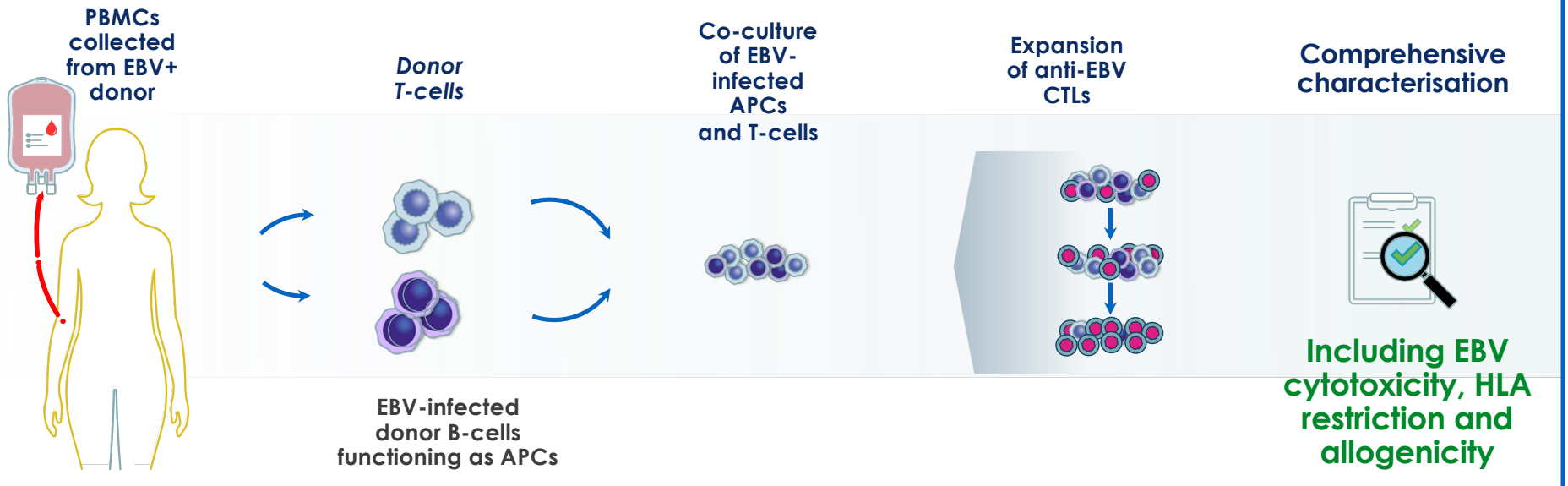
Tabelecleucel is licensed in Europe, including the UK and Switzerland in the outlined indication[1–3] and is not currently marketed in Italy.

EBV+, Epstein Barr virus positive; EU, European Union; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. tabelecleucel EU SmPC; 2. tabelecleucel UK SmPC; 3. tabelecleucel CH SmPC

Manufacturing of tabelecleucel

Tabelecleucel is manufactured from healthy EBV+ donors with diverse HLA profiles to produce expanded CTL lots that are characterised by EBV-specific cytotoxicity and HLA restriction[1–3]

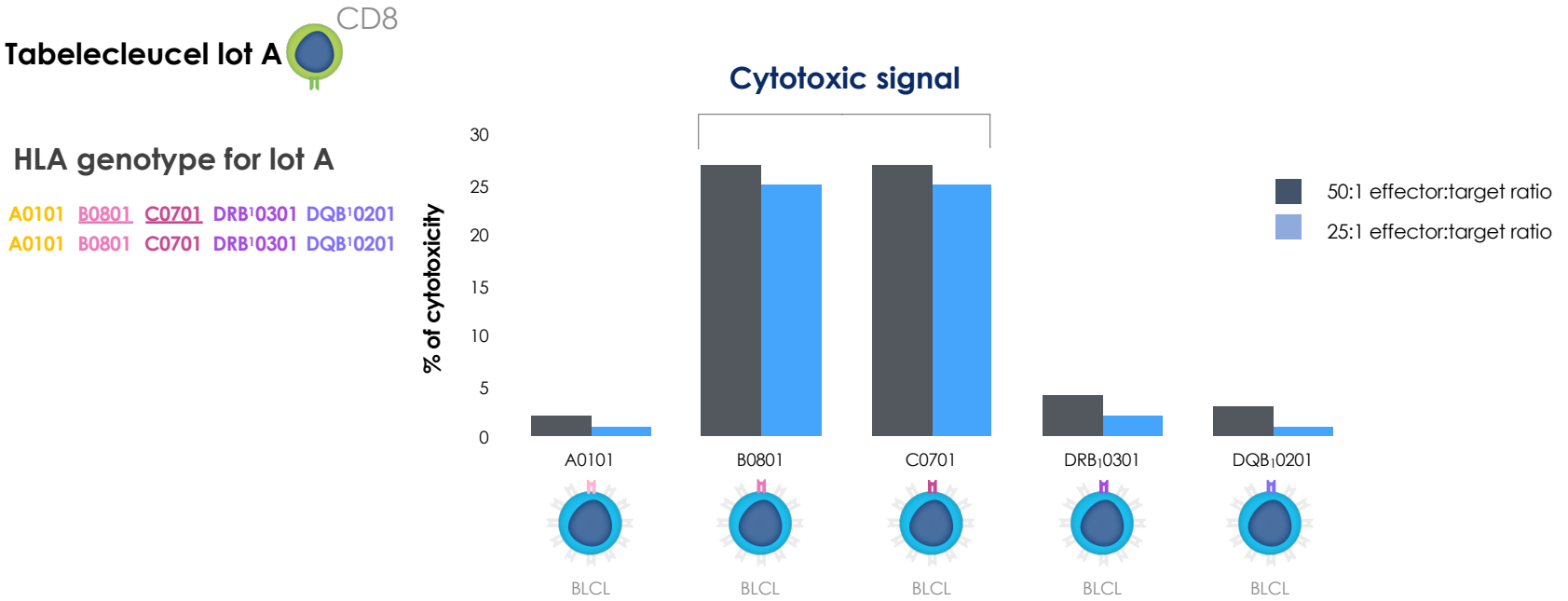


No genetic modification of T-cells

CD4/8, cluster of differentiation 4/8; DNA, deoxynucleic acid; EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; FasL, fas ligand; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease; TCR, T-cell receptor.

1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012; 3. tabelecleucel EU Summary of Product Characteristics.

Characterising the tabelecleucel lots with a cytotoxic assay: determining cytotoxicity (HLA restriction)[1]



Adapted from Barker JN, et.al. Blood. 2010;116(23):5045-9.

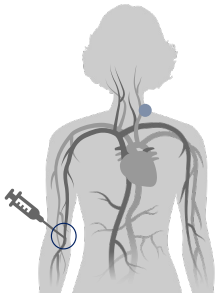
BLCL, B lymphoblastoid cell line; EBV-CTL, Epstein-Barr virus-specific cytotoxic T lymphocyte; HLA; human leukocyte antigen; NK, natural killer; PHA, phytohaemagglutinin.

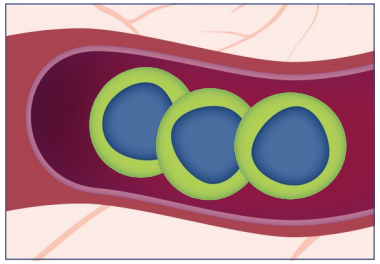
1. Barker JN et.al., Blood 2010;116(23):5045–5949.

Tabelecleucel mechanism of action

1. Tabelecleucel infusion[1,2] → **2. Trafficking and homing to PTLD tumor, and recognition of EBV antigens[1,2]** → **3. Induce lysis of EBV+ cancer cells[1,2]**

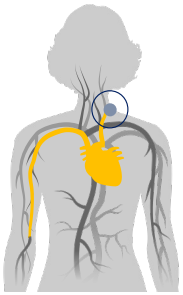
Patient with PTLD

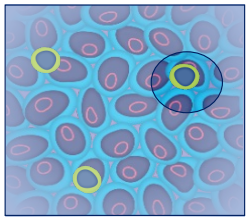




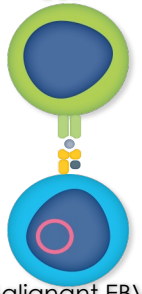
Tabelecleucel enters the blood stream and traffics to the EBV+ tumor

Patient with PTLD

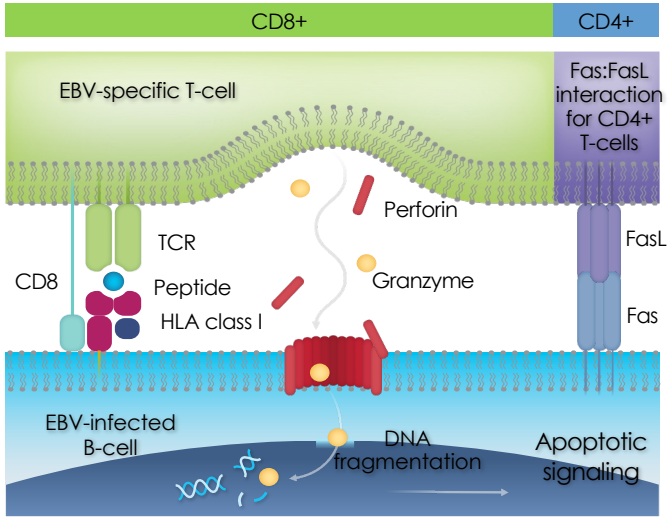




EBV-specific T-cell



Malignant EBV-infected B-cell



CD4/8, cluster of differentiation 4/8; DNA, deoxynucleic acid; EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; FasL, fas ligand; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease; TCR, T-cell receptor.

1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012.

How to establish the suspected origin of EBV+ PTLD disease

The suspected **origin of the disease** is required to ensure an appropriate tabelecleucel lot is selected

The **BEST OPTION** is to obtain **high resolution HLA typing** of the disease biopsy

If biopsy high resolution HLA typing is **not** available, the **origin of the disease must be defined:**

If the patient and donor gender are matched:

Use clinical assumptions:

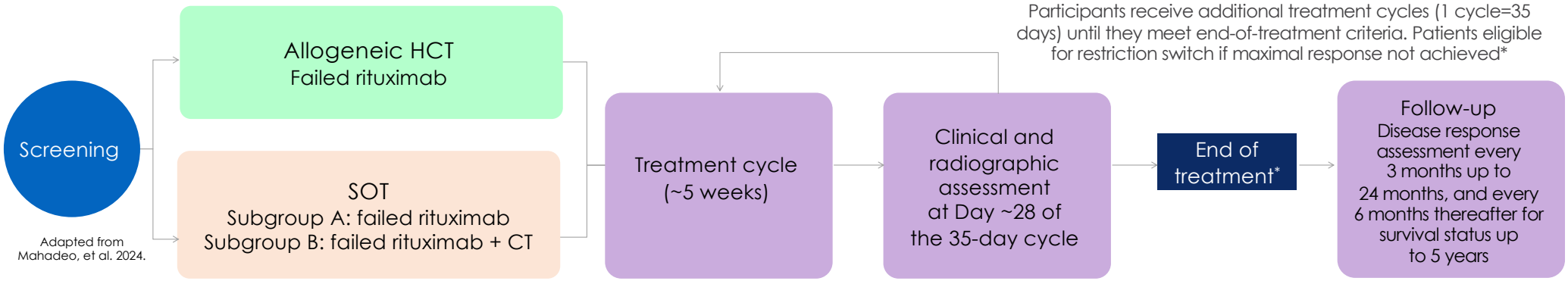
- Patient/donor EBV serostatus before transplant
- Timing of PTLD diagnosis from transplant
- Disease location (eg. organ involvement)

If the patient and donor gender are mis-matched:

Recommend to perform a **chromosome FISH test**

EBV+, Epstein-Barr virus positive; FISH, fluorescence *in situ* hybridisation; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder.

ALLELE: a global, multicentre, open-label Phase 3 study of tabelecleucel after failure of rituximab ± chemotherapy in patients with EBV+ PTLD following allogeneic HCT or SOT[1]



Adapted from Mahadeo, et al. 2024.

Key eligibility criteria:

- Prior allogeneic HCT or SOT
- Biopsy-proven EBV+ PTLD
- Previous rituximab or rituximab-CT failure
- ECOG PS ≤3 (Lansky score ≥20 for patients aged <16 years)

Key exclusion criteria:

- Patients with Grade ≥2 GvHD, active CNS PTLD, Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma

Primary endpoint: Objective response rate†

Secondary endpoints:

- OS
- Duration of response
- Objective response overall
- Overall PR and CR rates

* 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).[1] † Evaluated by independent review (IORA).[1]

DNA; deoxyribonucleic acid; CNS, central nervous system; CR, complete response; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EBV+, Epstein–Barr virus positive; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; IV, intravenous; OS, overall survival; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Mahadeo, K.M. et al. Lancet Oncol. 2024;25(3):376–387.

ALLELE: demographics and baseline characteristics

	Baseline patient characteristics[1]		
	Allogeneic HCT (n=14)	SOT (n=29)	All (n=43)
Median age, years (IQR)[1,2]	51.9 (21.9–65.1)	44.4 (23.8–67.0)	48.5 (21.9–65.4)
Male, n (%)	8 (57%)	16 (55%)	24 (56%)
ECOG score (age ≥16 years)	1.0 (0–1.0)	1.0 (0–2.0)	1.0 (0–2.0)
ECOG ≥2 (age ≥16 years)*	3 (23%)	8 (30%)	11 (28%)
Lansky score (age <16 years)	90 (n=1)	40, 90 (n=2)	40, 90, 90 (n=3)
PLTD-adapted prognostic index (age ≥16 years)*			
Low risk (%)	1 (8%)	2 (7%)	3 (8%)
Intermediate risk (%)	6 (46%)	13 (48%)	19 (48%)
High risk (%)	6 (46%)	11 (41%)	17 (43%)
Unknown risk (%)	0	1 (4%)	1 (3%)

Data are median (IQR) or n (%).
Data cut-off date: Nov 5, 2021.

The age range from all ALLELE cohorts was 3.2–81.5 years[2]

*There were 13 patients in the haematopoietic stem-cell transplant group, 27 in the solid organ transplant group, and 40 overall with available data
ECOG, Eastern Cooperative Oncology Group; HCT, haematopoietic cell transplantation; IQR, interquartile range; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplantation

1. Mahadeo KM, et al. Lancet Oncol 2024;25(3):376–387. 2. Tabelecleucel European Public Assessment Report (EPAR), 13 October 2022 (EMA/858618/2022).

ALLELE: demographics and baseline characteristics

	Baseline patient characteristics[1,2]		
	Allogeneic HCT (n=14)	SOT (n=29)	All (n=43)
Disease morphology and histology			
Diffuse large B-cell lymphoma	10 (71%)	19 (66%)	29 (67%)
Other	3 (21%)	8 (28%)	11 (26%)
Plasmablastic lymphoma	1 (7%)	2 (7%)	3 (7%)
Extra nodal disease	9 (64%)	24 (83%)	33 (77%)
Prior therapies			
No. of prior systemic therapies	1 (1–1)	1 (1–2)	1 (1–2)
Ritixumab monotherapy	14 (100%)	23 (79%)	37 (86%)
Chemotherapy in combination with rituximab*†	1 (7%)	13 (45%)	14 (33%)
Immunotherapy (other than rituximab)†	1 (7%)	1 (3%)	2 (5%)
Immunotherapy in combination with chemotherapy	1 (7%)	0	1 (2%)
Immunotherapy alone	0	1 (3%)	1 (2%)

Data are median (IQR) or n (%).
Data cut-off date: Nov 5, 2021.

*Administered as monotherapy. † Not mutually exclusive.
HCT, haematopoietic cell transplantation; IQR, interquartile range; SOT, solid organ transplantation.

1. Mahadeo KM, et al. Lancet Oncol 2024;25(3):376–387; 2. tabelecleucel European Public Assessment Report (EPAR), 13 October 2022 (EMA/858618/2022).

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

	Allogeneic HCT (n=14)	SOT (n=29)	All (n=43)
Responders, n (%)	7 (50)	15 (52)	22 (51)
95% CI	23–77	33–71	36–67
Best overall response, n (%)			
Complete response	6 (43)	6 (21)	12 (28)
Partial response	1 (7)	9 (31)	10 (23)
Stable disease	3 (21)	2 (7)	5 (12)
Progressive disease	2 (14)	7 (24)	9 (21)
Not evaluable	2 (14)	5 (17)	7 (16)
Median time to response, months (IQR)*	1.0 (1.0–1.0)	1.1 (1.0-3.0)	1.0 (1.0-2.1)
Median duration of response, months (95% CI)*,†	23.0 (15.9 – NE)	15.2 (1.2, NE)	23.0 (6.8, NE)
Median follow-up (IQR)	14.1 months (5.7–23.9)	6.0 months (1.8–18.4)	11 months (2.6–19.8)

Adapted from Mahadeo KM, et al. Lancet Oncol 2024.

Data cut off 5 November 2021.
*Secondary endpoints. † Median duration of response was estimated by the Kaplan–Meier method.
CI, confidence interval; HCT, haematopoietic cell transplantation; IQR, interquartile range; NE, not estimable; SOT, solid organ transplantation.

1. Mahadeo KM, et al. Lancet Oncol 2024;25(3):376–387.

Take Home messages

- EBV+ PTLD after SOT are rare and heterogenous diseases
- Multidisciplinary approach
- Dismal survival for R/R EBV+ PTLD post SOT
- EBV+ PTLD: EBV-CTLs now available
- Early detection of potential candidates for tabelecleucel treatment
- Prospective international trials to further improve outcome