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

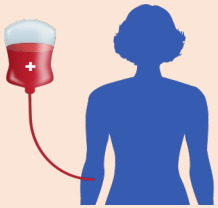
Come migliorare l'outcome con l'immunoterapia a cellule T EBV-specifica nel trapianto del midollo allogenico dell'adulto

S. Sica, Roma

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

Disclosures : Adv B Pierre FABRE, Novartis, Roche, Kyte Gilead, JAZZ, ALEXION, SOBI

EBV+ PTLD in allogeneic HCT patients



19,806[1]
allogeneic HCT in the EU in 2021[1]

- Incidence of PTLD: 0.8–4%[2]
- Almost 100% of PTLD cases are associated with EBV[3,4]
- Typically arises <1 year after transplant[4]

Patients with relapsed or refractory EBV+ PTLD that have received at least one previous treatment are considered ultra-rare haemopathies[7]

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

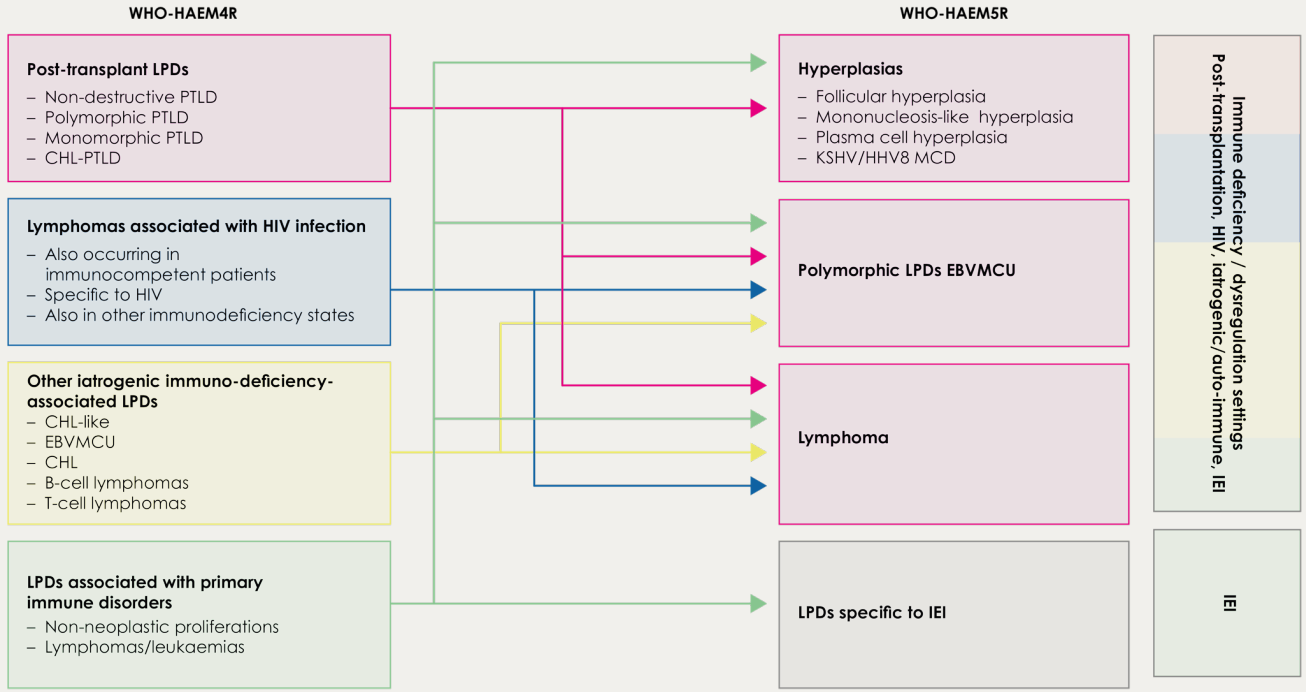
1.Passweg JR et al. BM 2023;58:647–658; 2. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 3. Styczynski J et al. Haematologica 2016;101(7):803–811; 4. Dierickx D et al. Curr Opin Oncol 2022;34(5):413–421; 5; La Moncla. Available at: https://www.lamoncloa.gob.es/lang/en/gobierno/news/Paginas/2023/20230830_eu-donors. Accessed June 2024; 6. Vergote VKJ. et al. Transpl Int 2022;35:10707; 7. DeStephano CB. et al. British Journal of Haematology 2018;182:330–343.

How is PTLD classified by the WHO?

In 2022, the WHO introduced major changes to the classifications of immunodeficiency-associated lymphoproliferative disorders[1]

The new standardised nomenclature builds on an integrated approach to diagnosis that combines all relevant data into a reporting system:[1]

1) Histological diagnosis according to accepted criteria and terminology
2) Presence or absence of one or more oncogenic viruses
3) The clinical setting/ immunodeficiency background



Adapted from Alaggio R, et al. Leukemia. 2022.

CHL, classic Hodgkin lymphoma; EBVMCU, Epstein-Barr virus-positive mucocutaneous ulcer; HAEM4R, revised 4th edition of the WHO Classification; HAEM5R, 5th edition of the WHO Classification; HIV; human immunodeficiency virus; IEI, inborn errors of immunity; KSHV/HHV8 MCD; Kaposi sarcoma herpesvirus/human herpesvirus 8-associated multicentric Castleman disease; LPD, lymphoroliferative disorder; PTLD, post-transplant lymphoproliferative disorder; WHO, World Health Organisation.

1. Alaggio R, et al. Leukemia. 2022;36(7):1720–1748.

How is PTLD classified by the WHO?

The WHO recognises distinct histological subtypes of PTLD[1]

	% of EBV+ disease[1]
Non-destructive PTLD (21%)[1,2] • Plasmacytic hyperplasia • Infectious mononucleosis-like PTLD • Florid follicular hyperplasia	**Most cases**
Destructive PTLD (79%)[1,2] • Polymorphic PTLD • cHL PTLD / cHL-like PTLD	**>90%**
• Monomorphic PTLD (DLBCL, Burkitt lymphoma, plasma cell neoplasms, T-cell/ NK-cell lymphomas)	**Variable %**

cHL, classical Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder; WHO, World Health Organisation

1. Atallah-Yunes S et al. Br J Haematol 2023;201:383–395; 2. Liu Y et al. Cancers 2023;15(3):976.

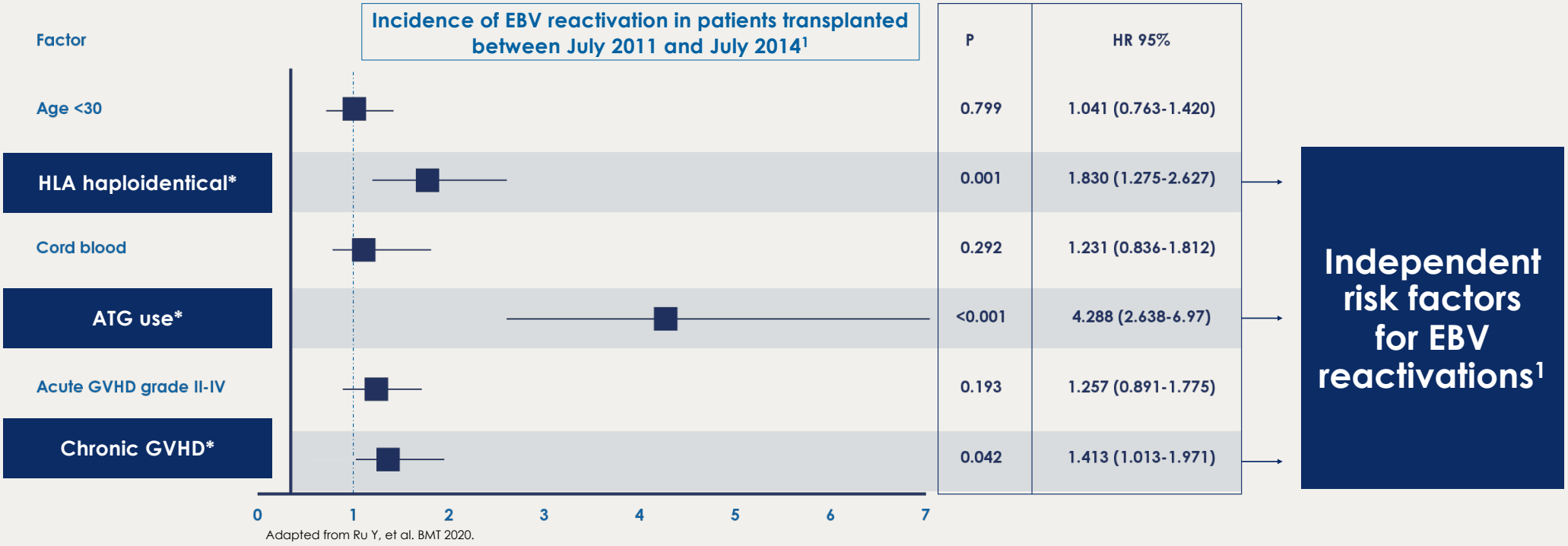
What are the key differences in the development of EBV+ PTLD in recipients of SOT or allogeneic HCT?

Variable	SOT	HCT
Typical cell of origin[1]	Recipient origin	Donor origin
Frequency[1]	1–33%	0.8–4%
EBV-associated[2]	~50%	~100%
Onset time	Variable ~50% >1-year post-transplant[3]	Within the first year post-transplant[4]

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

1. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 3. Ghobrial IM, et al. Transplantation. 2005;79(2):244–247;
4. Tai R, et all. Br J Radiol. 2015;88(1052):20140861.

What are the risk factors for EBV reactivation post-HCT?



Adapted from Ru Y, et al. BMT 2020.

*refers to independent risk factors identified by multivariate analysis

ATG, antithymocyte globulin; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; HLA, human leukocyte antigen.

1. Ru Y, et al. BMT 2020;55:1754–1762.

What are the risk factors for the development of EBV+ PTLD post-HCT?

	Factors which INCREASE the risk of developing EBV+ PTLD[1,2]	Factors which REDUCE the risk of developing EBV+ PTLD[1]
Before transplant	• Reduced intensity conditioning • Splenectomy	• Rituximab exposure within 6 months pre-HCT
Transplant characteristics	• Cord blood transplantation • HLA mismatch • Second HCT • EBV serology donor/ recipient mismatch (recipient-negative/donor-positive)	• Sirolimus use for GvHD Prophylaxis
After transplant	• ATG or certain immunosuppressants • Severe acute or chronic GVHD requiring intensive immunosuppressive therapy • *In vivo* T-cell depletion	• Post-transplant cyclophosphamide (without ATG) • CD4+ T-lymphocyte count >50 at Day 30+
Age	• Aged <20 or ≥50 years	• Aged 20–50 years
Other	• Infusion of mesenchymal stromal cells	

ATG, anti-thymocyte globulin; EBV, Epstein–Barr virus; GvHD, Graft-versus-host disease; HCT, haematopoietic cell transplantation; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder.

1. Lindsay J et al Curr Opin Infect Dis. 2021;34:635–645; 2. Ru Y, et al. Eur J Haematol. 2018;101:283–290.

EBV+ PTLD diagnoses

- Diagnosis must be based on symptoms and/or signs consistent with PTLD together with detection of EBV[1]
- Definitive diagnosis requires non-invasive and invasive techniques[1,2]

Non-invasive diagnostic methods[1,2]

- Quantitative determination of EBV-DNA-aemia*
- Imaging: CT or PET-CT** or MRI†

Invasive diagnostic methods[1,2]

- **Biopsy**: of the lymph node and/or other suspected sites
- Endoscopy: when GI symptoms present
- Histological examination
  a) Detection of viral antigens or *in situ* hybridisation for EBV-encoded RNA transcripts
  b) Immunohistochemistry
  c) Flow cytometry for B-cell, T-cell, and plasma cell lineage-specific antigens

* Currently the method of choice for early detection and monitoring progression and response to treatment of EBV+ PTLD starting no later than 4 weeks after HCT.1 ** For avid structures, localised in the lymph nodes, spleen, liver, GI tract, skin, lungs, bone,1 BM. † In CNS disease and non-avid histologies.1
ATG, anti-thymocyte globulin; BM, bone marrow; CNS, central nervous system; CT, computed tomography; EBV, Epstein–Barr virus; GI, gastrointestinal; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; MRI, magnetic resonance imaging; PET-CT; positron emission tomography–computed tomography; PTLD, post-transplant lymphoproliferative disorder; TCD, T-cell depletion.

1. Styczynski J and Giebel S EBMT Handbook 2019; Chapter 45; 2. Samant H, et al. Posttransplant Lymphoproliferative Disorders. StatPearls 2023.

Staging system for EBV+ PTLD[1]

- There is no official grading system for EBV+ PTLD
- The use of PET-CT is an important imaging tool for both PTLD diagnosis and staging

Possible staging of PTLD:		
Clinical end-organ staging: nodal vs. extra nodal disease	**Clinical severity staging:** limited (unifocal) vs. advanced (multifocal) disease	**ECIL-6 staging*:** limited (stages I–II), advanced forms (stages III–IV)

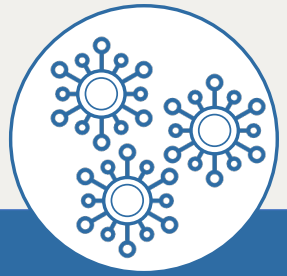
*Based on the Lugano lymphoma classification by PET-CT imaging.[1]

EBV, Epstein–Barr virus; ECIL, European Conference on Infections in Leukaemia; PET-CT, positron emission tomography–computed tomography; PTLD, post-transplant lymphoproliferative disorder.

1. Styczynski J and Giebel S EBMT Handbook 2019; Chapter 45.

EBV+ PTLD overview

EBV is one of the most common viruses in humans and maintains a life-long latent infection[1,2]



Patients undergoing HCT can experience PTLD due to dysfunction or suppression of the host immune system, or uncontrolled proliferation of EBV-infected cells[1,2]

~100% cases of PTLD post-HCT are EBV-associated[3]

Clinical presentation of EBV+ PTLD is heterogeneous, but the most common symptoms are lymphadenopathy and fever[2,4]

The diagnosis of EBV+ PTLD must be based on symptoms and/or signs consistent with PTLD together with detection of EBV, and ultimately confirmed by a biopsy[2,4]

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

1. Bednarska K et al. Br J Haematol 2024;204:415–433; 2. Styczynski J and Giebel S EBMT Handbook 2019; Chapter 45; 3. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 4. Samant H, et al. Posttransplant Lymphoproliferative Disorders. Stat Pearls 2023.

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

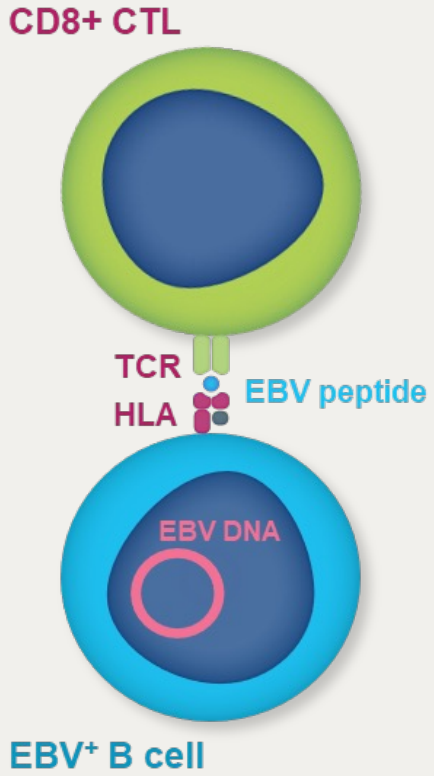
For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

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

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

Tabelecleucel is an allogeneic T-cell immunotherapy for the treatment of EBV+ malignancies and diseases

- **T cells specific against EBV**
- **No genetic modification**
- **Selected from an existing inventory based on an appropriate HLA restriction**
- **T cells directly delivered from existing inventory**



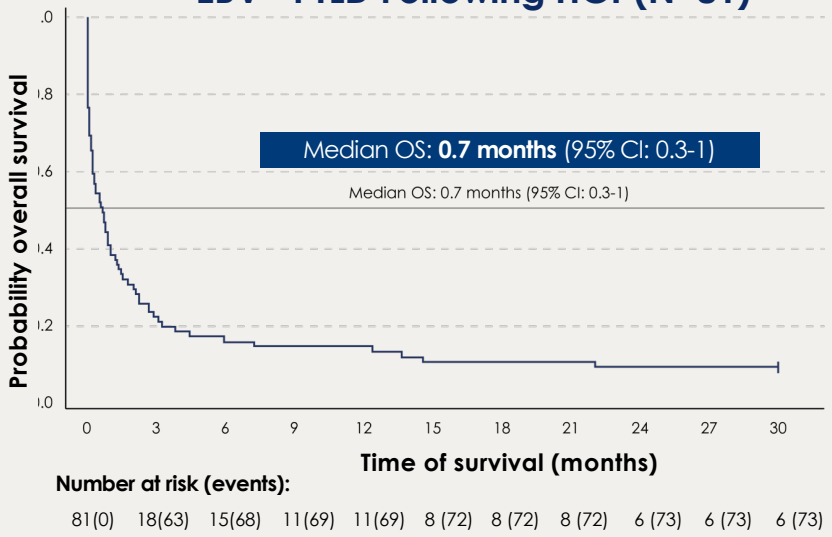
CTL = cytotoxic T lymphocyte; EBV = Epstein Barr virus; HLA = human leukocyte antigen; TCR = T cell receptor.

1. Prockop S *et al.* J Clin Invest 2020;130(2):733–747; 2. EMA Tabelecleucel Summary of Product Characteristic.

Outcomes of HCT and SOT recipients with relapsed/refractory EBV+ PTLD

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

Overall survival in Patients with R/R EBV+ PTLD Following HCT (N=81)[1]



Adapted from Socié G, et al. 2022.

* 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-versus-host disease; HCT, haematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplantation.

1. Socié G, et al. Bone Marrow Transplant. 2024;59:52–58;

ALLELE: 51% of patients achieved an objective response[1]

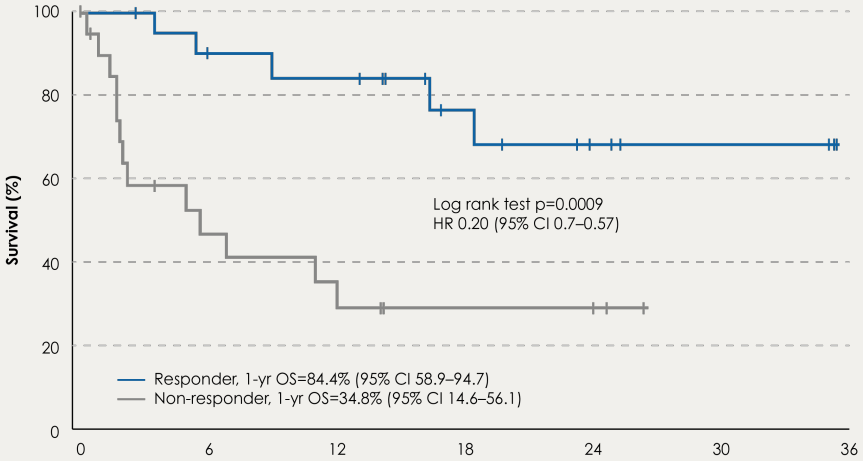
	Allogeneic HCT (n=14)	SOT (n=29)	All (n=43)
Responders, n (%)	7 (50)	15 (52)	22 (51)
95% CI	23–77	33–71	36–67
Best overall response, n (%)			
Complete response	6 (43)	6 (21)	12 (28)
Partial response	1 (7)	9 (31)	10 (23)
Stable disease	3 (21)	2 (7)	5 (12)
Progressive disease	2 (14)	7 (24)	9 (21)
Not evaluable	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.

ALLELE: Patients responding to tabelecleucel had a longer overall survival than non-responders[1]

Overall survival in patients with EBV-PTLD[1]



Number at risk (events)

Responder,	22 (0)	17 (3)	15 (4)	9 (9)	5 (12)	3 (14)	0 (17)
Non-responder	21 (0)	8 (3)	6 (3)	3 (5)	3 (5)	0 (8)	

	1-year OS	Estimasted mOS
Tabelecleucel responders	84.4%	Not reached
Non-responders	34.8%	5.7 months

Adapted from Mahadeo KM, et al. Lancet Oncol 2024.
Data cut-off date: Nov 5, 2021.
Response assessed per Lugano Classification with LYRIC modification by IORA. OS was estimated by the KM method.
CI, confidence interval; EBV, Epstein–Barr virus; HCT, haematopoietic cell transplant; mOS, median overall surivial; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.
1. Mahadeo KM, et al. Lancet Oncol 2024;25(3):376–387.

ALLELE: tabelecleucel was generally well tolerated in R/R EBV+ PTLD patients[1]

Event type, n (%)	HCT (n=14)	SOT (n=29)	All (N=43)
Any TESAEs*	8 (57.1)	15 (51.7)	23 (53.5)
Grade ≥3 TESAEs	8 (57.1)	15 (51.7)	23 (53.5)
Fatal TESAEs**	1 (7.1)	4 (13.8)	5 (11.6)

* 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®.[1]
** Fatal TESAEs were disease progression (n=3), respiratory failure (n=1), multiple organ dysfunction syndrome (n=1).[1]

Treatment-related event type, n (%)	All (N=43)
Treatment-related serious AEs	4 (9.3)
Grade ≥3 treatment-related serious AEs	2 (4.7)
Treatment-related serious AEs that led to treatment discontinuation	0 (0)

- None of the five fatal TEAEs were related to tabelecleucel
- There was no trend in treatment-related TESAEs, as all except for pyrexia were reported in single patients
- There were no reports of tumour flare reaction, infusion-related reaction, cytokine release syndrome, marrow rejection, or transmission of infectious disease
- There were no events of GvHD or organ rejection reported as related to tabelecleucel®

Data cut-off date: Nov 5, 2021.
For a full list of adverse events please consult your local tabelecleucel® Summary of Product Characteristics.
EBV+, Epstein–Barr virus positive; GvHD, graft vs host disease; HCT, haemopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; R/R: relapsed/refractory;
SOT, solid organ transplantation; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387.

ALLELE: No evidence of safety concerns seen with other adoptive T-cell therapies[1]

Event Category, n (%)	HCT (n = 14)	SOT (n = 29)	All (n = 43)
Patients reporting any AEs of identified or potential risk	**1 (7.1)**	**1 (3.4)**	**2 (4.7)**
Patients reporting any AEs of special interest	1 (7.1)	0	1 (2.3)
Tumor flare reaction	0	0	0
Any GvHD	1 (7.1)	0	1 (2.3)
• Acute GvHD	0	0	0
• Chronic GvHD*	1 (7.1)	0	1 (2.3)
• Unknown acute or chronic	0	0	0
Infusion-related reaction	0	0	0
Cytokine release syndrome	0	0	0
Transmission of infectious disease	0	0	0
Marrow or organ rejection	0	1 (3.4)	1 (2.3)
• Solid organ transplant rejection	0	1 (3.4)	1 (2.3)
Immune effector cell-associated neurotoxicity syndrome	0	0	0
Immunogenicity	0	0	0
Decrease in cell viability due to inappropriate handling of the product	0	0	0

None of the events were considered by the investigator to be related to tabelecleucel®

For a full list of adverse events please consult your local tabelecleucel® Summary of Product Characteristics.
Data cut-off date: Nov 5, 2021.
AE, adverse events; HCT, haematopoietic cell transplant; GvHD, graft vs host disease; SOT, solid organ transplantation.
1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387.

ALLELE key takeaways: A potentially transformative treatment for patients with R/R EBV+ PTLD[1]

Phase 3 ALLELE study demonstrated:[1]

- **Overall response rate of 51%** among all patients, with a best overall response of complete response (28%) or partial response (23%)[1]
- **Median time to response of 1.0 month**; median duration of response was not reached[1]
- **Estimated median OS of 18.4 months** among all patients, and **patients responding** to tabelecleucel® had a **longer survival compared with non-responders (OS rate at 1 year: 84.4% vs 34.8%)**[1]
- The most common TEAEs of any grade were **disease progression** (36% HCT; 55% SOT; 49% total), **pyrexia** (36% HCT; 28% SOT; 30% total), and **diarrhoea** (29% HCT; 28% SOT; 28% total)[1]
- **TESAEs were reported in 53% of patients** and **fatal TEAEs in 12%; no fatal TEAE was treatment-related**[1]
  - In the ALLELE study there were no reports of tumour flare reaction, infusion reactions, marrow rejection, or cytokine release syndrome[1]

HCT, haematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplantation; TEAE, treatment-emergent adverse event; TESAEs, treatment-emergent serious adverse events.

1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387; 2. tabelecleucel EU Summary of Product Characteristics.

What is needed to order tabelecleucel?

1 Patient Information

Tabelecleucel is specifically selected for each patient, based on their disease HLA profile[1]

Top-line patient information is required to order from the Pierre Fabre online platform:

- **Patient HLA genotyping*** in high resolution
- **Donor HLA genotyping*** in high resolution (highly recommended), or low resolution (donor ethnicity required)
- **Suspected origin of EBV+ PTLD disease** (i.e., donor or patient)
- General information (brief medical history SOT/ allogeneic HCT/ other, weight, CMV serostatus)

2 Hospital Preparation

A short training & minimal logistics preparation are needed prior to administering tabelecleucel

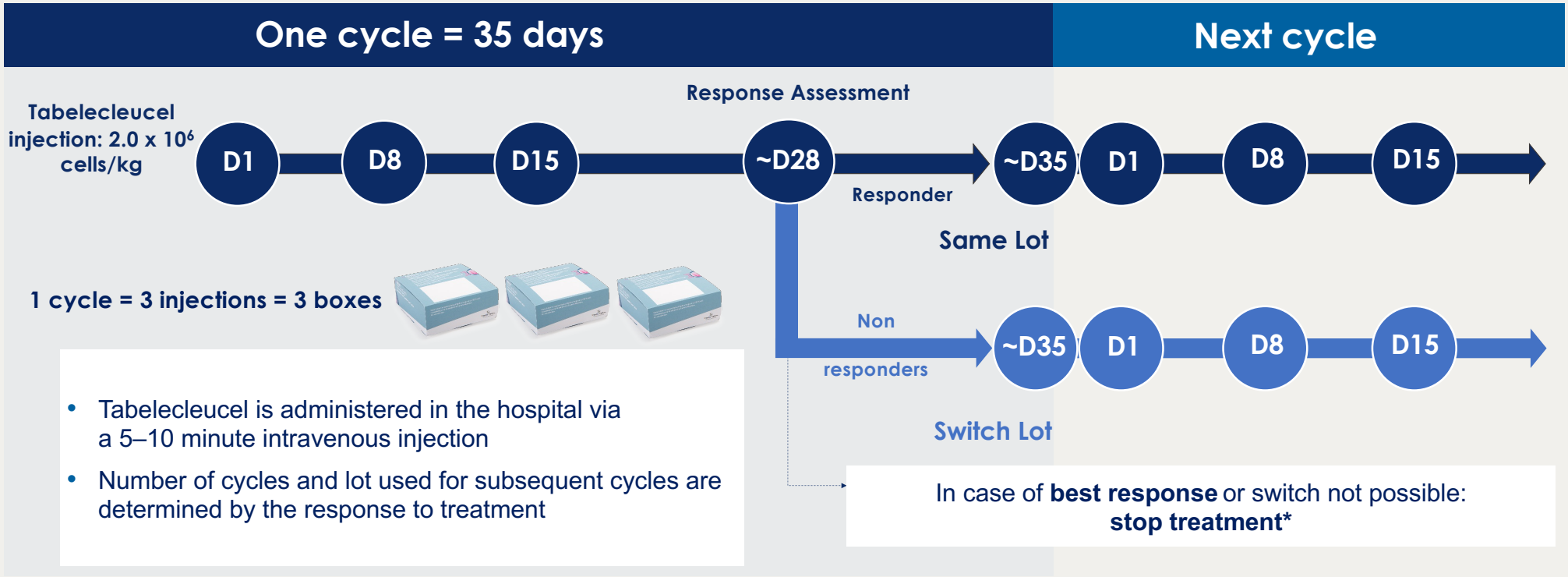
- **Hospital staff training** (1h)
  - Clinical setting & treatment algorithm
  - Product preparation, administration & monitoring
- **Delivery preparation**
  - Gather logistics information (address, storage on site)
  - Point of contact for the delivery

*HLA for alleles: A, B, C, DRB1, DQB1. All reports uploaded are anonymised to PF. High resolution: 4 digits (00:00).

CMV, cytomegalovirus; HLA, human leukocyte antigen; HCT, haematopoietic cell transplantation; HCP, Healthcare Professional; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. tabelecleucel EU SmPC

Tabelecleucel administration schedule[1]



- Tabelecleucel is administered in the hospital via a 5–10 minute intravenous injection
- Number of cycles and lot used for subsequent cycles are determined by the response to treatment

*Best response: two consecutive CRs or three consecutive PRs.[1]

Tabelecleucel treatment algorithm

The Switch and Stop Criteria are determined by the response to treatment[1]

Response observed*	Action
CR	Administer another cycle with the same HLA restriction. If the patient achieves 2 consecutive CRs (maximal response), no further treatment with tabelecleucel is recommended
PR	Administer another cycle with the same HLA restriction. If the patient achieves 3 consecutive PRs (maximal response), no further treatment with tabelecleucel is recommended
SD	Administer another cycle with the same HLA restriction. If the subsequent cycle results in a second SD, administer tabelecleucel with a different HLA restriction
PD	Administer another cycle with a different HLA restriction
IR	Administer another cycle with the same HLA restriction. If the subsequent cycle results in a second IR, administer tabelecleucel with a different HLA restriction

*CR at the end of a cycle, followed by PR or other response at any subsequent cycle, is considered PD.

1. Tabelecleucel EU SmPC

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Take home messages

- PTLD is a difficult diagnosis
- Should be kept in mind in patients with different symptoms and signs
- EBV viremia is mandatory during transplant and at follow up
- Requires a strict collaboration with other specialists including pathologist in particular
- Rituximab and /or chemo have a high percentage of failure and side effects could can be serious
- Specific T-cell therapy is highly active and safe

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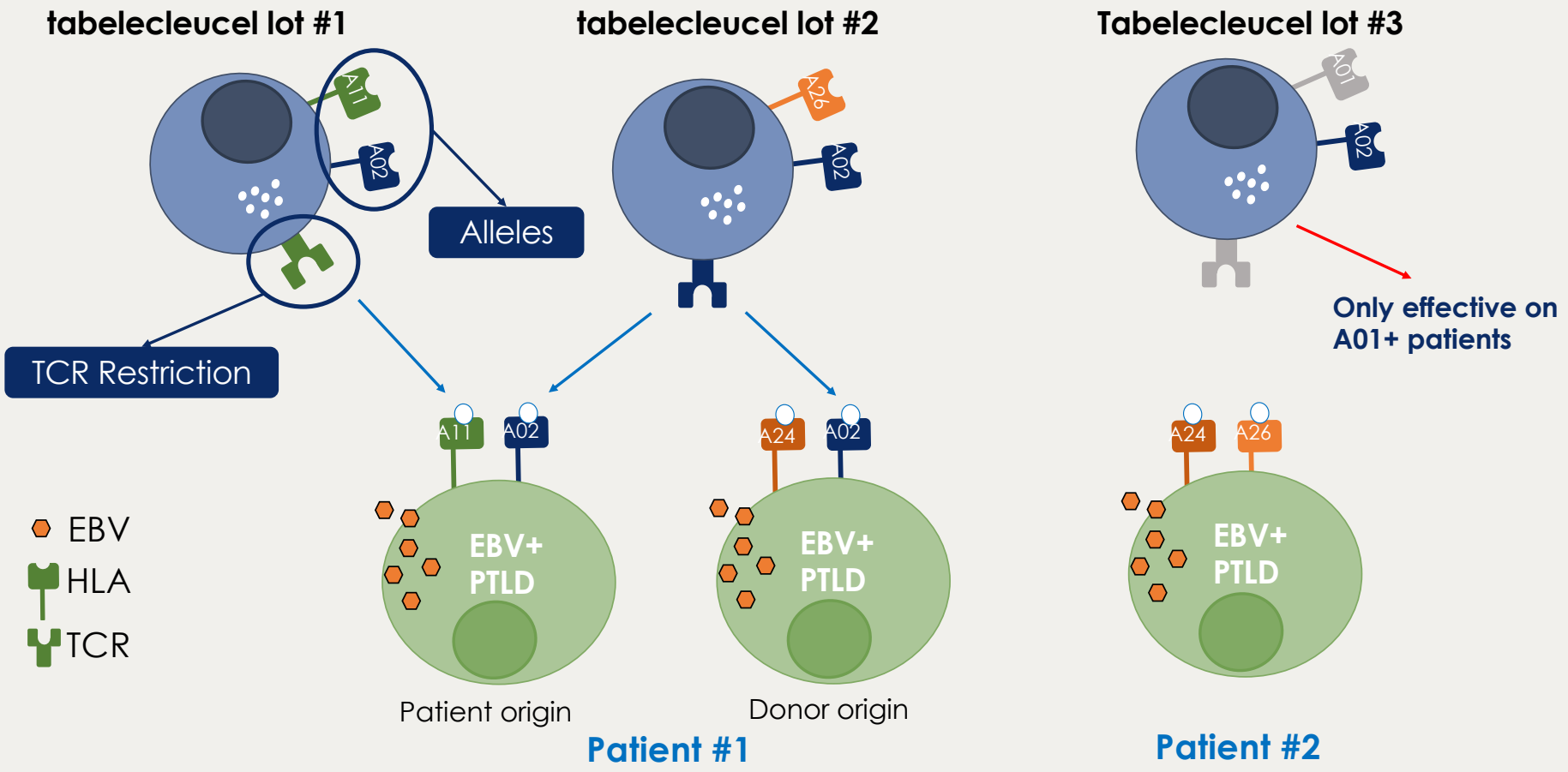
Lot selection for tabelecleucel

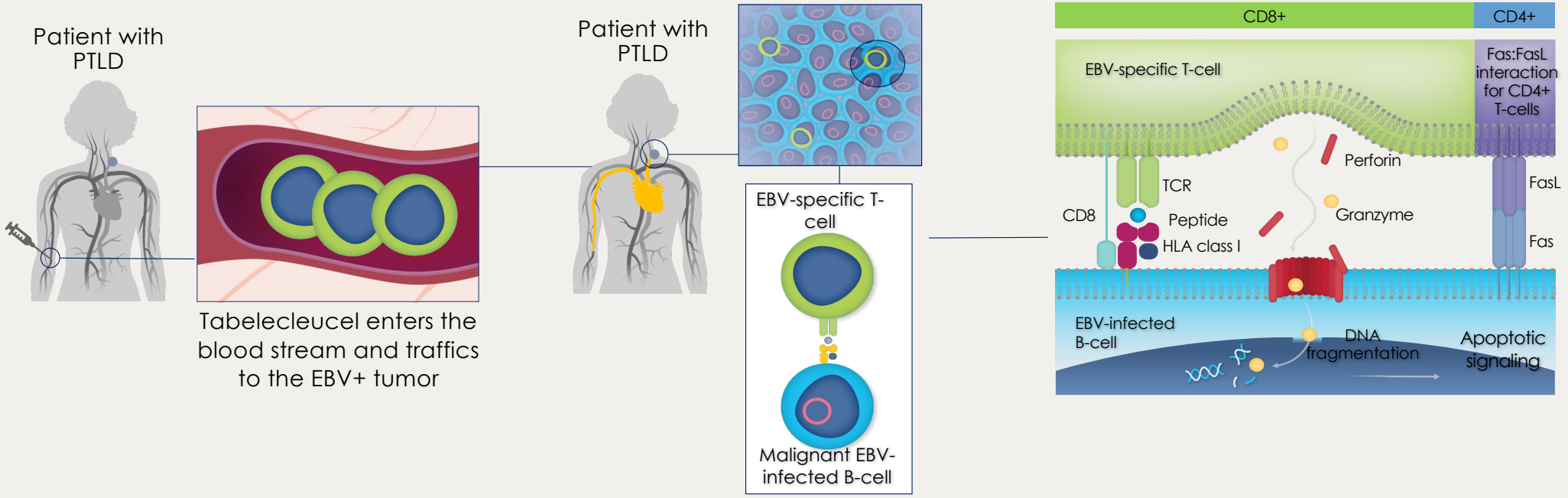


Mechanism of action

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]



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.

Take home messages