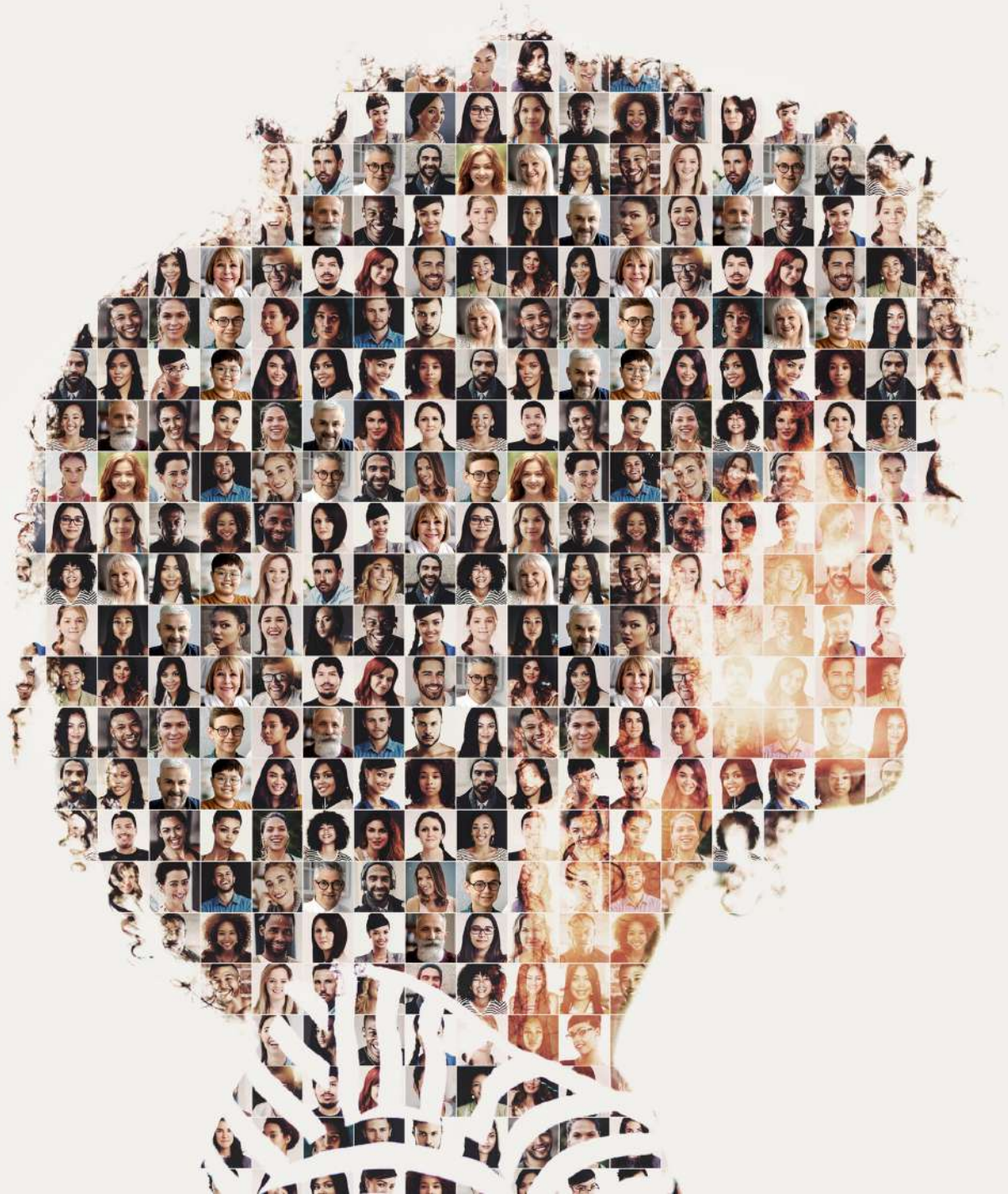

Facing the facts in **EBV+ PTLD management**

Prof. Simona Sica
Catholic University of the Sacred Heart
Rome, Italy

EBVALLO® is not commercialized in Spain/ EBVALLO® no está comercializado en España.

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

HQ-EBV-05-24; June 2024.

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Disclosures

- Performed an advisory role for Amgen, Astellas, Novartis, Kyte Gilead, Sobi, Alexion, Jazz

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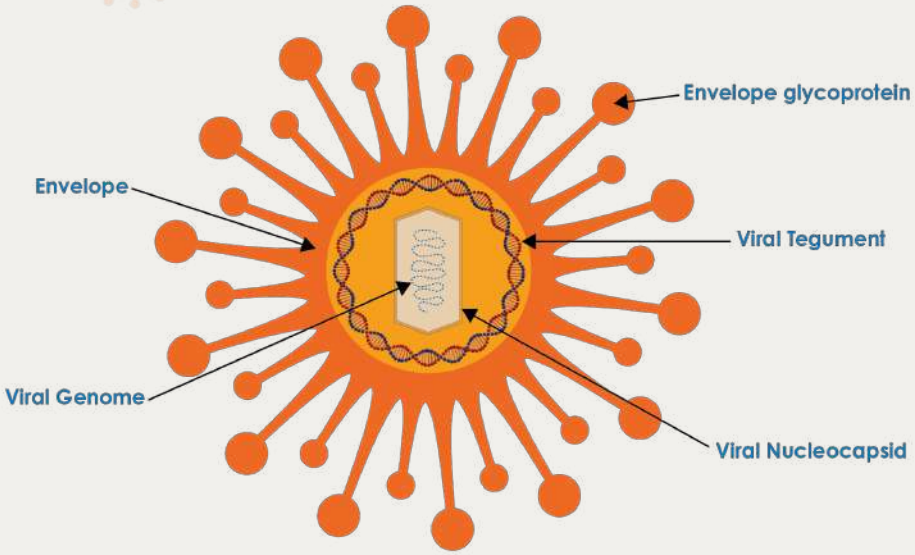
What is Epstein-Barr Virus?

- EBV is a gamma-herpes virus that is transmitted orally (via infected saliva)[1]
- It is one of the most common viruses in humans[1]
  - ~90% of adults and 50% of children are infected globally[1]
- EBV infection is largely asymptomatic in immunocompetent hosts[2]
  - In adolescents and young adults, it can manifest clinically with symptoms such as fever, painless swollen glands and sore throat known as infectious mononucleosis[1,2]
- EBV establishes a life-long latent infection in memory B-cells which is controlled by immunocompetent T-lymphocytes and natural killer cells[1,2]



Adapted from CUBASIO® Epstein-Barr virus.[3]

EBV, Epstein-Barr virus.

1. Bednarska K, et al. Br J Haematol 2024;204:415–433; 2. Kimura H, et al. Rev Med Virol. 2008;18(5):305–319. 3. CUSABIO®. Epstein-Barr virus. Available at: https://www.cusabio.com/infectious-diseases/epstein-barr-virus.html. Accessed June 2024.

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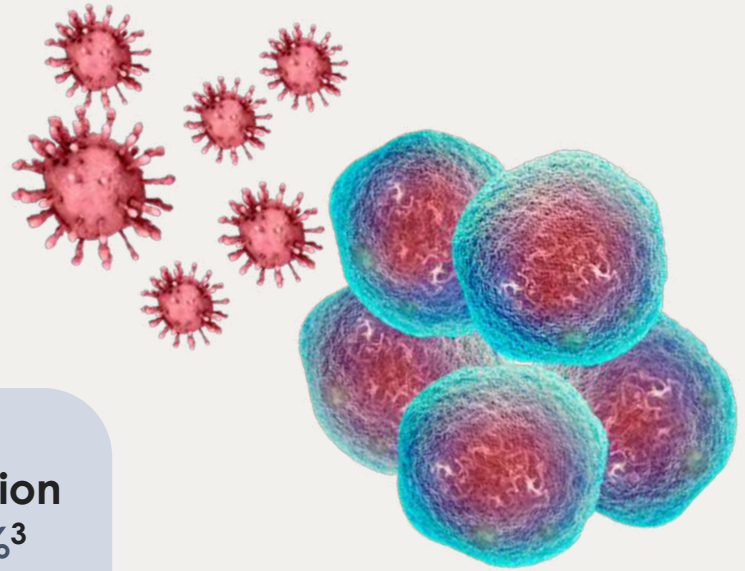
How does a latent EBV infection become reactivated?

- Latent EBV can become reactivated in patients with **dysfunction or suppression of the host immune system** after transplantation[1]
- Once reactivated B-cells may transform and rapidly proliferate, causing a range of neoplasms attributable to the dysregulated proliferation of infected B-cells[1]



The incidence of EBV reactivation post-HCT ranges from 0.1–63%[2]
Impacted by transplant type, antiviral agents, monitoring protocol, and assay sensitivity

The incidence of EBV reactivation post-SOT ranges from 13–48%[3]
Impacted by immunosuppressive regimes and analytical techniques

Recipients of SOT or allogeneic HCT have an increased risk of EBV-associated cancers such as PTLD[4]

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

1. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 2. Ru Y, et al. BMT 2020;55:1754–1762; 3. Blazquez-Navarro A, et al. Transpl Int; 2021;34:1680–1688.
4. Cohen JI. N Engl J Med. 2000;343:481–492.

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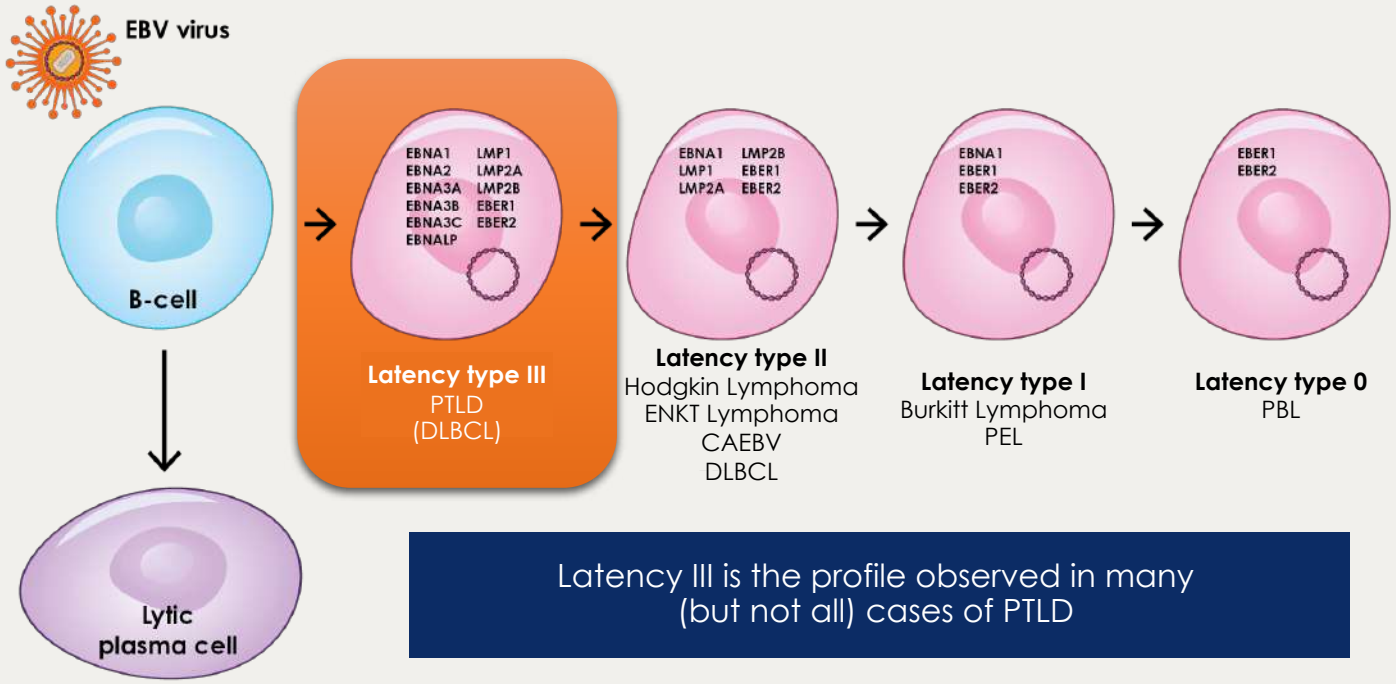
Pathogenesis of distinct EBV-driven disorders

- In a latent phase infection, EBV is maintained in a circular chromatinised state within the nucleus of a host cell[1]
- There are four distinct EBV-latent gene expression patterns (Types 0, I, II and III)[1]
  - Defined by the expression of specific sets of viral genes and promoters
  - The unique functions and role in lymphomagenesis of the EBV-latency proteins impact the pathogenesis of distinct EBV-driven disorders



Adapted from Bednarska K, et al. Br J Haematol 2024.

CAEBV, chronic active; EBV, Epstein-Barr virus; DLBCL, diffuse large B-cell lymphoma; ENKT, extra-nodal NK/T-cell; PBL, plasmablastic lymphoma; PEL, primary effusion lymphoma; PTLD, post-transplant lymphoproliferative disorder.

1. Bednarska K, et al. Br J Haematol 2024;204:415–433.

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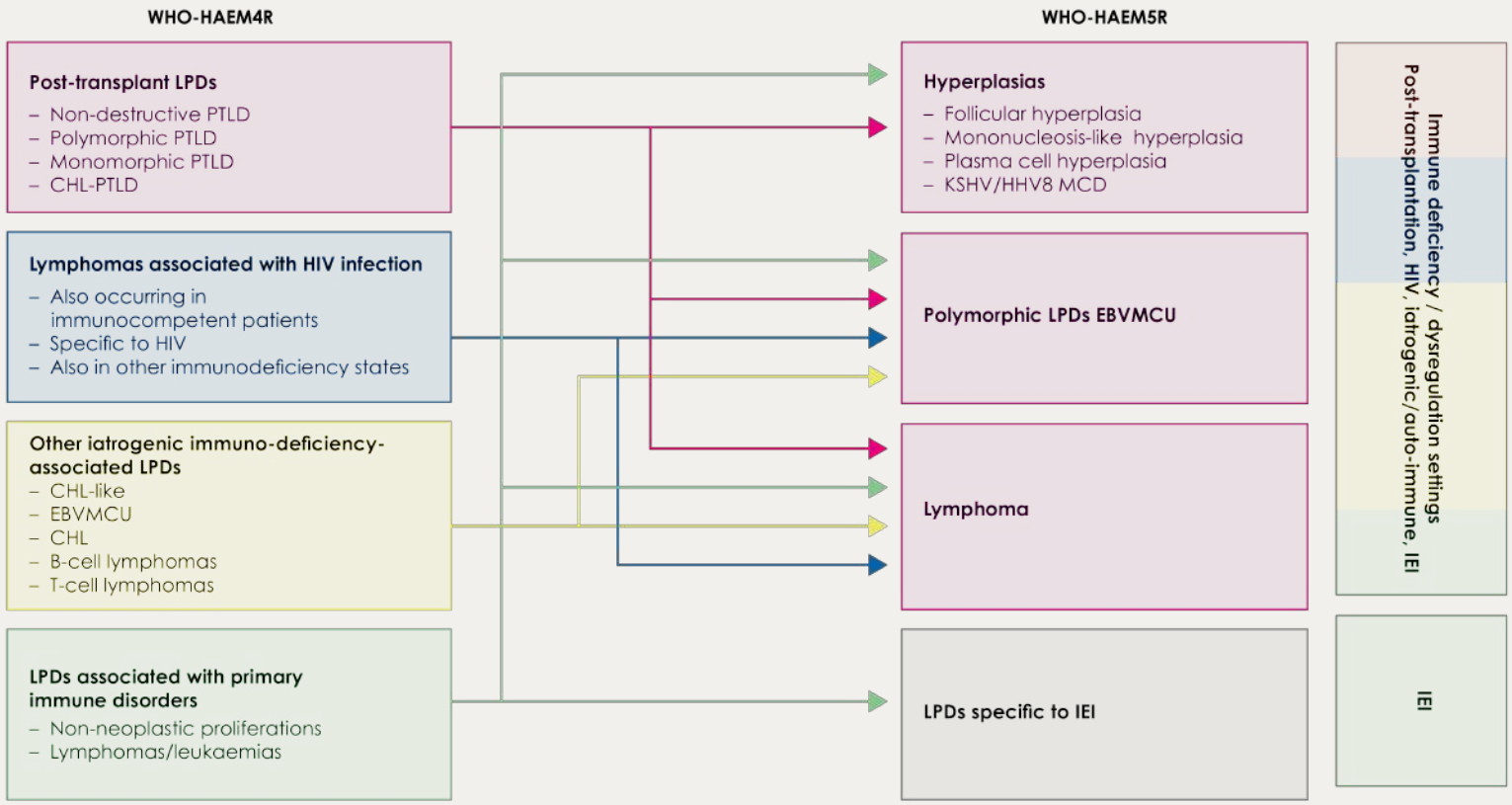
How is PTLD classified by the WHO?

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.

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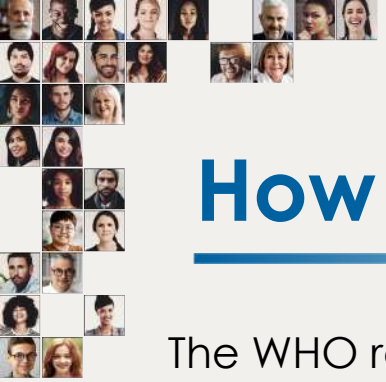

How is PTLD classified by the WHO?

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.

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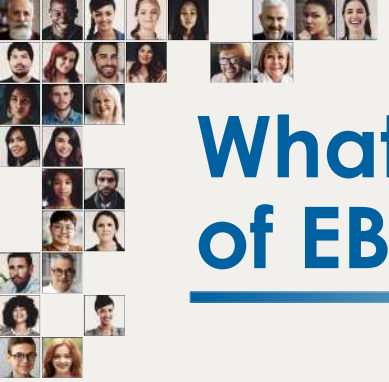

What are the key differences in the development of EBV+ PTLD in recipients of SOT or allogeneic HCT?

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.

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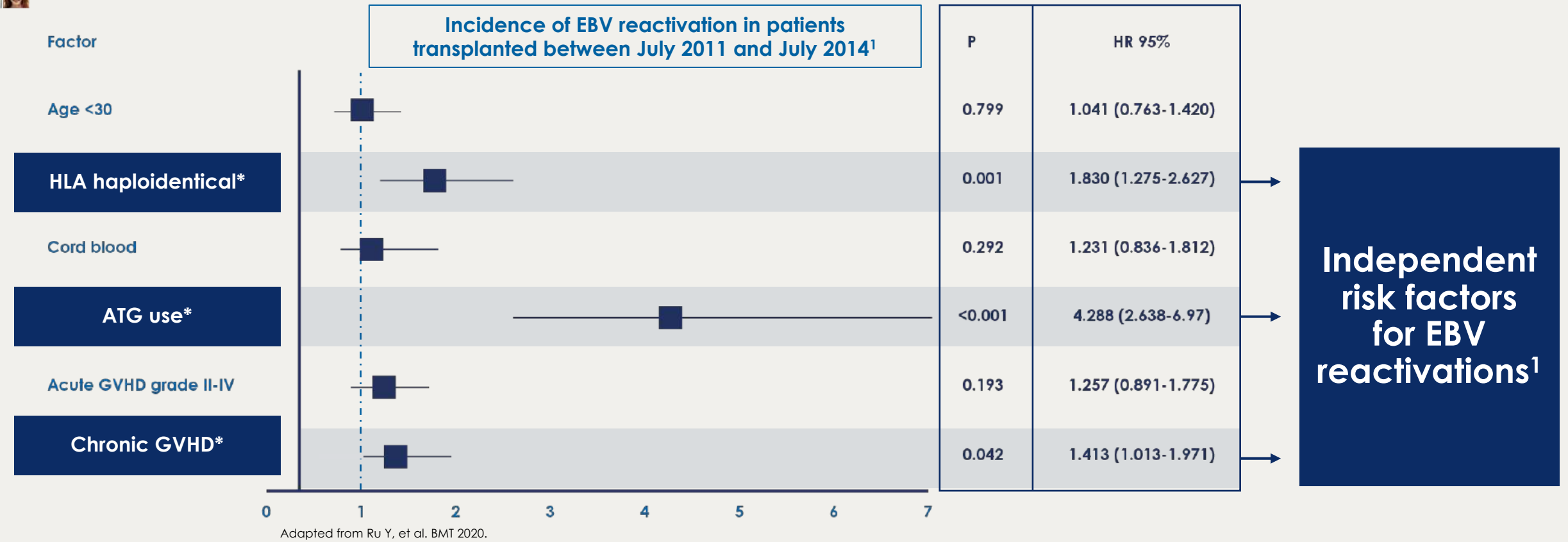
What are the risk factors for EBV reactivation post-HCT?



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.

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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.

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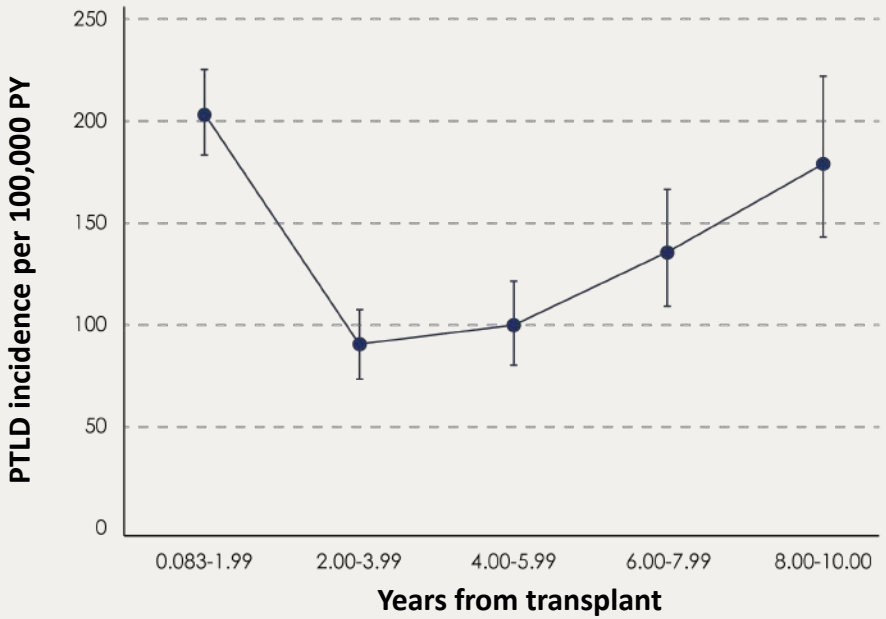
PTLD development post-SOT

- Incidence of PTLD post-SOT: bimodal curve[1]
  - Initial spike during the 1st post-transplant year (mostly EBV-positive transplant recipients)
  - Second spike 5–15 years after transplant (often EBV-negative recipients)
  - Very late cases (>20 years after transplant)

Incidence of PTLD among 156,740 US kidney transplant recipients during 1999–2007[2]*



*Retrospective cohort study. Follow-up for all recipients began 30 days after transplantation.[2]
EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation; US, United States.
1. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 2. Quinlan SC, et al. Am J Hematol. 2011;86:206–209.

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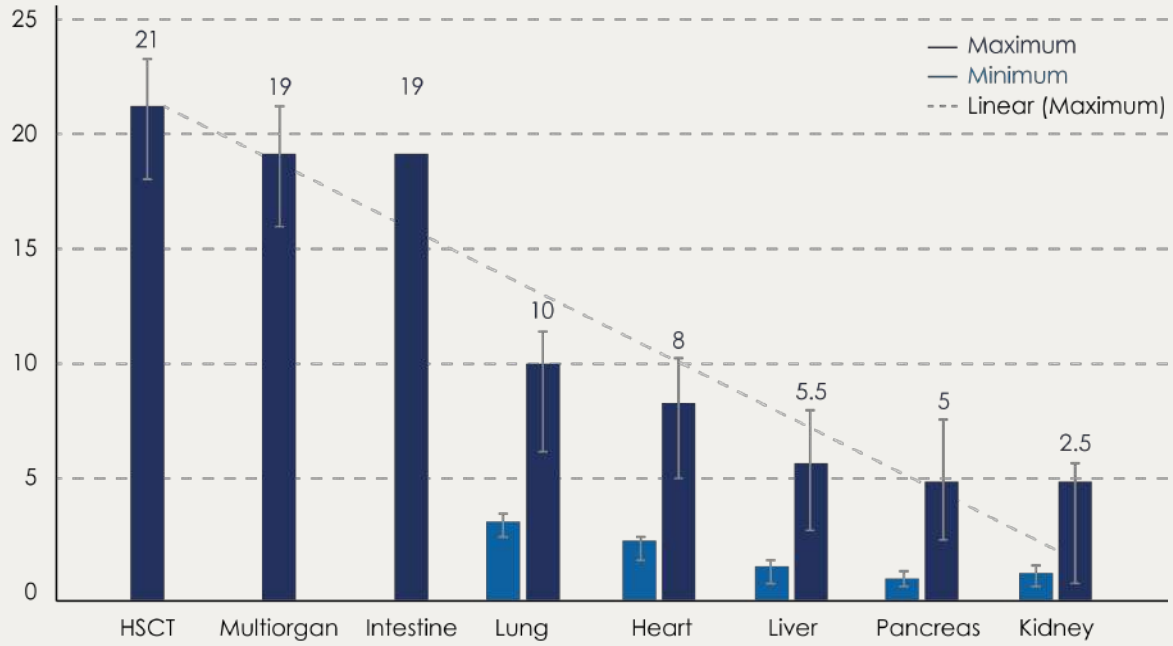
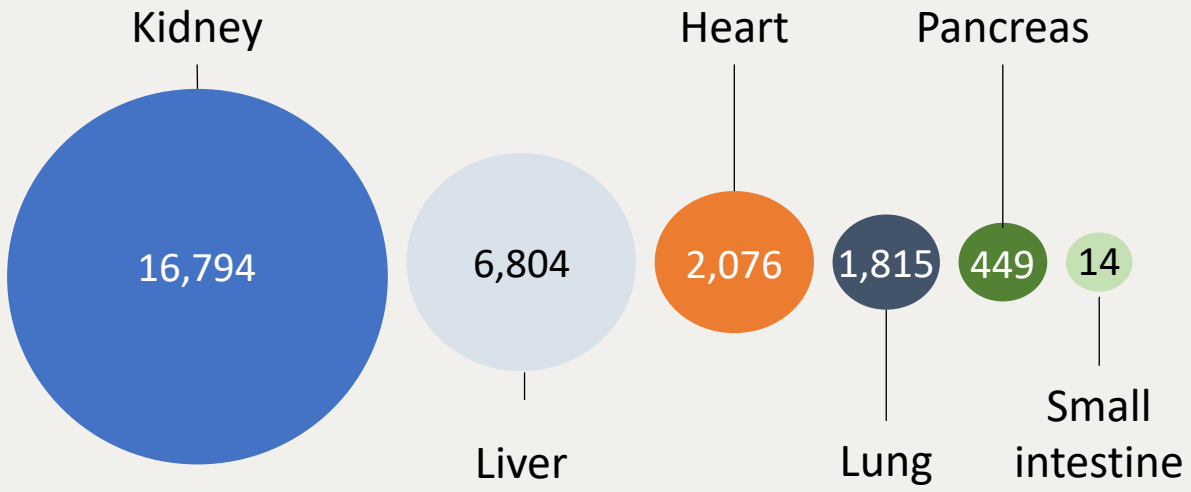
Incidence of PTLD post-SOT varies by organ transplant site

Incidence of PTLDs in various transplants[1]*



	HSCT	Multiorgan	Intestine	Lung	Heart	Liver	Pancreas	Kidney
Maximum (%)	21	19	19	10	8	5.5	5	2.5
Minimum (%)				3	2	1	0.5	0.8

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.

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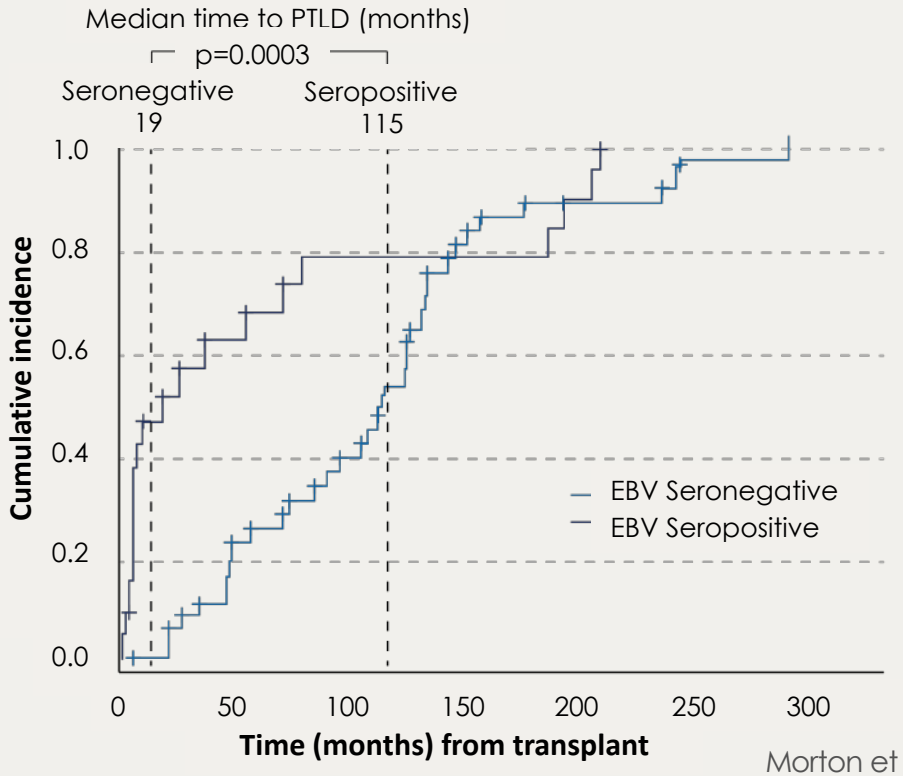
EBV status and PTLD development post-SOT

- Pre-transplant EBV seronegativity increases the incidence of PTLD from 10- to 75-fold over that of EBV-seropositive recipients[1,2]

Time to PTLD onset according to EBV status at the time of transplantation[3]



Morton et al. 2013[6]

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

1. Walker RC, et al. Clin Infect Dis. 1995;20:1346–1353; 2. Cockfield SM. Transpl Infect Dis. 2001;3:70–78; 3. Morton M, et al. Transplantation. 2013;95:470–480.

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

	Factors which INCREASE the risk of developing EBV+ PTLD[1]	Factors which REDUCE the risk of developing EBV+ PTLD[1]
Time after transplant[1]	• EBV reactivation/primary infection < 12 months after transplant	EBV reactivation/primary infection > 12 months after transplant
Organ[1,2]	Multiorgan > intestine > lung > heart > liver > pancreas > kidney	Kidney > pancreas > liver > heart > lung > intestine > multiorgan
EBV status[1]	EBV mismatch at time of transplant: Donor EBV+/ Recipient EBV-	Recipient EBV+
Age[1]	Child	Adults
IS[1]	Certain immunosuppressive agents	-

EBV, Epstein–Barr virus; IS, immunosuppression; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant.

1. Lindsay J et al Curr Opin Infect Dis. 2021;34:635–645; 2. Abbas F, et al. World J Transplant 2020;10(2):29–46.

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What is the clinical presentation of EBV+ PTLD?

Factor	Clinical presentation
Heterogeneity[1]	**Heterogeneous** (from incidental asymptomatic findings to fulminant presentation), including organ failure and spontaneous tumour lysis
Symptoms[2]	Most common: **lymphadenopathy** and **fever** Rare (EBV end-organ disease): encephalitis/myelitis, pneumonitis, hepatitis, and haemophagocytic lymphohistiocytosis
Target organs[2]	Frequently: **lymph nodes** Rarely: CNS, GI tract, lungs, liver
Progression[3]	After HCT, PTLD often progresses **rapidly** and is more frequently at an advanced stage than after SOT

CNS, central nervous system; EBV, Epstein–Barr virus; GI, gastrointestinal; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 2. Styczynski J and Giebel S EBMT Handbook 2019; Chapter 45;
3. Fujimoto A, et al. Cancers (Basel). 2020;12:328.

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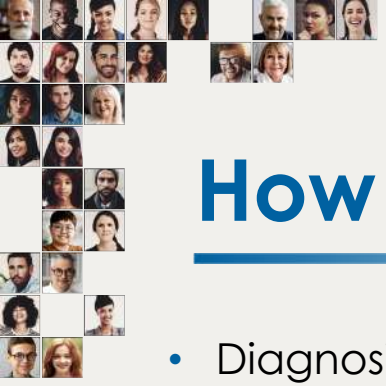

How do we diagnose EBV+ PTLD?

- 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-emia
- Imaging: CT or PET-CT* or MRI**

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]

Longer monitoring recommended in patients considered to have poor T-cell reconstitution, with severe GvHD, after haplo-HCT, with the use of TCD, after conditioning with ATG/alemtuzumab, or in those having experienced an early EBV reactivation[1]

* For avid structures, localised in the lymph nodes, spleen, liver, GI tract, skin, lungs, bone, BM.
** In CNS disease and non-avid histologies.

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.

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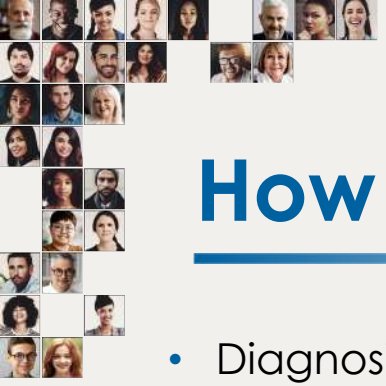

How do we diagnose EBV+ PTLD?

- 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]

Invasive diagnostic methods[1,2]

- **Biopsy**: of the lymph node and/or other suspected sites → **Currently key to diagnose PTLD**
- 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

EBV, Epstein–Barr virus; GI, gastrointestinal; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; RNA, ribonucleic acid.

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

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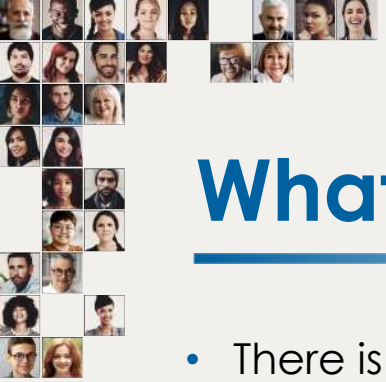

What is the staging system for EBV+ PTLD?[1]

- 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.

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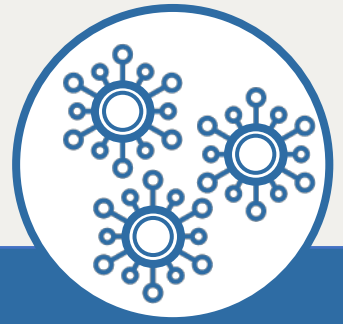
Facing the facts in EBV+ PTLD management

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



Patients undergoing HCT or SOT 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 and ~50% cases post-SOT 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.

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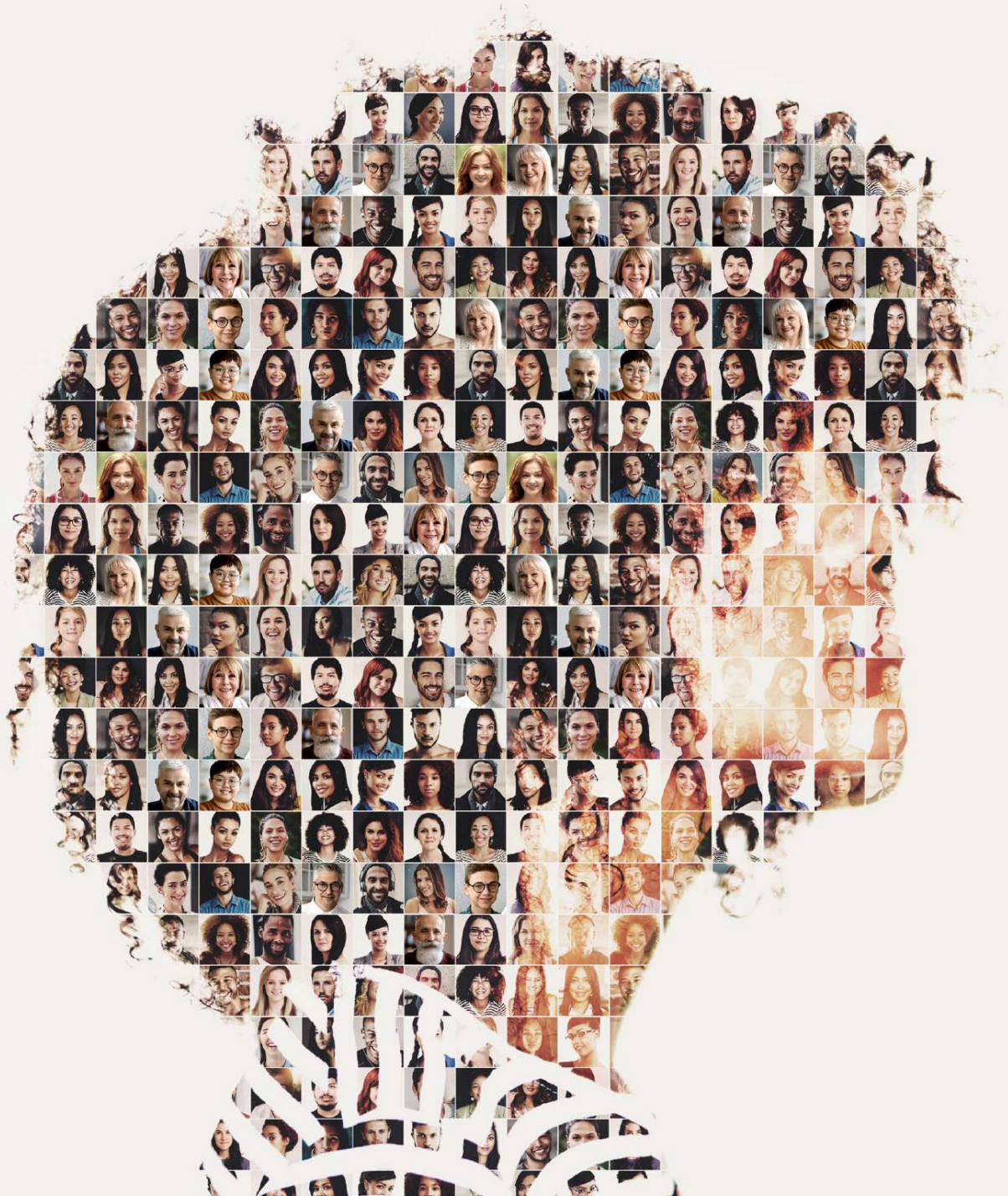

The current face of

EBV+ PTLD management

Prof. Christof Scheid
Professor of Haematology,
Department of Internal Medicine, University of Cologne, Germany

EBVALLO® is not commercialized in Spain/ EBVALLO® no está comercializado en España.

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

HQ-EBV-05-24-2400001; June 2024.

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Disclosures

- Speaker's fees and travel support from Pierre Fabre
- Received honoraria from Amgen, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Novartis, Pierre Fabre, Oncopeptides, Sanofi, Takeda
- Performed an advisory role for Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Roche
- Received research support from Novartis, Takeda, Janssen

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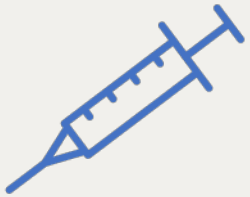
Current treatment options for EBV+ PTLD



Restoring T-cell function[1,2]

- Reduction of immune suppression
- Adoptive immunotherapy

Reducing tumour mass[1,2]

- Local therapy
- Rituximab and/or chemotherapy

Decreasing EBV viral load[1–3]

- Inducers of lytic cycle
- Antiviral agents

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

1. Gottschalk S, et al. Annu Rev Med. 2005;56:29–44; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562;
3. Atallah–Yunes SA, et al. Br J Haematol. 2023;201:383–395.

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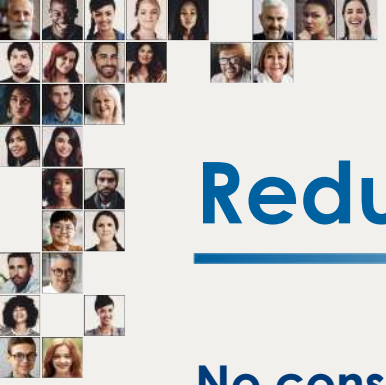

Reduction of immune suppression

No consensus/uniform guidelines on RIS:[1–4]

- Stop antimetabolites
- Reduce calcineurin inhibitor dose
- Continue or decrease steroids

1–4 weeks → response rates: 0 – ~50%[1,2]

	Treatment	Overall response rate (CR)
Pennsylvania[2]	RIS only	45% (37%)
Baltimore[1]	Sequential therapy (RIS – IFNα – chemo)	6% (0%)

Organ dependent risk in graft failure
Kidney: dialysis rescue Heart: risk sudden death[6]
Rejection rates: 18–40%[4]

CR: complete response; IFNa: interferon alpha; GvHD, graft-versus-host disease; PTLD, post-transplant lymphoproliferative disorder; RIS: reduction of immunosuppression; SOT: solid organ transplantation.

1. Swinnen LJ, et al. Transplantation. 2008;86:215-222; 2. Reshef R, et al. Am J Transplant. 2011;11:336-347; 3. Zimmermann H, et al. Transplantation. 2018;102:1914-1923; 4. Pan K, et al. Leuk Lymphoma. 2021;62:1123-1128; 5. Aull MJ, et al. Transplantation. 2004;78(11):1676-1682.

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Data on treatment and outcomes are limited for patients with EBV+ PTLD after HCT

Retrospective analyses

- Response to 1st-line rituximab monotherapy varies greatly: CR 20–80%[1–3]
- Median OS <12 months, 1- and 2-year OS of approx. 40–46%[1]
- Only two studies have reported treatment outcomes in patients refractory to rituximab:[1,4]

	Patients achieving treatment success (n/N)*	Type of treatment	Response rate	Relapses
Hou (2009)[4]	3/12	RIS + rituximab (n=1) DLI (n=2)	**RIS + rituximab: 1/1 CR** **DLI: no CR (2/2 PR)**	**NR**
Fox (2014)[1]	10/62	CHOP (n=5) CHOP followed by DLI (n=2) DLI (n=3)	**CHOP: no CR/PR** **DLI: 3/5 CR**	**None**

*n: the total number of patients who achieved a CR; N: the number of patients constituting the study population.[1,4]
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CR, complete response; DLI, donor lymphocyte infusion; EBV, Epstein-Barr virus; HCT, haematopoietic cell transplantation; NR, not reported; OS, overall survival; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; RIS, reduction of immunosuppression.

1. Fox CP, et al. Bone Marrow Transplant. 2014;49:280–286; 2. Shahid S, Prockop SE. Cancer Drug Resist. 2021;4:646–664; 3. Stynczynski J, et al. Clin Infect Dis. 2013;57:794–802; 4. Hou HA, et al. Bone Marrow Transplant. 2009;43:315–321.

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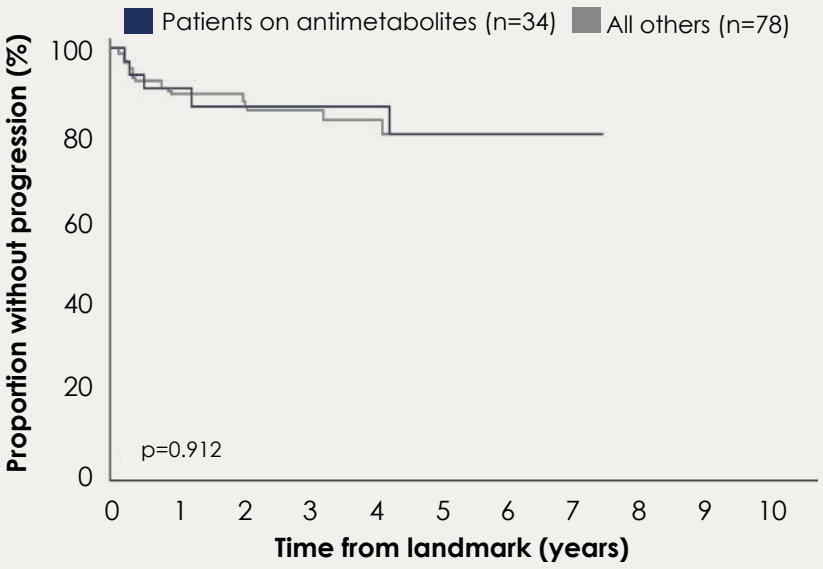
Reduction of immune suppression post-SOT

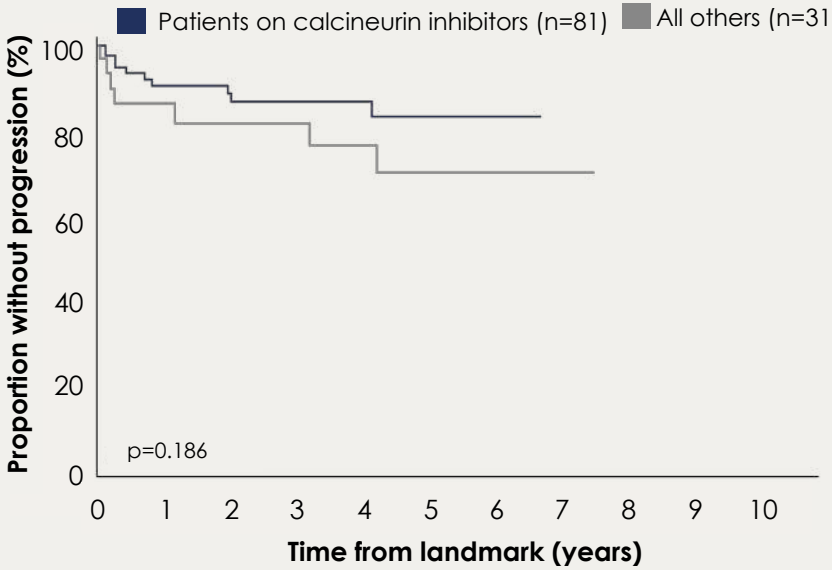
Retrospective analysis of IS, patient baseline characteristics, and relapse risk measured as landmark TTP starting one year after start of therapy in 159 patients with PTLD post-SOT from the PTLD-1 trial

Landmark analysis of TTP in 112 patients with no evidence of progression 1 year after start of treatment with IS[1]

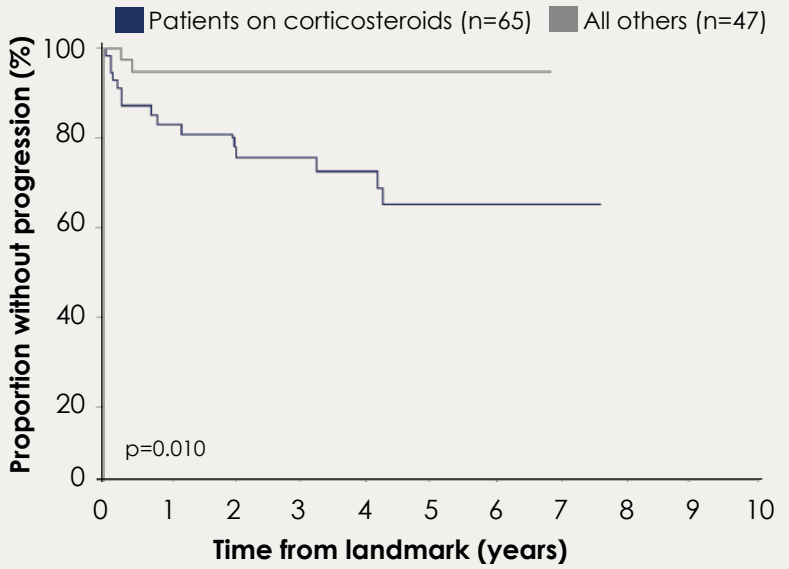
Antimetabolites



Calcineurin inhibitor



Corticosteroids



Corticosteroid-use was associated with an increased risk of PTLD relapse, unlike antimetabolite-containing regimens[1]

IS, immunosuppression; PTLD, post-transplant lymphoproliferative disorder; TTP, time to progression.

1. Zimmermann H, et al. Transplantation. 2018;102:1914-1923.

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Adoptive immunotherapy

EBV antigens expressed in the different latency programmes can be targeted by different immunotherapies[1]

Different sources and applications for adoptive immune therapy in EBV+ PTLD[1]

Transplantation cell type	AHCT: donor origin	SOT: recipient origin
Donor lymphocytes	Yes (GvHD risk)	No
Autologous EBV-CTLs	No (donor derived)	Yes (often EBV-naïve, ongoing IS)
Donor-derived EBV-CTLs	Yes	No (mostly receptor derived)
Third party EBV-CTLs	Yes	Yes

Adapted from Dierickx et al. 2022

CTL, cytotoxic T-lymphocyte; EBV, Epstein-Barr virus; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; IS, Immunosuppression; SOT, solid organ transplantation.

1. Dierickx D, et al. Curr Opin Oncol 2022;34:413–421.

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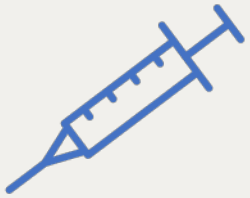
Current treatment options for EBV+ PTLD



Restoring T-cell function[1,2]

- Reduction of immune suppression
- Adoptive immunotherapy

Reducing tumour[1,2]

- Local therapy
- Rituximab and/or chemotherapy

Decreasing EBV viral load[1–3]

- Inducers of lytic cycle
- Antiviral agents

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

1. Gottschalk S, et al. Annu Rev Med. 2005;56:29–44; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562;
3. Atallah–Yunes SA, et al. Br J Haematol. 2023;201:383–395.

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Local therapy – radiotherapy and surgery

- Surgery or radiotherapy is rarely used to treat PTLD, however can be considered in specific situations[1,2]
- Suitable for both SOT and HCT EBV+ PTLD[1]
- Can be combined with RIS and used to rapidly relieve symptoms[2]

Indications for local therapy[2]

Radiotherapy	Surgery
• Limited stage of disease • After chemotherapy in Hodgkin's lymphoma • Whole-brain radiotherapy in primary central nervous system lymphoma if chemotherapy contraindicated • Palliative care	• Limited stage of disease • Palliative care

EBV+, Epstein-Barr virus positive; HCT, haemopoietic cell transplant; PTLD, post-transplant lymphoproliferative disorder; RIS, reduction in immunosuppression; SOT, solid organ transplantation.

1. Dierickx D, Vergote V. Hemasphere. 2019;3:74–77; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562.

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Chemotherapy vs. rituximab post-SOT

Chemotherapy retrospective analysis IPITTR (n=193)[1]

Regimen	n	5-year OS (%)	PTLD-specific mortality (%)
CHOP	90	24	34
ProMACE	12	25	34
Other multidrug	65	32	40
Monotherapy	23	5	48

Rituximab prospective studies*[2–5]

Author	Year	Phase	n	ORR (%)
Oertel[2]	2005	2	17	70.5
Blaes[3]	2005	2	11	64
Choquet[4]	2006	2	43	44.2
Gonzalez-Barca**[5]	2007	2	38	60.5 (CR)

* In most studies: rituximab 375 mg/m²/week during 4 consecutive weeks.[2–5]
** Risk-adapted extended treatment: Over 34% of patients achieved CR after four cycles of rituximab, and 26.3% more responded after two to four additional cycles of rituximab for a delayed CR rate of 60.5%.[5]

CHOP, cyclophosphamide/hydroxydaunorubicin/oncovin/prednisone; CR, complete remission; IPITTR, Israel Penn international Transplant Tumour Registry; ORR, objective response rate; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder.

1. Buell JF, et al. Transplant Proc. 2005;37:956–957; 2. Oertel SH, et al. Am J Transplant. 2005;5:2901–2906; 3. Blaes AH, et al. Cancer. 2005;104:1661–1667; 4. Choquet S, et al. Blood. 2006;107:3053–3057; 5. Gonzalez–Barca E, et al. Haematologica. 2007;92:1489–1494.

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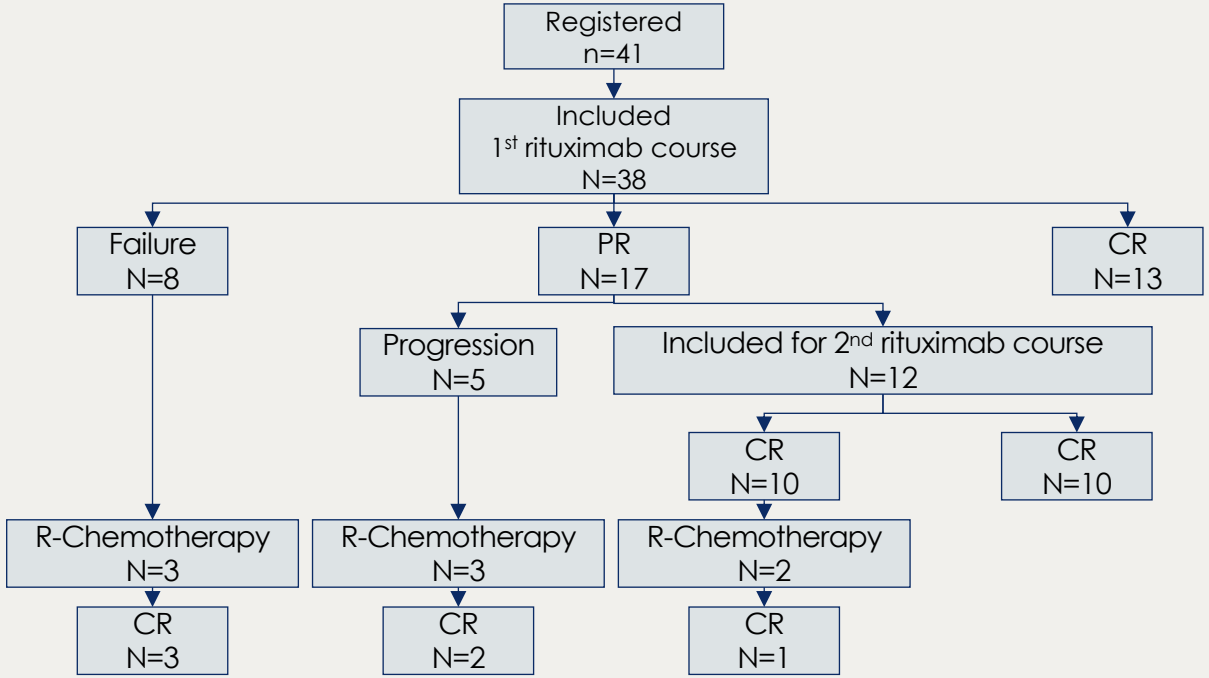
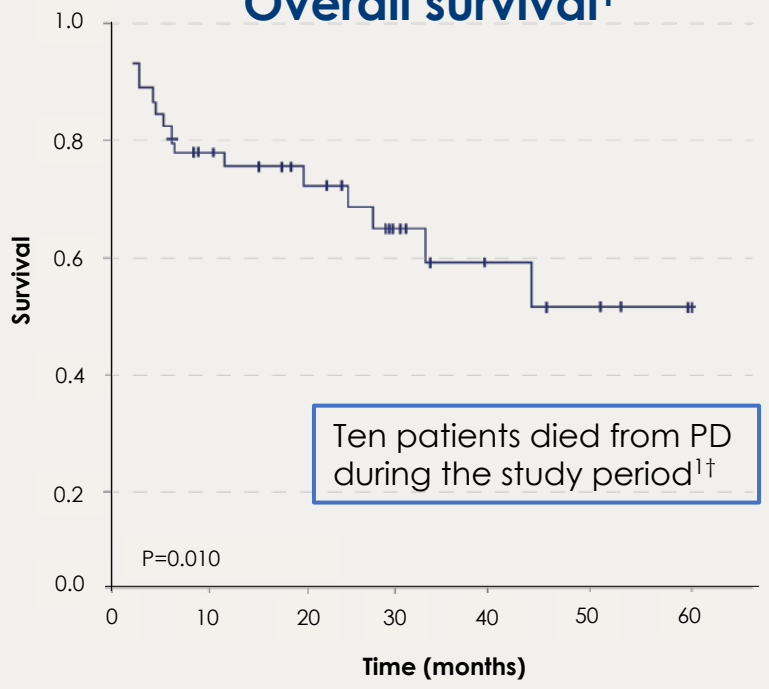
Extended treatment with rituximab in patients with PTLD post-SOT

Prospective Phase 2 study of extended treatment* with rituximab in CD20+ PTLD after SOT[1]

Treatment and outcome of the study group[1]**



Overall survival[1]



Extended treatment with rituximab can obtain a good rate of CR in patients with PTLD after SOT and should be the recommended initial therapy for these patients

* Patients were treated with RIS and four weekly infusions of rituximab. Those patients who did not achieve CR received a second course of four rituximab infusions (extended treatment). Primary end-point of the study: CR rate.
** Among the 17 patients with PR, 8 patients died of PD. This included five patients who had failed the initial course of rituximab (n=8) and three patients who had achieved PR with the initial course of rituximab; two of these died prior to receiving subsequent R-chemotherapy treatment and one died during or after R-chemotherapy.[1]
† 14 patients died during the study period, ten (26.3%) patients died of DP, three patients of infection without evidence and one patient suffered a cardiac arrest of unknown cause.
CR: complete remission; PD, progressive disease; PTLD, post-transplant lymphoproliferative disorder; PR: partial remission; R-chemotherapy: rituximab combined with chemotherapy; RIS: reduction of immunosuppression; SOT: solid organ transplantation. 1. Gonzalez-Barca E, et al. Haematologica. 2007;92:1489–1494.

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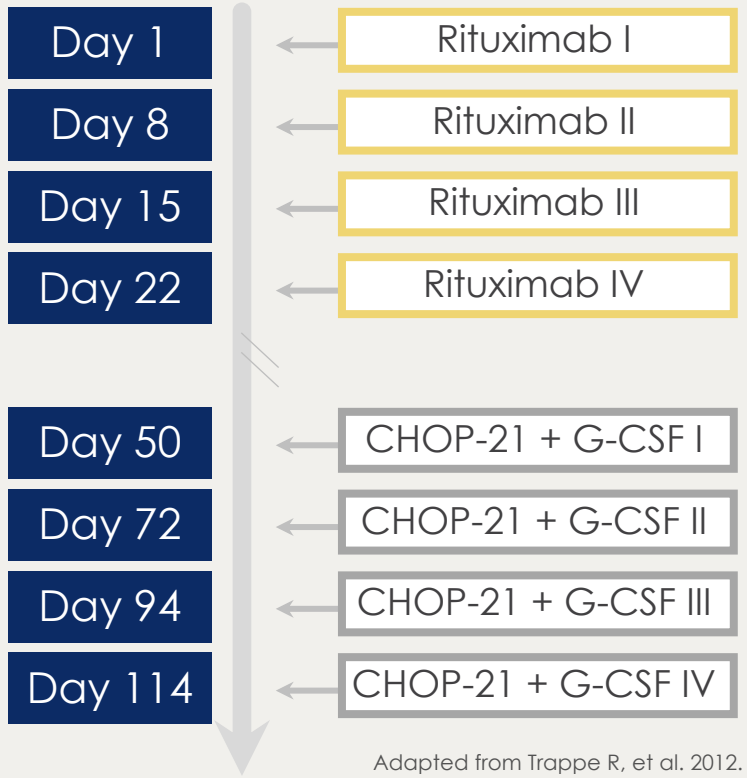
Sequential treatment with rituximab and CHOP results in durable long-term disease control in PTLD-1

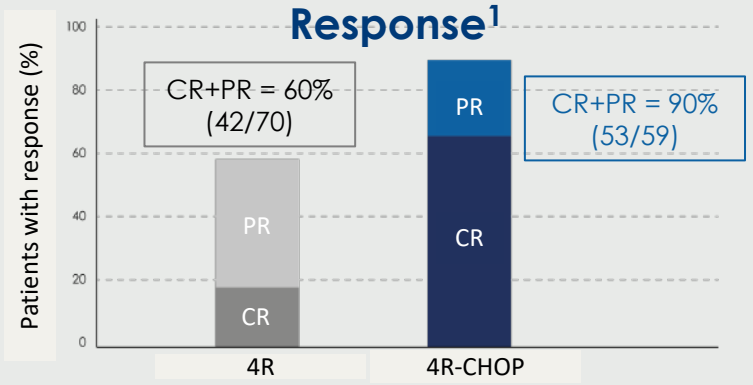
PTLD-1 ST: an international multicentre open-label Phase 2 PTLD-1 trial in patients with CD20+ PTLD post-SOT who had failed to respond to IS reduction[1]

Sequential treatment[1]

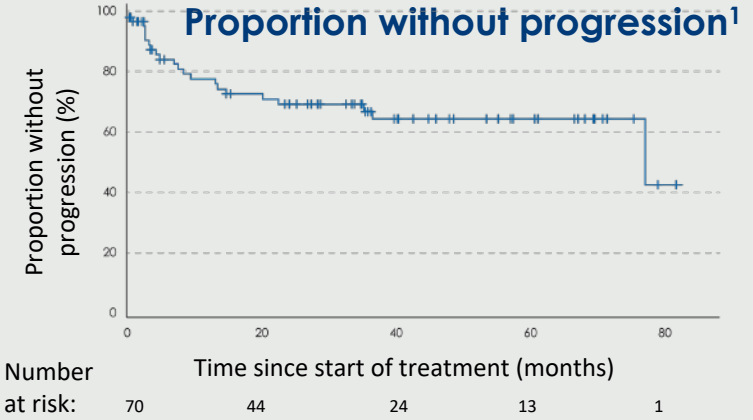


Adapted from Trappe R, et al. 2012.

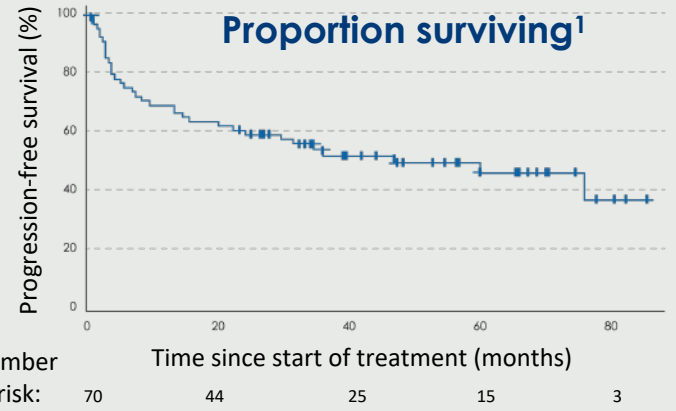
Response[1]



Proportion without progression[1]



Proportion surviving[1]



Graphs adapted from Trappe R, et al. 2012.

N=70 patients eligible to receive treatment

Median OS: 6.6 years

Median PFS: 4.0 years

R-CHOP, rituximab plus CHOP; CHOP, cyclophophoamide/hydroxydaunorubicin/oncovin/prednisone; CR, complete response; CT, computed tomography; G-CSF, granulocyte-colony stimulating factor; ORR, overall response rate; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder.

1. Trappe R, et al. Lancet Oncol. 2012;13:196–206.

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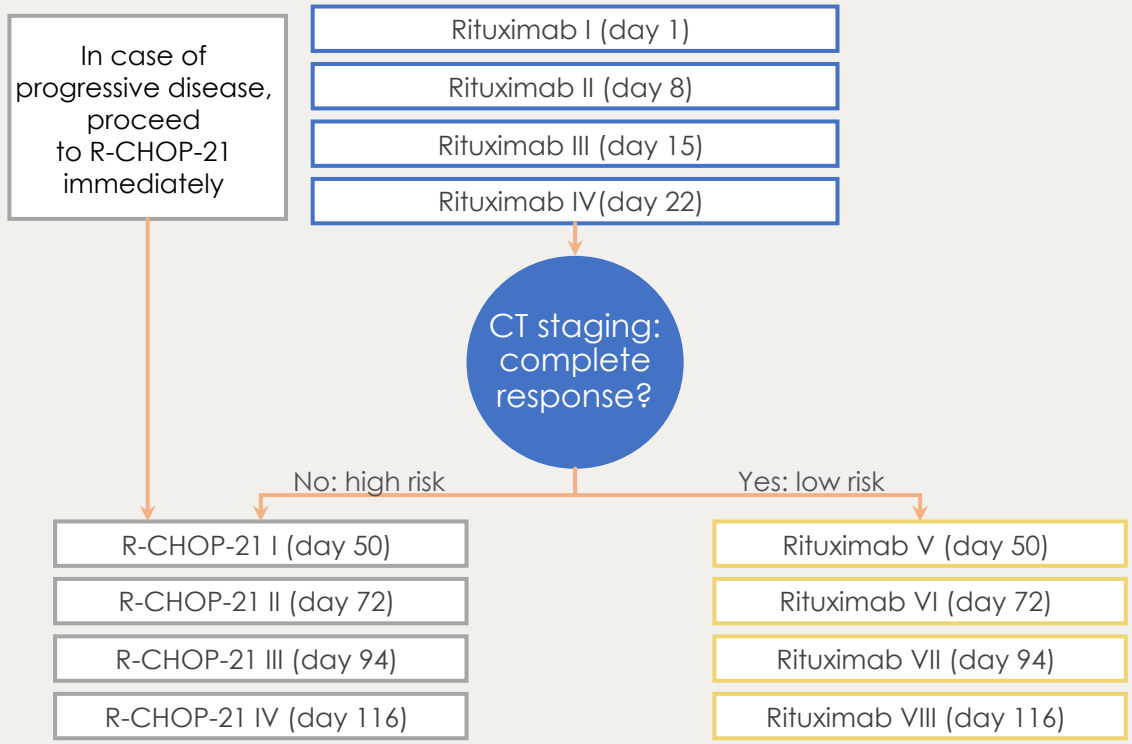
Risk-stratified sequential treatment with rituximab and CHOP in PTLD (PTLD-1 RSST)

PTLD-1 RSST: an international, multicentre, open-label, Phase 2 trial in patients with CD20+ PTLD post-SOT who had failed to respond to IS reduction[1]

Risk-stratified sequential treatment[1]



Adapted from Trappe et al. 2017.

Intention to treat (N=152)

Interim staging: **CR 25%**

Final staging: **CR 70%, ORR 88%**

Toxicity:

Grade 3–4 leukopenia: 63%

Grade 3–4 infections: 34%

Treatment-related mortality: 8%

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete response; D, day; IS, immunosuppression; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; R, rituximab; S, stratification; SD, stable disease; SOT, solid organ transplant.

1. Trappe R, et al. J Clin Oncol. 2017;35:536–543.

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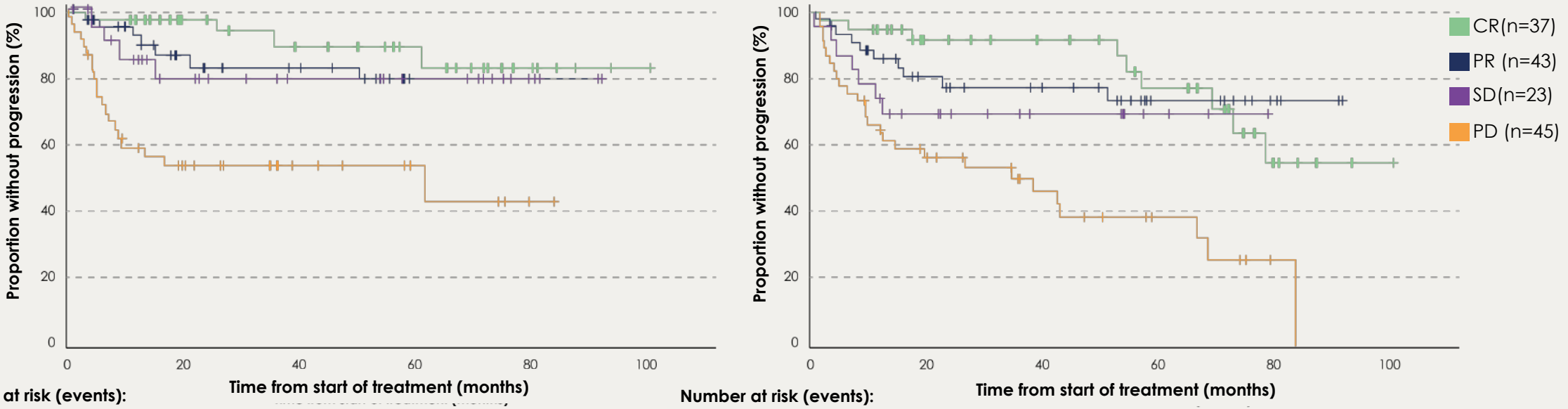
Risk-stratified sequential treatment with rituximab and CHOP in PTLD (PTLD-1 RSST)

PTLD-1 RSST: an international, multicentre, open-label, Phase 2 trial in patients with CD20+ PTLD post-SOT who had failed to respond to IS reduction[1]

Risk-stratified sequential treatment: outcome by interim response to rituximab[1]



Number at risk (events):

CR	37	25	19	14	6	1
PR	43	26	21	10	4	
SD	23	11	5	2		
PD	45	18	9	5	1	

Number at risk (events):

CR	37	25	21	15	6	1
PR	43	27	21	10	4	
SD	23	13	7	3		
PD	45	22	12	6	1	

CHOP, cyclophophoamide/hydroxydaunorubicin/oncovin/prednisone; CR, complete response; CT, computed tomography; G-CSF, granulocyte-colony stimulating factor; ORR, overall response rate; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder.

1. Trappe RU, et al. J Clin Oncol. 2017,35:536–543.

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Modified risk-stratified sequential treatment with rituximab and CHOP in PTLD (PTLD-2 RSST)

PTLD-2 RSST: a prospective, multicentre, open-label, Phase 2 trial in patients with CD20+ PTLD post-SOT who had failed to respond to IS reduction[1]

In case of progressive disease, proceed to R-CHOP or R-DHAOx immediately

- Rituximab I (day 1)
- Rituximab II (day 8)
- Rituximab III (day 15)
- Rituximab IV (day 22)

Intention to treat (N=60)

Interim staging (n=58):
ORR 45%, CR 9%

CT staging (day 40–50)

Very high risk
(PD and thoracic SOT)
- R s.c.-CHOP+GCSF (day 50)
- R s.c.-DHAOx+GCSF (day 72)
- R s.c.-CHOP+GCSF (day 94)
- R s.c.-DHAOx+GCSF (day 116)
- R s.c.-CHOP+GCSF (day 138)
- R s.c.-DHAOx+GCSF (day 160)

High risk
(No PR or PR and IPI > 3 or PD and non-thoracic SOT)
- R-CHOP-21 I (day 50)
- R-CHOP-21 II (day 72)
- R-CHOP-21 III (day 94)
- R-CHOP-21 IV (day 116)

Low risk
(CR at interim staging or PR and IPI < 3)
- Rituximab V (day 50)
- Rituximab VI (day 72)
- Rituximab VII (day 94)
- Rituximab VIII (day 116)

Adapted from Zimmermann R, et al. 2022.

Final staging

	Very high risk (n=5)	High risk (n=22)	Low risk (n=21)
ORR	60%	100%	95%
CR	40%	41%	52%

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete response; DHAOx, oxaliplatin, cytarabine, dexamethasone; GCSF, granulocyte colony stimulating factor; IPI, international prognostic index; IS, immunosuppression; ORR, overall response rate; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; R, rituximab; s.c., subcutaneous; SOT, solid organ transplant.

1. Zimmermann H et al. Leukemia. 2022;36:2468–2478.

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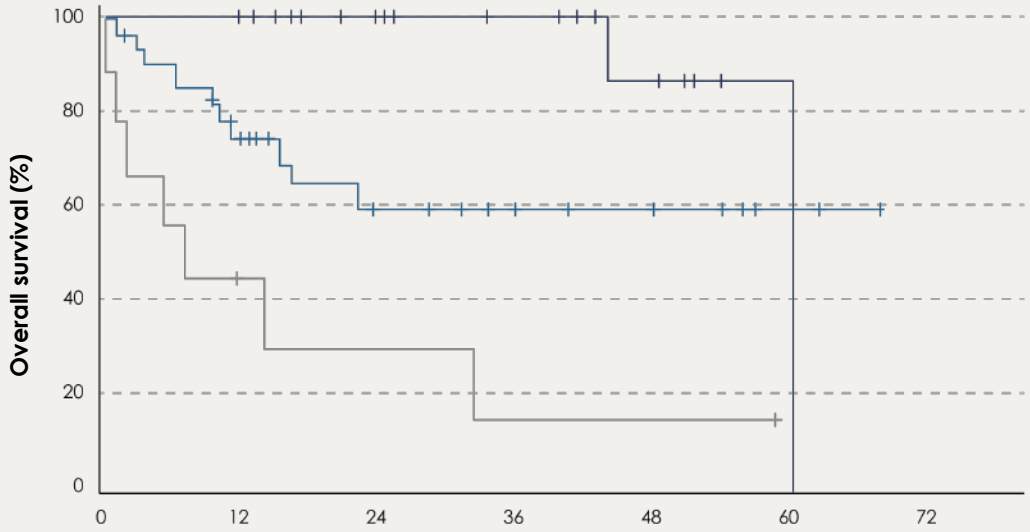
Modified risk-stratified sequential treatment with rituximab and CHOP in PTLD (PTLD-2 RSST)

PTLD-2 RSST: a prospective, multicentre, open-label, Phase 2 trial in patients with CD20+ PTLD post-SOT who had failed to respond to IS reduction[1]

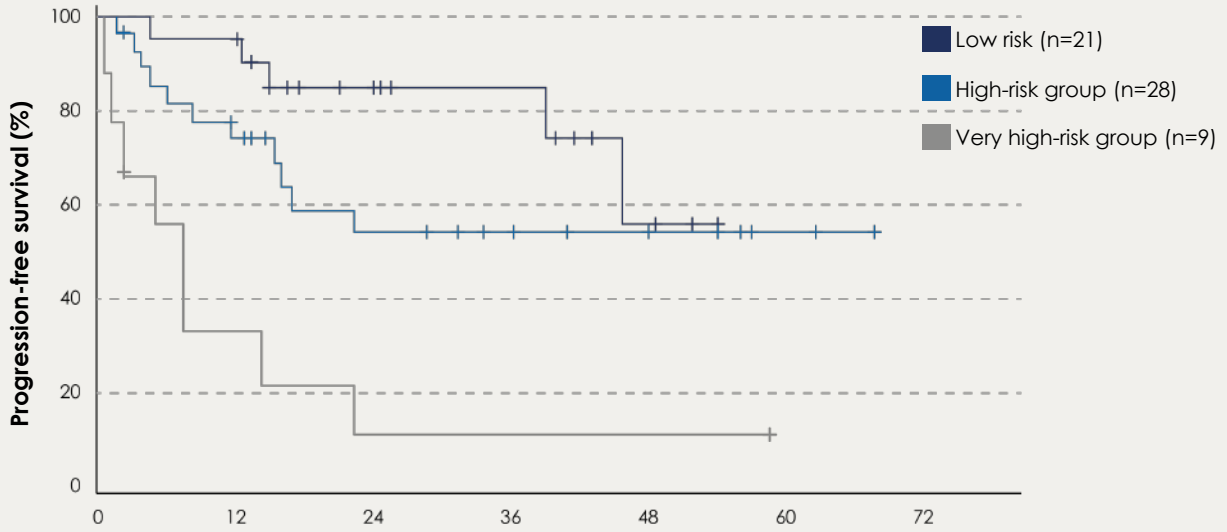
Overall survival[1]



Number at risk (events):

Low	21	21	15	10	6	1
High	28	19	11	8	6	2
V high	9	4	2	1	1	0

Progression-free survival[1]



Number at risk (events):

Low	21	21	12	8	3	0
High	28	19	11	8	6	2
V high	9	3	1	1	1	0

IPI, international prognostic index; IS, immunosuppression; ORR, overall response rate; PTLD, post-transplant lymphoproliferative disorder; R, rituximab; S, stratification; s.c., subcutaneous; SOT, solid organ transplant.

1. Zimmermann H et al. Leukemia. 2022;36(Suppl):2468–2478.

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Patient characteristics (PTLD-1 ST, PTLD-1 RSST, PTLD-2 RSST)

Protocol	PTLD-1 ST[1]	PTLD-1 RSST[2]	PTLD-2 RSST[3]
No. of patients	70	152	60
Age at diagnosis			
Median (years)	53.3	56.4	53.8
Transplant type			
Kidney	41%	45%	48%
Liver	23%	26%	15%
Heart	20%	10%	7%
Lung	6%	12%	23%
Kidney + pancreas	6%	2%	3%
Heart + other*	3%	4%	0%
SCT	1%	0%	0%
Median time from transplant to PTLD			
<1 year	24%	21%	22%
≥1 year	76%	79%	78%

Protocol	PTLD-1 ST[1]	PTLD-1 RSST[2]	PTLD-2 RSST[3]
Histology (WHO, 2001)			
Polymorphic PTLD	4%	15%	3%
Monomorphic PTLD	96%	85%	97%
Burkitt	3%	4%	7%
DLBCL	81%	74%	75%
Plasma cell myeloma	3%[2]	–	2%
Others	9%[2]	7%[3]	12%
Ann Arbor stage			
I + II	26%	33%	27%
III + IV	74%	67%	73%
LDH			
Elevated	75%	65%	57%
Normal	25%	35%	43%
EBV-association			
Yes	44%	47%	38%
No	56%	53%	62%

*Heart + kidney (3%), heart + lung (1%).
DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disorder; RSST, risk-stratified sequential treatment; SCT, stem cell transplant; ST, sequential treatment; WHO, World Health Organization.
1. Trappe R, et al. Lancet Oncol. 2012;13:196–206; 2. Trappe R, et al. J Clin Oncol. 2017;35:536–543; 3. Zimmermann H, et al. Leukemia. 2022;36:2468–2478.

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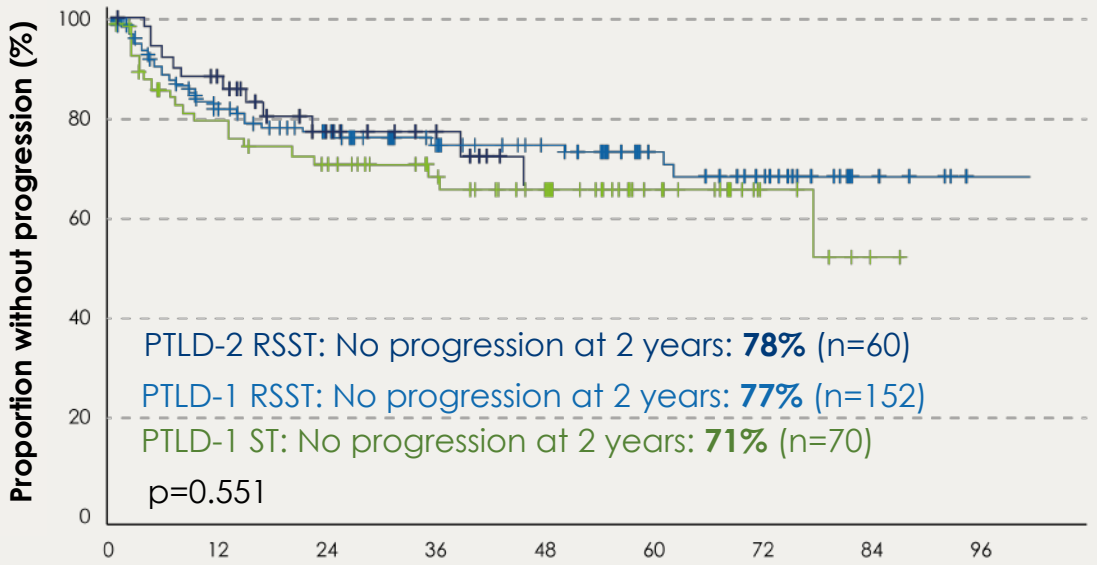
Time to progression and overall survival (PTLD-1 ST, PTLD-1 RSST, PTLD-2 RSST)

Proportion without progression[1]

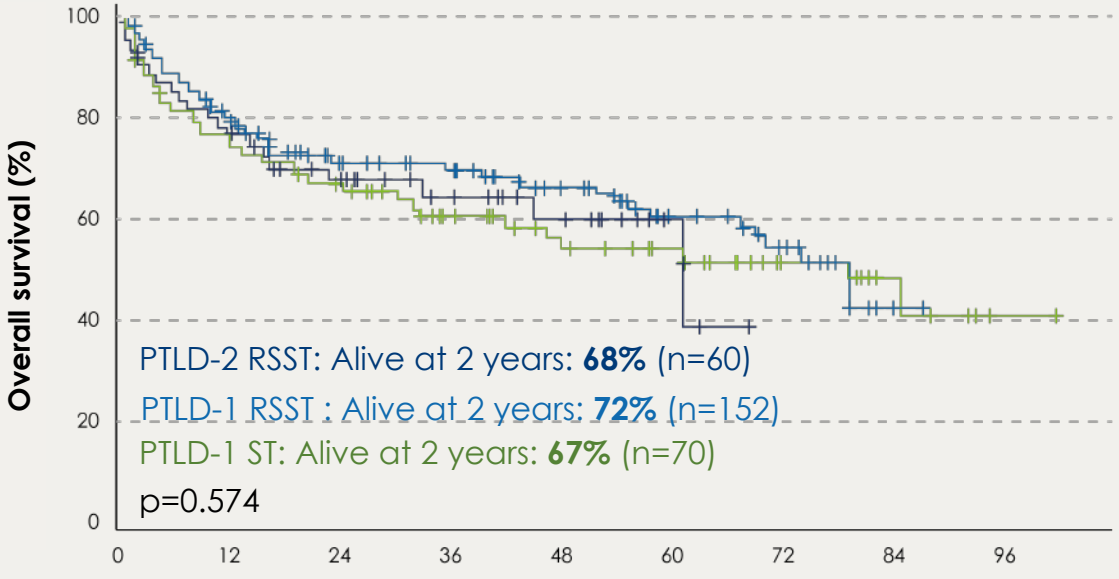


Time since start of treatment (months)

Number at risk (events):

PTLD-1 RSST	152	108	73	64	49	31	24	7	1
PTLD-2 RSST	60	42	24	17	10	2	0	0	0
PTLD-1 ST	70	48	41	28	21	15	6	1	0

Overall survival[1]



Time since start of treatment (months)

Number at risk (events):

PTLD-1 RSST	152	115	80	68	55	34	26	7	1
PTLD-2 RSST	60	44	28	19	13	3	0	0	0
PTLD-1 ST	70	53	46	34	26	20	8	1	0

Graphs adapted from Zimmermann H, et al. 2022.

Disease control and overall survival of PTLD-1 RSST and PTLD-2 RSST compare favourably with PTLD-1 ST[1]

eRSST, extended risk-stratified sequential treatment; PTLD, post-transplant lymphoproliferative disorder; RSST, risk-stratified sequential treatment; ST, sequential treatment.

1. Zimmermann H, et al. Leukemia. 2022;36(Suppl.):2468–2478.

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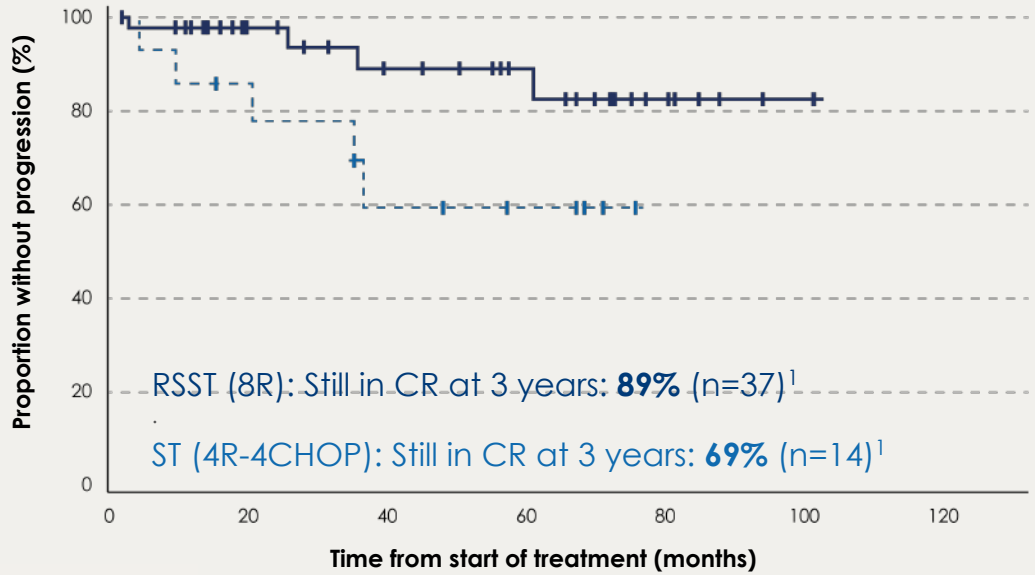
Rituximab monotherapy consolidation is superior to CHOP-consolidation in low-risk patients[1]

Proportion without progression[1]



Number at risk (events):

RSST	37	25	19	14	6	1
CR	14	11	6	4		

Adapted from Trappe et al. 2017.

Time to progression by study[1,2]

n=51
p<0.05

Low-risk patients, i.e. those in CR after four courses of rituximab

RSST: Benefit from continued rituximab monotherapy consolidation

ST: More than from CHOP consolidation

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete response; R, rituximab; RSST, risk-stratified sequential treatment; ST, sequential treatment.

1. Trappe R, et al. J Clin Oncol. 2017;35:536–543; 2. Trappe R, et al. Blood. 2015;126(23):Abstract 816.

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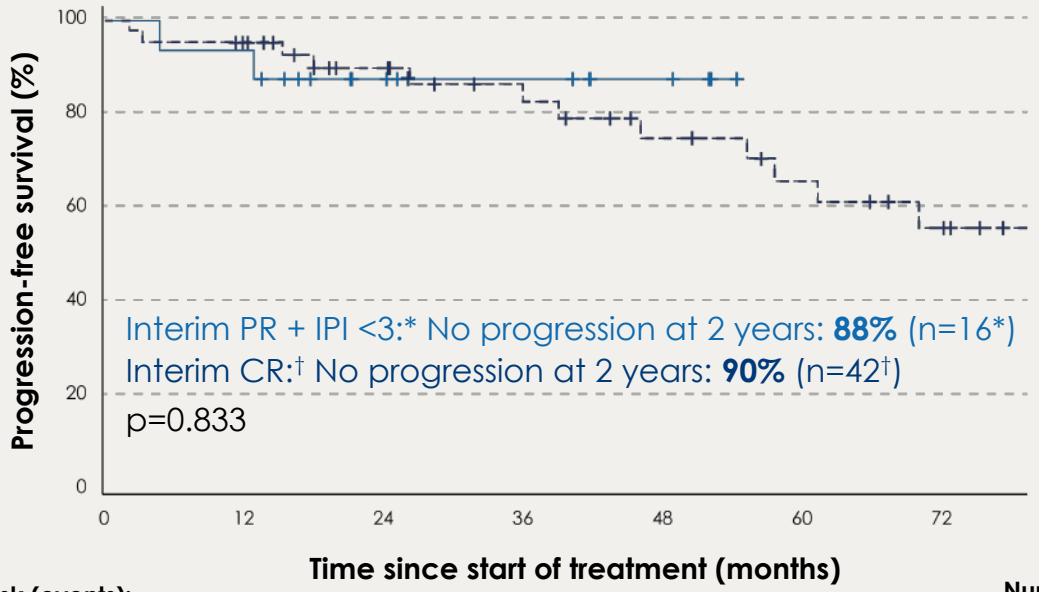
Rituximab monotherapy consolidation is also an option in low-risk interim PR patients

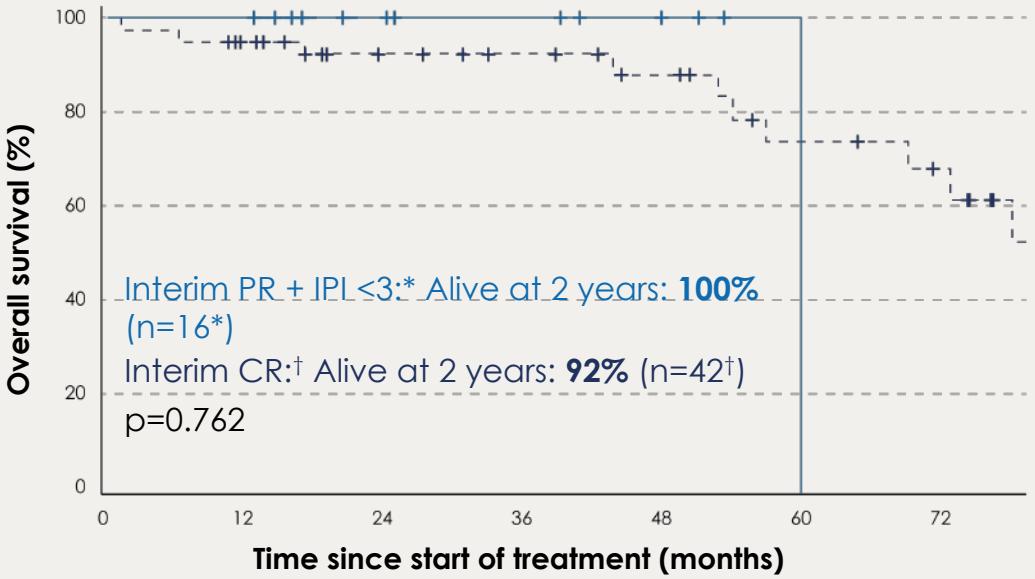
Progression-free survival[1]



Number at risk (events):

PR	16	15	9	5	3	1	
CR	42	38	28	23	18	14	10

Overall survival[1]



Number at risk (events):

PR	16	16	12	8	5	1	
CR	42	38	29	25	21	15	12

Graphs adapted from Zimmermann H, et al. 2022.

* PTLD-2 trial.[1]

† Thirty-seven patients from PTLD-1 RSST; five patients from PTLD-2.[1]

CR, complete response; IPI, international prognostic index; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; RSST, risk-stratified sequential treatment.

1. Zimmermann H, et al. Leukemia. 2022;36:2468–2478.

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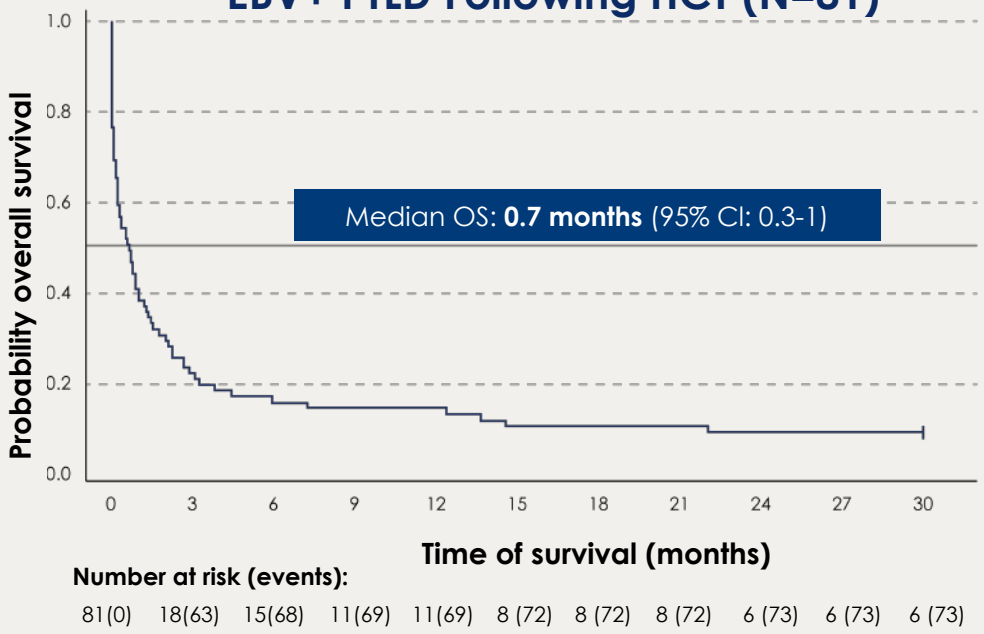
Outcomes of HCT and SOT recipients with relapsed/refractory EBV+ PTLD

- A large multinational, multicenter* retrospective chart review study of EBV+ PTLD patients following HCT 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]

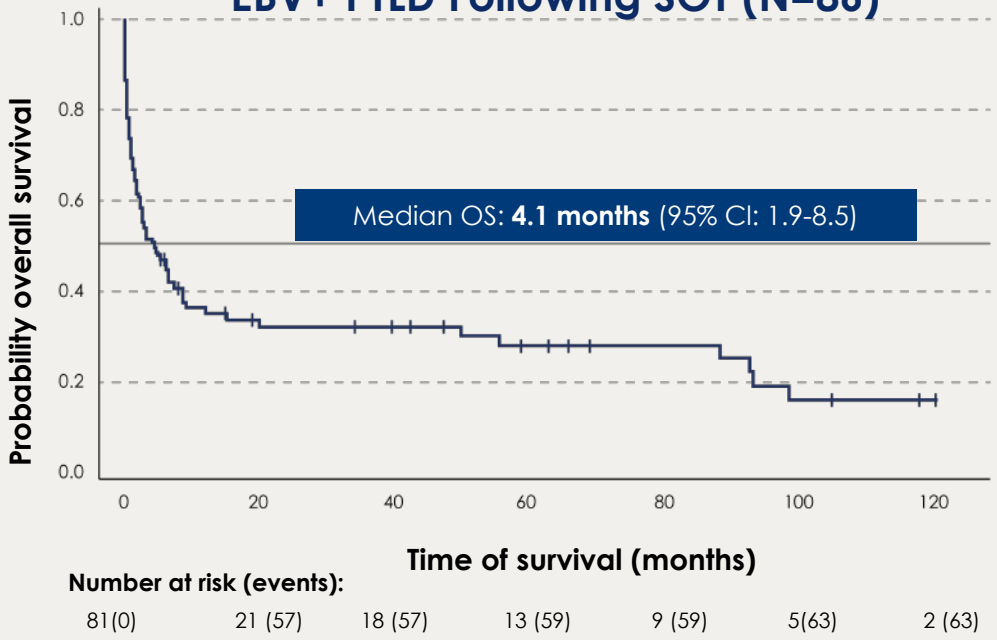
Overall survival in Patients with R/R EBV+ PTLD Following HCT (N=81)[1]



Number at risk (events):										
81 (0)	18 (63)	15 (68)	11 (69)	11 (69)	8 (72)	8 (72)	8 (72)	6 (73)	6 (73)	6 (73)

Adapted from Socié G, et al. 2022.

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



Number at risk (events):						
81 (0)	21 (57)	18 (57)	13 (59)	9 (59)	5 (63)	2 (63)

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

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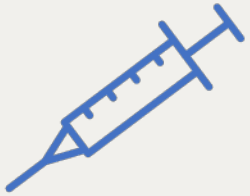
Current treatment options for EBV+ PTLD



Restoring T-cell function[1,2]

- Reduction of immune suppression
- Adoptive immunotherapy

Reducing tumour mass[1,2]

- Local therapy
- Rituximab and/or chemotherapy

Decreasing EBV viral load[1–3]

- Inducers of lytic cycle
- Antiviral agents

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

1. Gottschalk S, et al. Annu Rev Med. 2005;56:29–44; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 3. Atallah-Yunes SA, et al. Br J Haematol. 2023;201:383–395.

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Targeting EBV: Inducing the lytic cycle and anti-viral agents

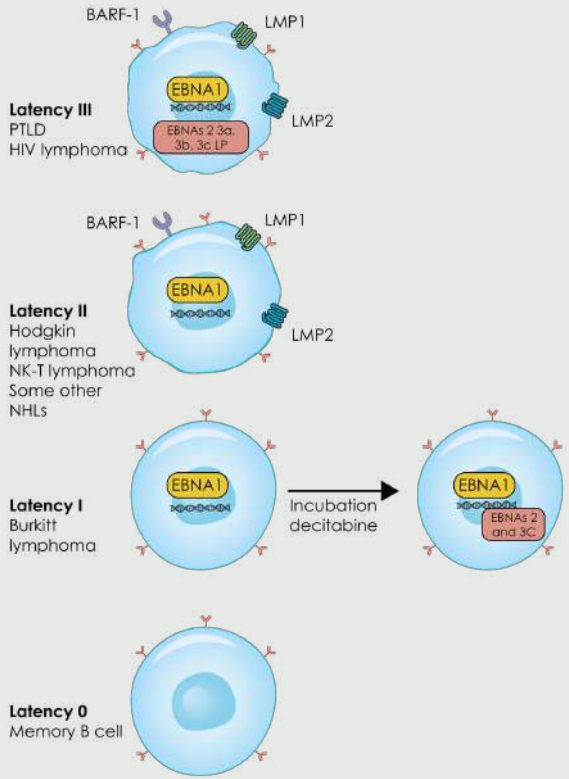
EBV is predominantly latent in infected tumour cells, and should be re-sensitised to become susceptible to antivirals[1,2]

Options for lytic induction:[3]

- Traditional chemotherapies
- Steroids
- HDAC inhibitors

The use of antivirals and HDAC inhibitors in treatment of PTLD is currently limited to investigational settings[1]

Latency programmes[2]



Adapted from Heslop HE, et al. 2020.

BARF, bamh1-a reading frame; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; HDAC, histone deacetylase; HIV, human immunodeficiency virus; LMP, latent membrane protein; NHL, non-Hodgkin lymphoma; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder.

1. Atallah-Yunes SA, et al. Br J Haematol. 2023;201:383–395; 2. Heslop HE. Blood. 2020;135:1822–1823; 3. Dugan JP, et al. Front Oncol. 2019;9:127.

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The current face of EBV+ PTLD management

There are a **range of therapy options** for treating EBV+ PTLD[1]

Some patients experience **inadequate response** to these treatments[2,3]

Patients not responding to 1L **face poor outcomes** (**0.7m** mOS post-HCT and **4.1m** mOS post-SOT in R/R EBV+ PTLD patients) and **limited treatment** options[2,3]

Alternative treatment options for patients with EBV+ PTLD **after failure of initial therapy** represent a significant **unmet clinical need**[2]

EBV+, Epstein-Barr virus positive; HCT, haematopoietic cell transplantation; mOS, median overall survival; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplant.

1. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 2. Socié G, et al. Bone Marrow Transplant. 2024;59:52–58;
3. Dharnidharka V, et al. HemaSphere 2022;6(Abstract):997–998.

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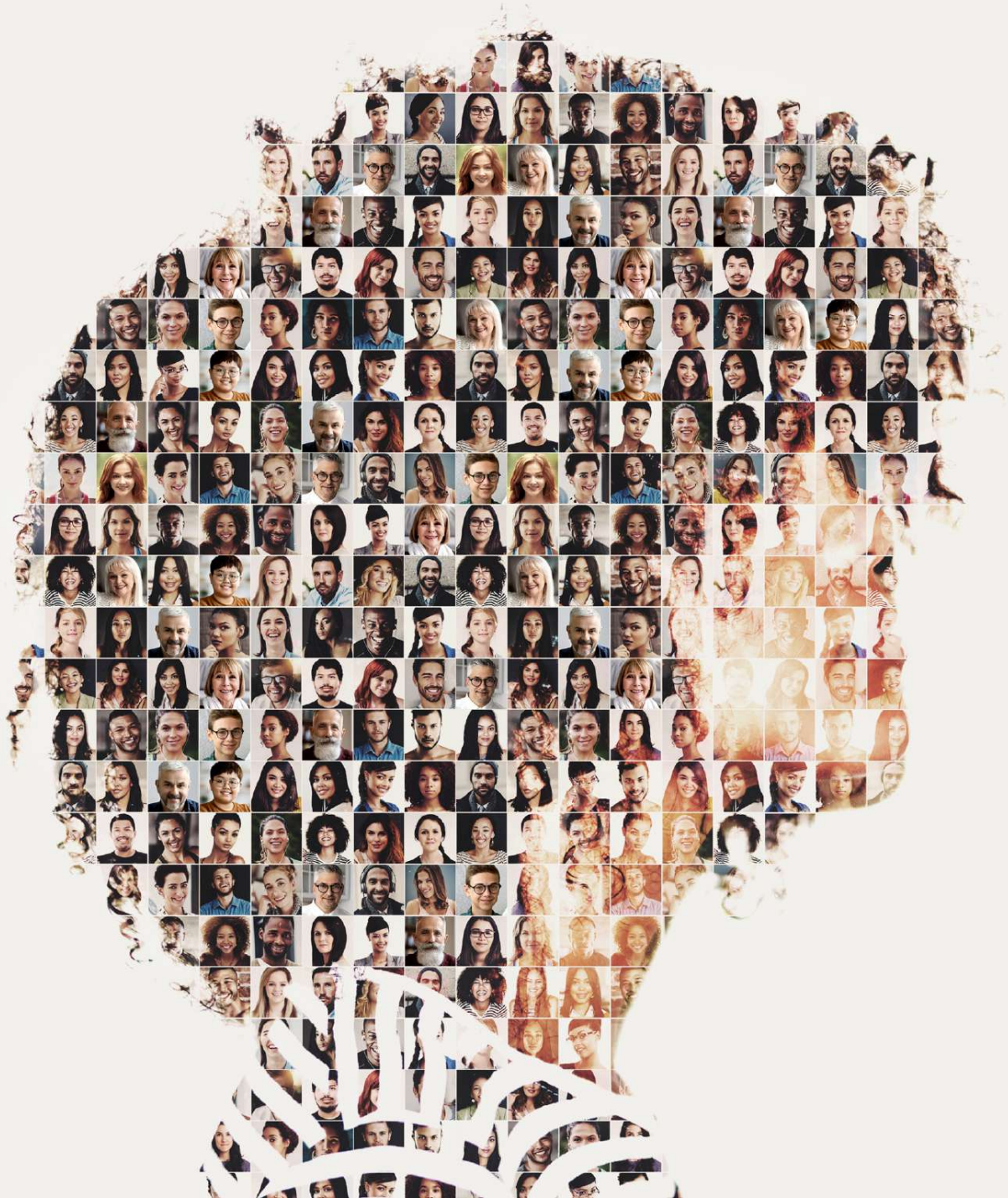

Changing the face of EBV+ PTLD management

with EBV-specific T-cell immunotherapy

Manuel Guerreiro
La Fe University and Polytechnic Hospital, Valencia, Spain

Portuguese Oncology Institute, Porto, Portugal

EBVALLO® is not commercialized in Spain/ EBVALLO® no está comercializado en España.

EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

HQ-EBV-05-24-2400012; June 2024.

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Disclosures

- Consultancy/advisory: Pierre Fabre, Novartis, Kite/Gilead, BMS, MSD

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Changing the face of EBV+ PTLD management with EBV-specific T-cell immunotherapy: Outline

Introduction to third-party anti-viral CTLs

- Outline
- Evidence
- Strategies
- HLA restriction

EBVALLO® (tabelecleucel)

- Product overview
- Mechanism of action
- Manufacturing
- Inventory / cell line selection

ALLELE study

- Study design and patient characteristics
- Efficacy data (primary and key secondary endpoints)
- Safety

CTL, cytotoxic T lymphocyte; EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disorder.

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Current therapeutic strategies for treatment of EBV+ PTLD

Restoring T-cell function[1]

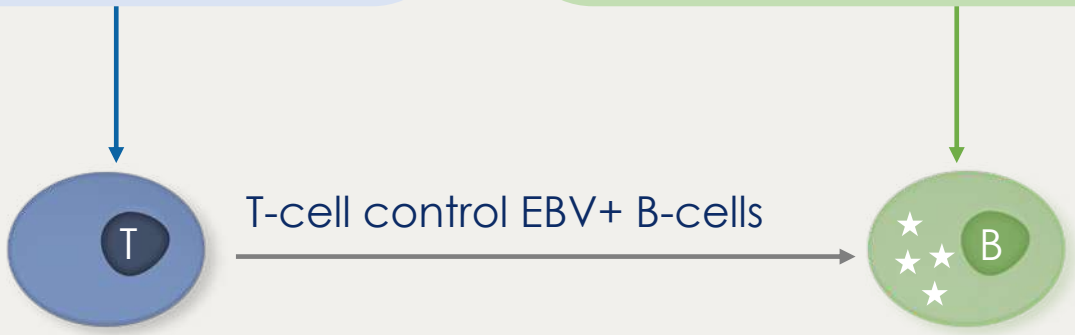
- Reduction of immunosuppression
- Donor lymphocyte infusion
- EBV+ CTLs
- Checkpoint inhibitors
- CAR-Ts

Reduction of B-cell mass[1]

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

Decreasing EBV viral load[1]

- 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 Res. 2022;42(11):5181–5186.

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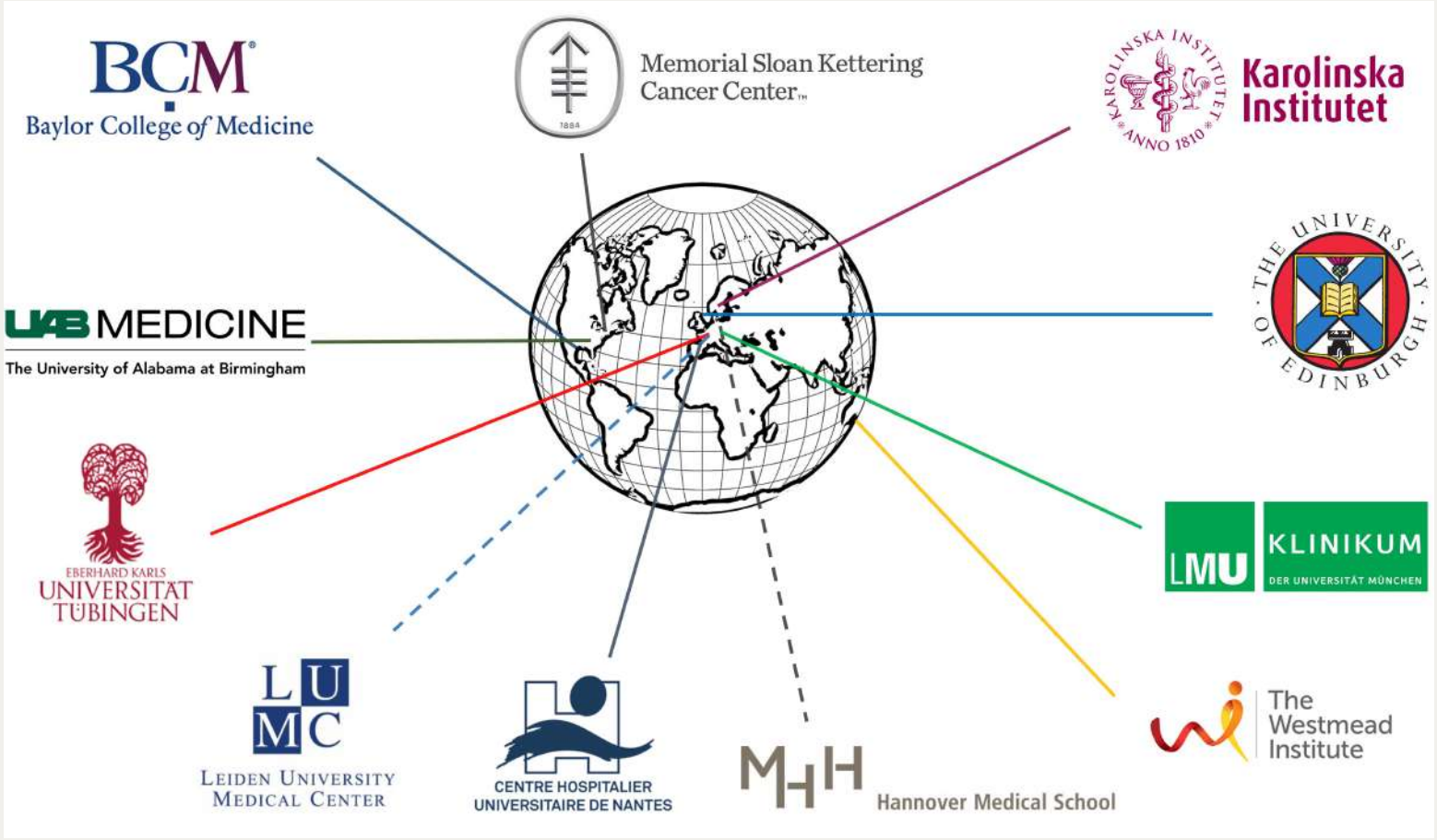
Years of evidence on the efficacy and safety of virus-specific T-cell therapy[1–11]



Slide courtesy of Dr. Guerreiro.

1. Uhlin M, et al. Clin Infect Dis. 2012 Oct;55(8):1064-73; 2. Feucht J, et al. Blood. 2015 Mar 19;125(12):1986-94; 3. Doubrovina E, et al. Blood. 2012 Mar 15;119(11):2644-56; 4. Haque T, et al. Blood. 2007 Aug 15;110(4):1123-31; 5. Leen AM, et al. Blood. 2013 Jun 27;121(26):5113-23 6.; Feuchtinger T, et al. Blood. 2010;116(20):4360–4367; 7. Withers B, et al. Biol Blood Marrow Transplant. 2018 Dec;24(12):2433-2442; 8. Tischer S, et al. J Transl Med. 2014 Dec 16;12:336; 9. Gallot G, et al. J Immunother. 2014 Apr;37(3):170-9; 10. Sun Q, et al. Br J Haematol. 2002 Sep;118(3):799-808; 11. Roex MCJ, et al. Leukemia. 2020 Mar;34(3):831-844.

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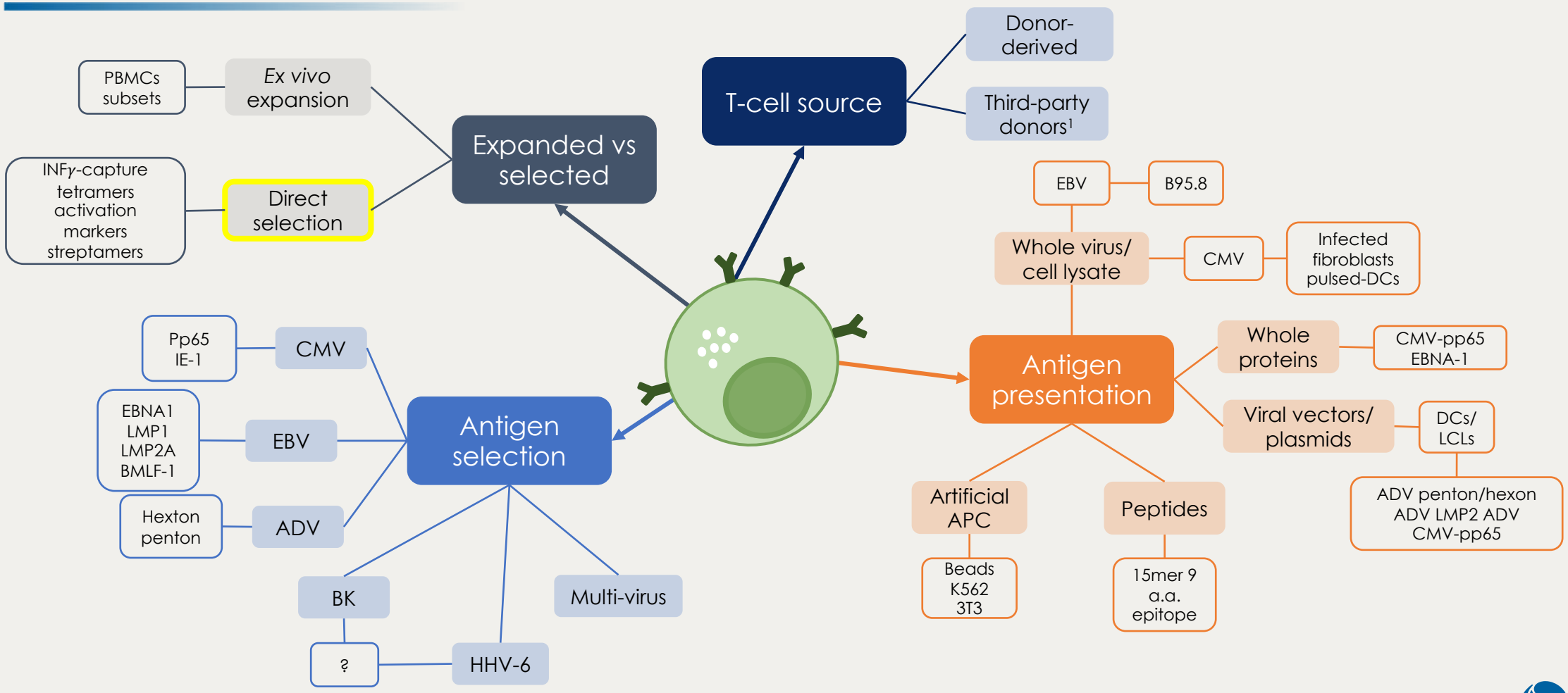
Different strategies to obtain virus-specific T-cells: Breakthrough of expanded third-party T-cells



Slide courtesy of Dr. Guerreiro.

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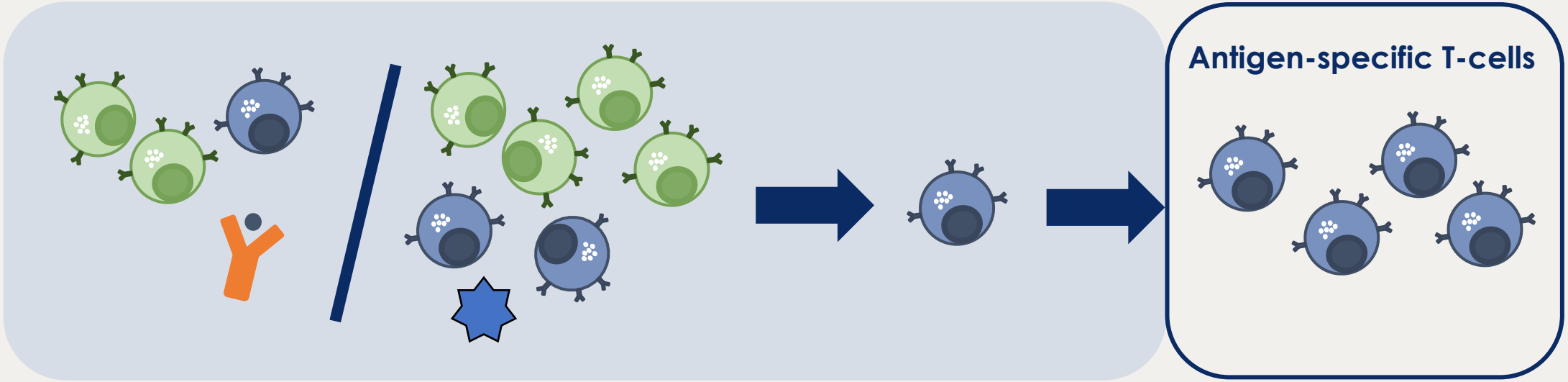
Virus-Specific T-cells: Manufacturing strategies

Method A: Direct selection[1]

- Capture antibodies/multimers
- Bind and select out T-cells recognizing the relevant antigen

TRACE Trial Phase III
(*EudraCT* No.: 2018-000853-29)

AdV, CMV and EBV magnetically selected multivirus-specific T cells



CTL specific for antigen via native TCR

Non-specific T-cell

INFγ and INFγ capture antibody

Multimer

1. Bollard, C.M. et al. Blood. 2016;127(26):3331–3340.

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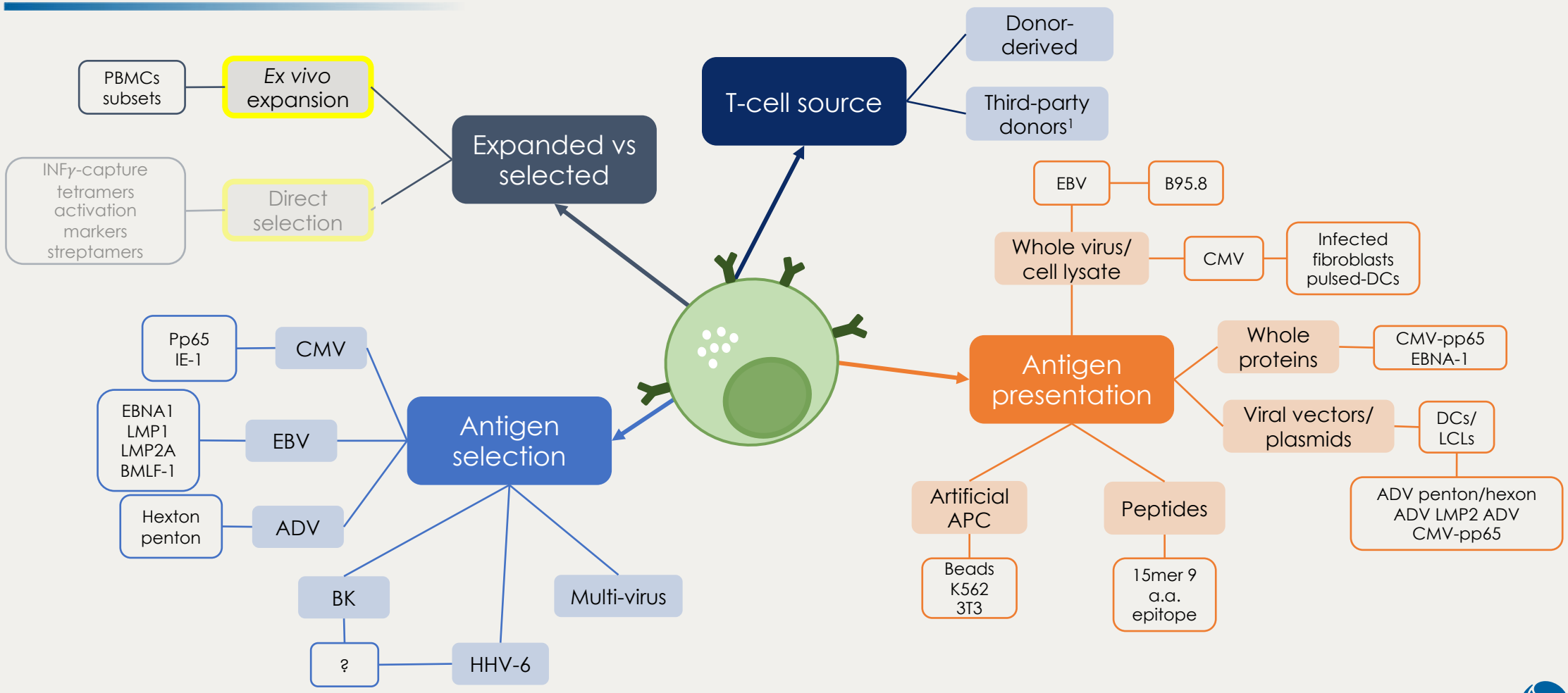
Different strategies to obtain virus-specific T-cells: Breakthrough of expanded third-party T-cells



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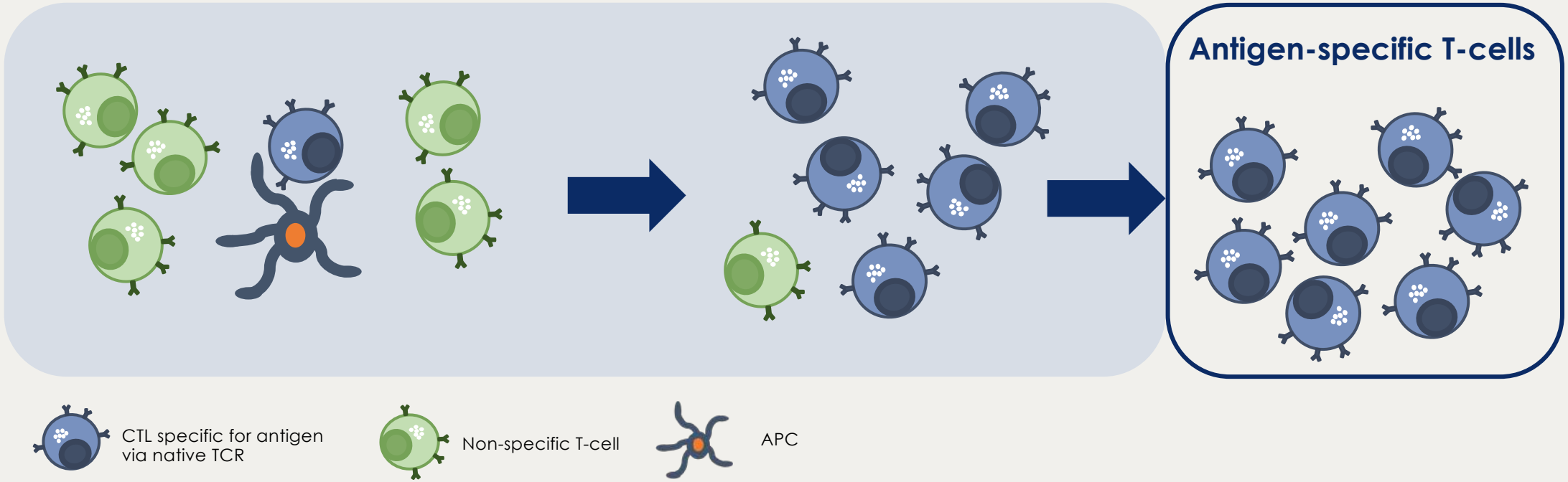
Virus-Specific T-cells: Manufacturing strategies

Method B: Ex vivo expansion1

- APC only stimulates T-cell recognising antigen



1. Bollard, C.M. et al. Blood. 2016;127(26):3331–3340.

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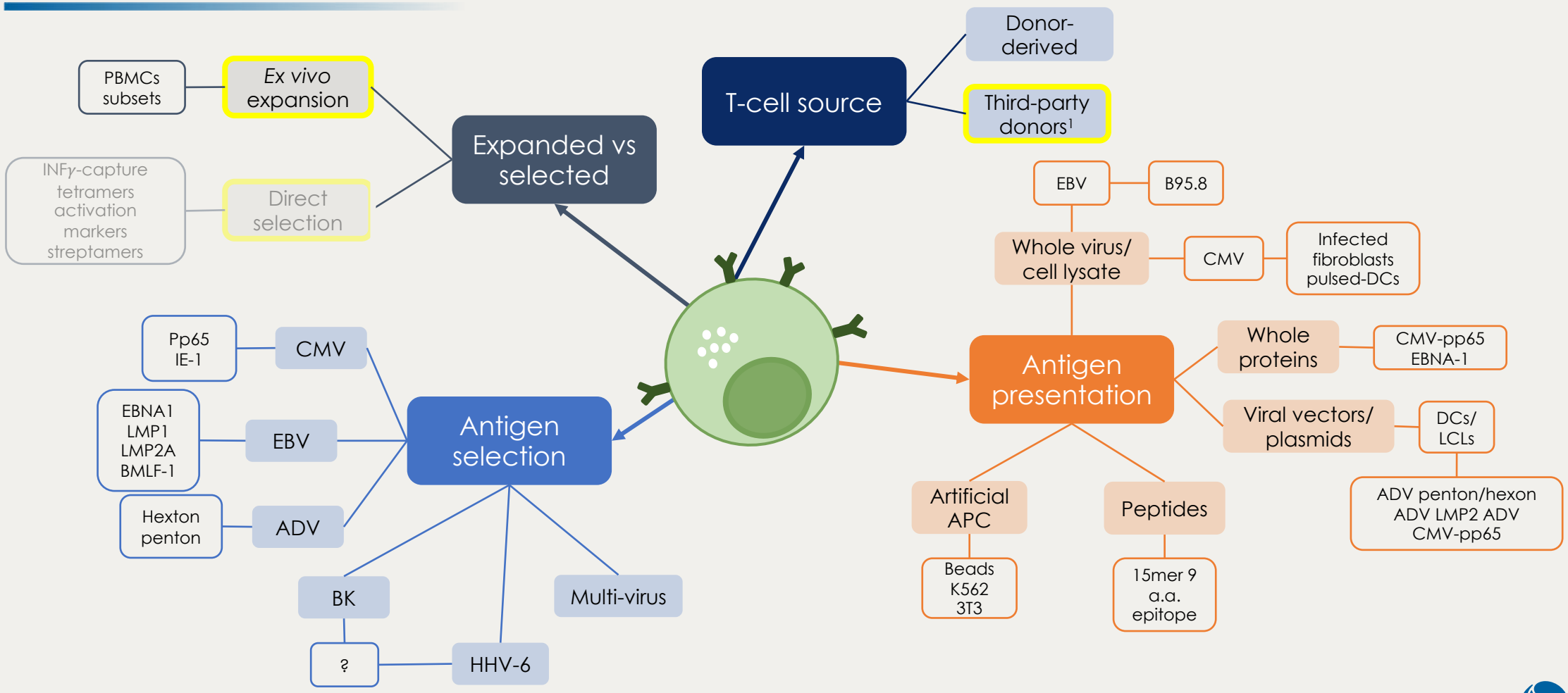
Different strategies to obtain virus-specific T-cells: Breakthrough of expanded third-party T-cells



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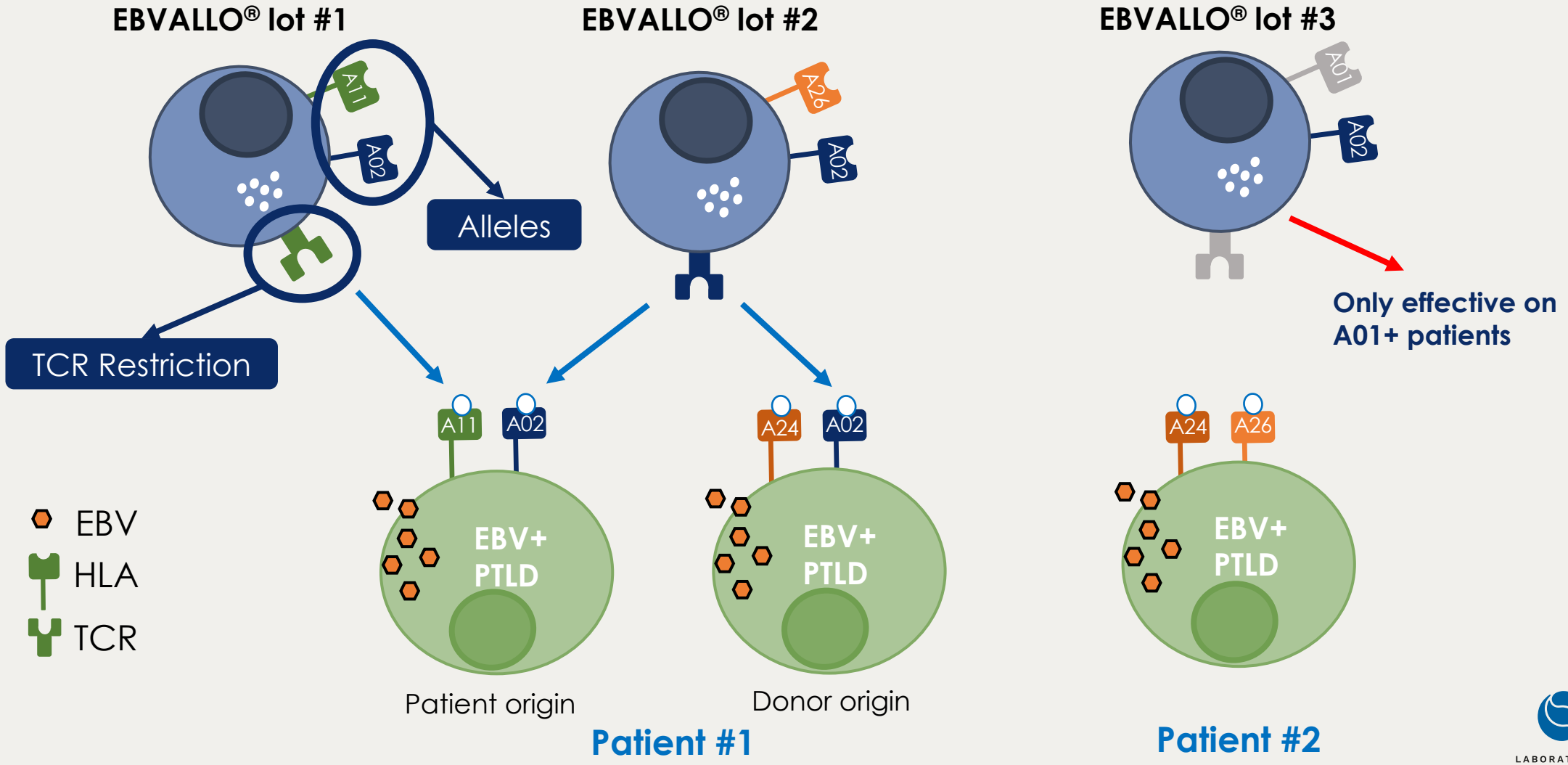
Lot selection for EBVALLO®



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Published experience: 3rd Party EBV CTLs

Center	Method of selection	Indication for CTLs	Prior therapy	N	HLA	Response
Alabama	EBV-BLCL-sensitised	SOT (EBV+ PTLD)	RT	1	4/6	1/1 (100%)
Sun, et al. 2002[1]	EBV CTLs		Rituximab + CT	1	6/6	1/1 (100%)
Edinburgh	EBV-BLCL-sensitised	HCT (EBV+ PTLD)	RIS ± rituximab ± other	2	2–5/6	2/2 (100%)
Haque, et al. 2007[2]	EBV CTLs	SOT (EBV+ PTLD)	RIS ± rituximab ± other	31	2–5/6	19/31 (61%)
MSKCC	EBV-BLCL-sensitised	HCT (EBV+ PTLD)	Rituximab ± CT	2	5/6, 4/6	2/2 (100%)
Barker, et al. 2010[3]	T-cell line					
Baylor	Transduced multi-virus CTLs	HCT (EBV+ PTLD)	Rituximab	8	1–3/6	6/8 (75%)
Leen, et al. 2013[4]		HCT (viraemia)	Rituximab	1	1 HLA	0/1 (0%)
Aberdeen	EBV-BLCL-stimulated	HCT (EBV+ PTLD)	NA	6	≥3	4/6 (67%)
Vickers, et al. 2014[5]	EBV CTLs	SOT (EBV+ PTLD)	NA	4	≥3	4/4 (100%)
Inserm	EBV-BLCL-sensitised	HCT	Rituximab ± CT	6	≥2	3/6 (50%)
Gallot, et al. 2014[6]	EBV CTLs	SOT	CT ± rituximab/RT	3	≥2	1/3 (33%)
Multi-centre	EBV-BLCL- and	HCT (EBV+ PTLD)	None or rituximab	12		9/12 (75%)
Naik, et al. 2016[7]	multi-virus-sensitised CTLs					
Baylor	Peptide-stimulated CTLs	HCT (EBV+ PTLD)	Antiviral therapy	1	3/8	1/1 (100%)
Tzannou, et al. 2017[8]		HCT (viraemia)	None	2	5/8, 2/8	2/2 (100%)
Aberdeen	EBV-BLCL-stimulated	SOT (EBV+ PTLD)	Rituximab RIS	10		10/10 (100%)
Chiou, et al. 2018[9]	EBV CTLs					
MSKCC	EBV-BLCL-sensitised	HCT (EBV+ PTLD)	Rituximab ± CT/RT	33	2–5/10	22/33 (67%)
Prockop, et al. 2020[10]	T-cell line	SOT (EBV+ PTLD)	Rituximab ± CT/RT	13	2–4/10	7/13 (54%)
Germany	EBV-BLCL-sensitised	HCT (EBV+ PTLD)	CT or rituximab	25	At least 3/6	9/10 (90%)
Bonifacius et al. 2023[11]	T-cell line	SOT (EBV+ PTLD)	CT ± rituximab	5		4/5 (80%)

BLCL, EBV-transformed B-lymphoblastoid cell; CT, chemotherapy; CTL, cytotoxic T lymphocyte; EBV+, Epstein–Barr virus positive; HCT, haematopoietic cell transplantation; HLA, human leukocyte antigen; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not available; PTLD, post-transplant lymphoproliferative disorder; RIS, reduction in immunosuppression; RT, radiotherapy; SOT, solid organ transplantation.

1. Sun Q, et al. Br J Haematol. 2002;118:799–808; 2. Haque T, et al. Blood. 2007;110:1123–1131; 3. Barker JN, et al. Blood. 2010;116:5045–5049; 4. Leen AM, et al. Blood. 2013;121:5113–5123; 5. Vickers MA, et al. Br J Haematol. 2014;167:402–410; 6. Gallot G, et al. J Immunother. 2014;37:170–196; 7. Naik S, et al. J Allergy Clin Immunol. 2016;137:1498–1505.e1; 8. Tzannou I, et al. J Clin Oncol. 2017;35:3547–3557; 9. Chiou FK, et al. Pediatr Transplant. 2018;22:e13133; 10. Prockop S, et al. J Clin Invest. 2020;130:733–747; 11. Bonifacius A, et al. J Clin Invest. 2023;133(12):e163548.

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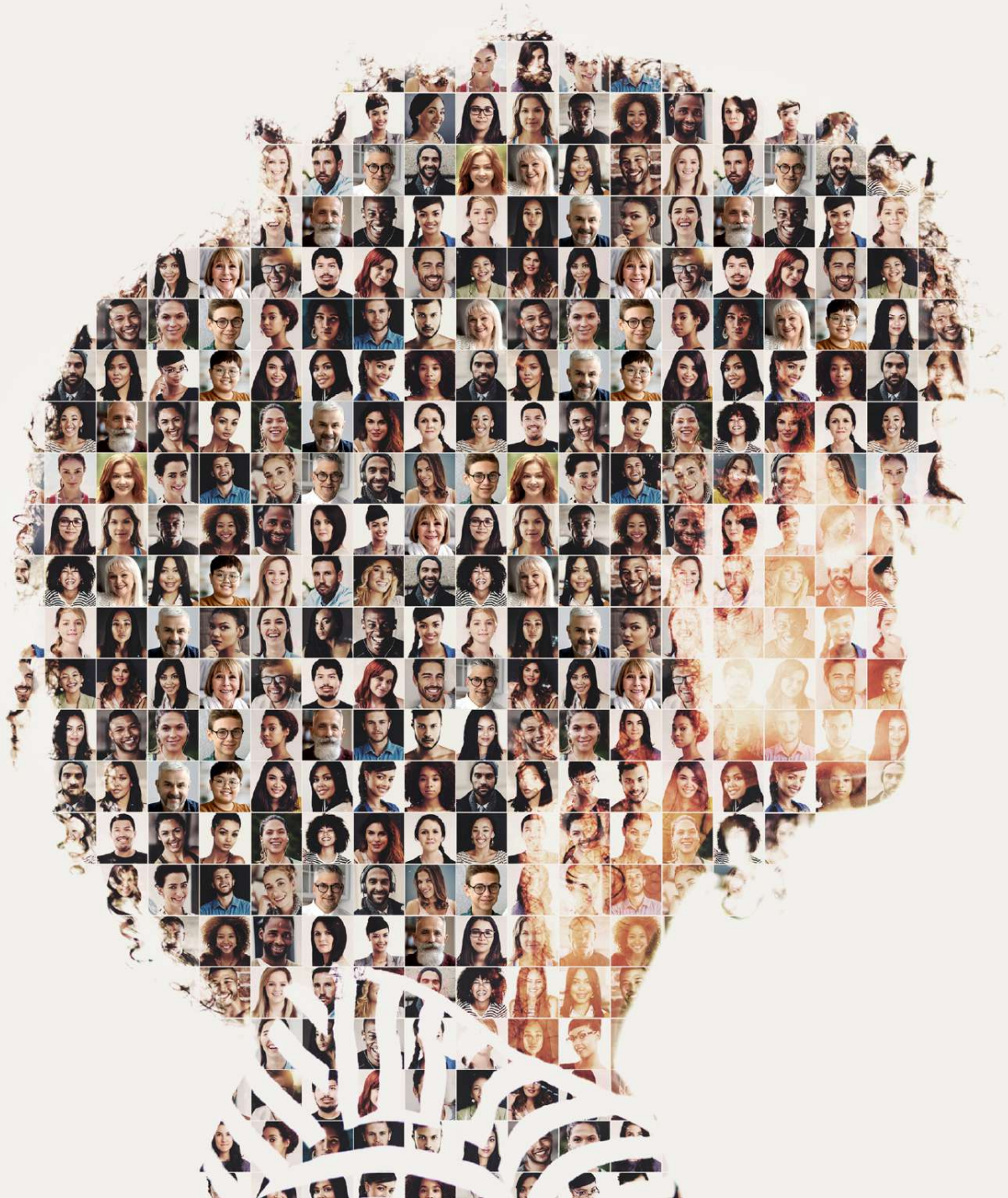

Changing the face of EBV+ PTLD management

with EBV-specific T-cell immunotherapy

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EBV+, Epstein-Barr virus positive; PTLD, post-transplant lymphoproliferative disorder.

HQ-EBV-05-24-2400012; June 2024.

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Changing the face of EBV+ PTLD management with EBV-specific T-cell immunotherapy: EBVALLO®

Introduction to third-party anti-viral CTLs

- Outline
- Evidence
- Strategies
- HLA restriction

EBVALLO® (tabelecleucel)

- Product overview
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ALLELE study

- Study design and patient characteristics
- Efficacy data (primary and key secondary endpoints)
- Safety

CTL, cytotoxic T lymphocyte; EBV+, Epstein–Barr virus positive; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder; RIS, reduction in immunosuppression; RT, radiotherapy; SOT, solid organ transplantation.

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EBVALLO® is an allogeneic T-cell immunotherapy approved for the treatment of relapsed/refractory EBV+ PTLD[1,2]

EBVALLO® (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

- EBVALLO® is licensed in Europe, including the UK and Switzerland in the outlined indication[1–3]
- The EBVALLO® license has been granted conditional upon the generation and submission to regulatory authorities of further data[1]
  - An observational, real-world Post-Authorisation Safety Study (PASS) called EBVOLVE is underway, data will be submitted to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) upon completion[1]

EBVOLVE

Please consult your local Summary of Product Characteristics before prescribing EBVALLO®

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

1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics; 2. EBVALLO® (tabelecleucel) UK Summary of Product Characteristics; 3. EBVALLO® (tabelecleucel) CH Summary of Product Characteristics.

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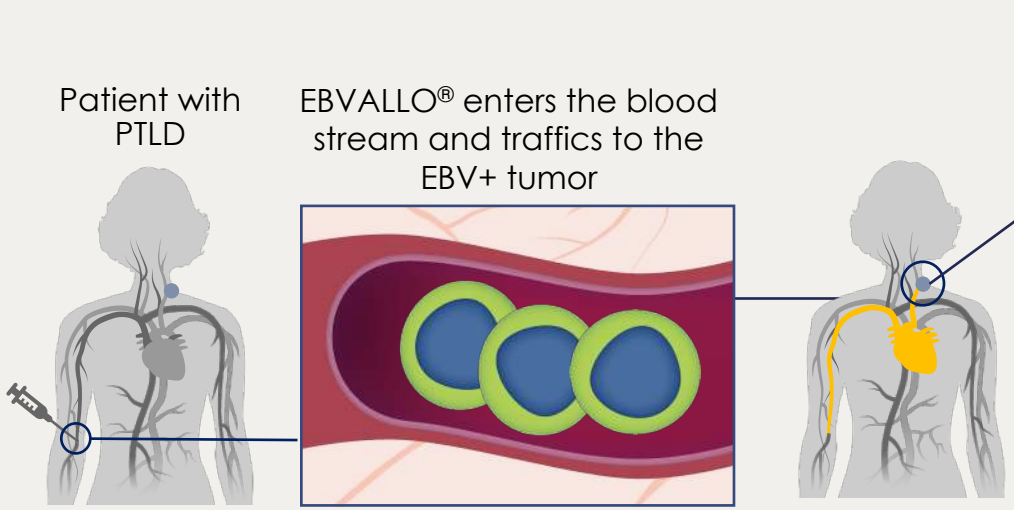
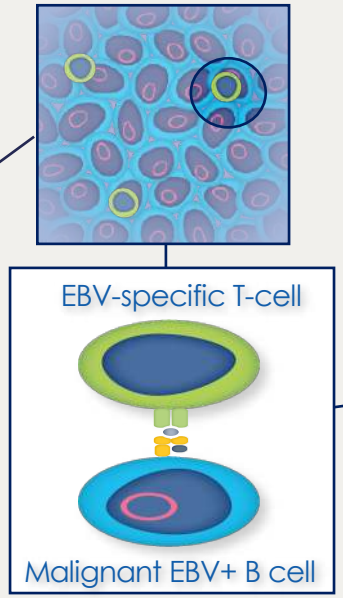
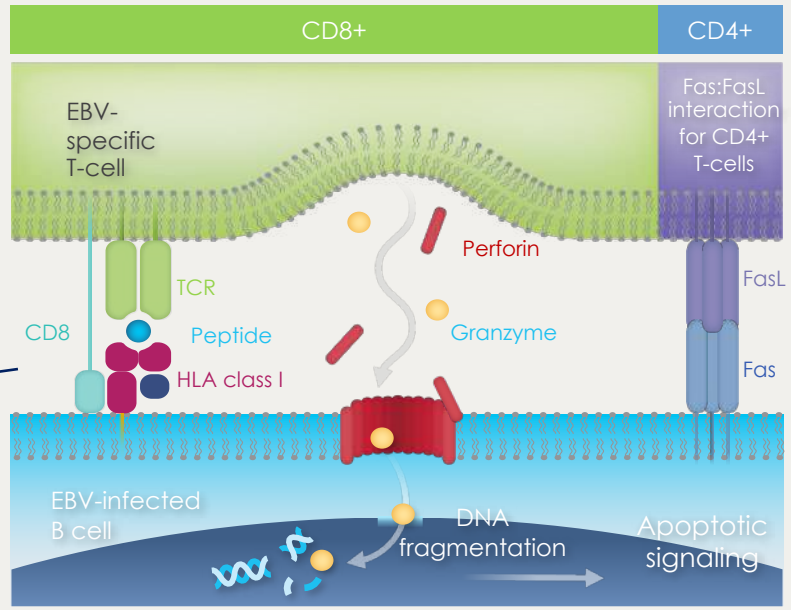
EBVALLO® is an allogeneic, EBV-specific T-cell immunotherapy which targets and eliminates EBV-infected cells in an HLA-restricted manner[1,2]

1. EBVALLO® infusion
2. Trafficking and homing to PTLD tumor and recognition of EBV antigens
3. Killing of EBV+ cancer cells







Adapted from EBVALLO® (tabelecleucel) Summary of Product Characteristics.

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

1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics. 2. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42.

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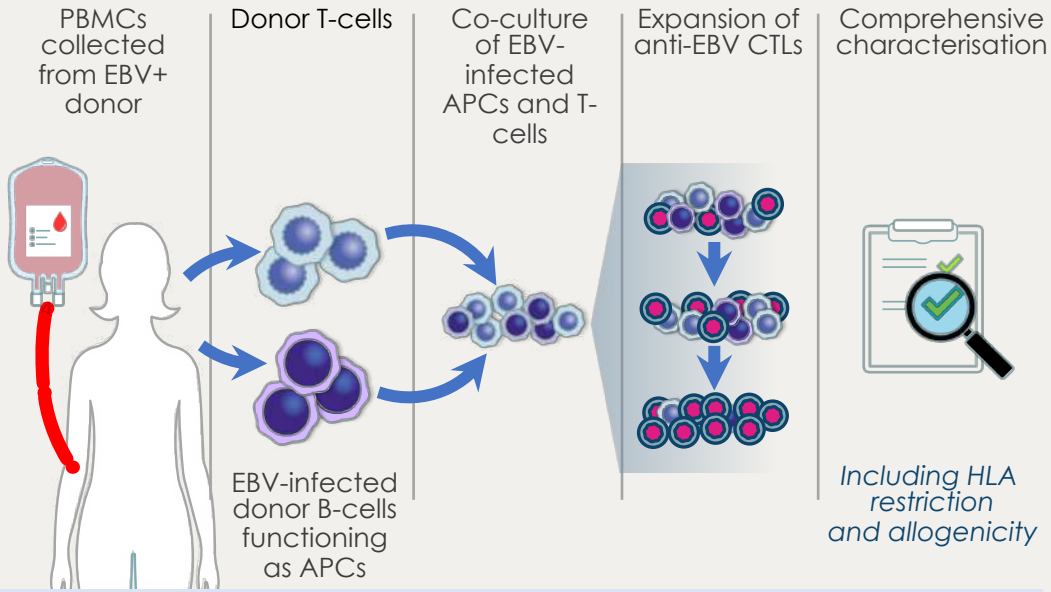
EBVALLO® is readily available, stored in a biobank, and can be delivered to patients rapidly[1]

EBVALLO® is manufactured from healthy EBV+ donors with diverse HLA profiles to produce expanded CTL lots that are characterised by EBV-specific cytotoxicity & HLA restriction

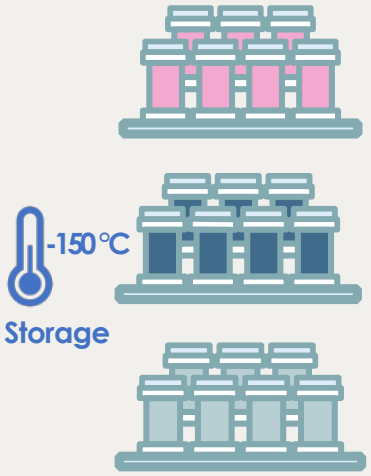
EBVALLO® is specifically selected for each patient, based on the patient's disease HLA profile, and directly shipped to hospital

Manufacturing

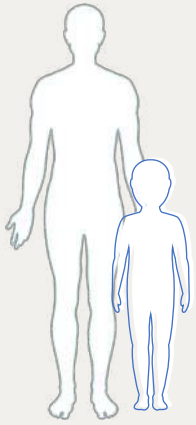


No genetic modification of T-cells

Biobank



EBVALLO® is stored and ready for dispatch when required



Lot selection and Order

Go Cell Therapy™

Enter patient's characteristics and order EBVALLO® on a dedicated and secure online platform

On-site delivery

EBVALLO® lot matching patient's requirement can be delivered rapidly within a few days from the order

APC, antigen presenting cell; CTL, cytotoxic T cell; EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; HLA, human leukocyte antigen; PBMC, peripheral blood mononuclear cell.

1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics.

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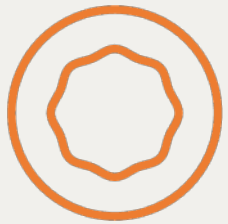
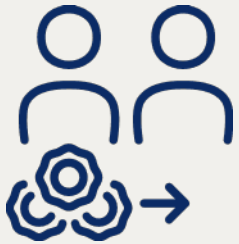
Key features of EBVALLO®[1]



Targets and eliminates **EBV-infected cells** in an HLA-restricted manner



Allogeneic: expanded from healthy EBV+ donors with diverse HLA profiles

No genetic modification of T-cells

Comprehensively characterised including HLA restriction and allogenicity

Stocked in a **biobank** and is readily available for delivery

EBV+, Epstein-Barr virus positive; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant.

1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics.

LABORATOIRES Pierre Fabre

Changing the face of EBV+ PTLD management with EBV-specific T-cell immunotherapy: ALLELE study

Introduction to third-party anti-viral CTLs

- Outline
- Evidence
- Strategies
- HLA restriction

EBVALLO® (tabelecleucel)

- Product overview
- Mechanism of action
- Manufacturing
- Inventory / cell line selection

ALLELE study

- Study design and patient characteristics
- Efficacy data (primary and key secondary endpoints)
- Safety

CTL, cytotoxic T lymphocyte; EBV+, Epstein–Barr virus positive; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder; RIS, reduction in immunosuppression; RT, radiotherapy; SOT, solid organ transplantation.

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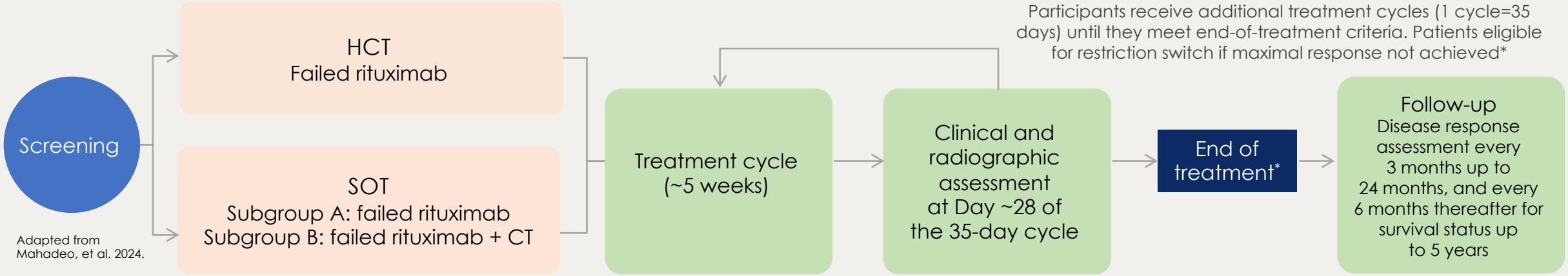
ALLELE: A global, multicentre, open-label Phase 3 study of EBVALLO® after failure of rituximab ± chemotherapy in patients with EBV+ PTLD following HCT or SOT[1]



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)

Primary endpoint: Objective response rate†

Secondary endpoints:

- OS
- Duration of response
- Objective response overall
- Overall PR and CR rates
- Time to response and time to best response
- Rates of allograft loss/rejection episodes (SOT)
- Safety

* 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 EBVALLO® 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.

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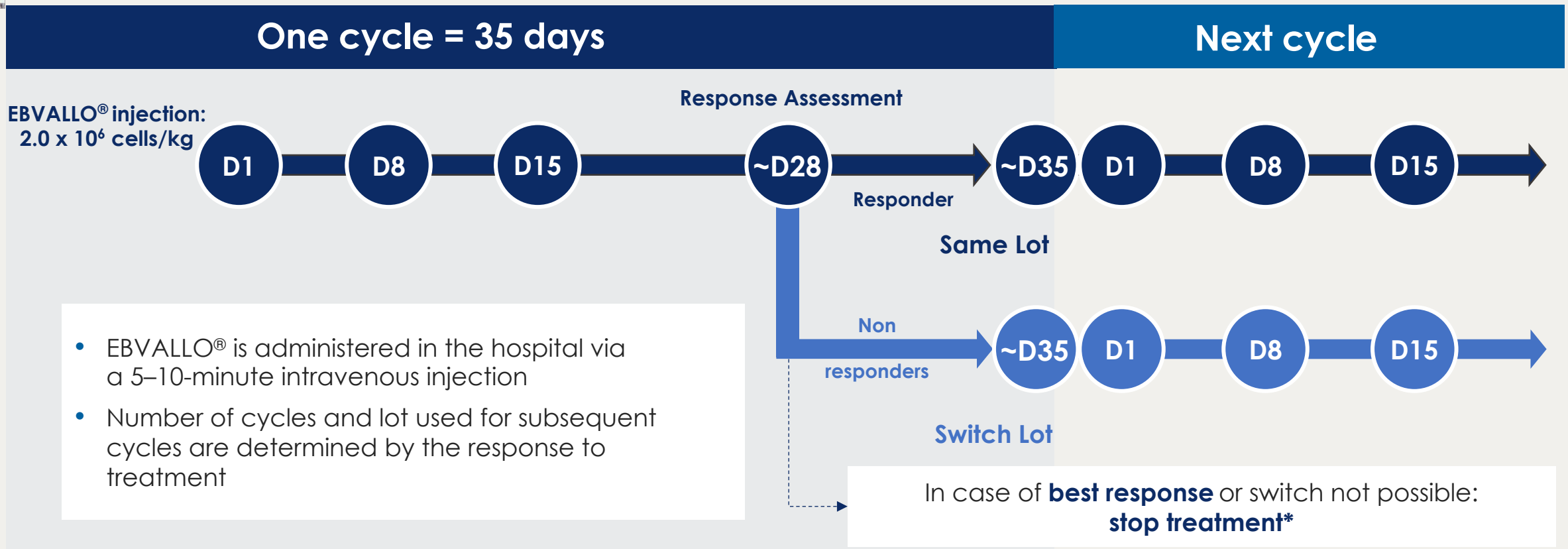
EBVALLO® administration schedule[1]



- EBVALLO® 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. Up to 4 switches to a lot with a different HLA restriction (if available) are possible if CR or PR is not obtained[1]

Please refer to the EBVALLO® Summary of Product Characteristics before prescribing this medication[1]
CR, complete response; HLA, human leukocyte antigen; PR, partial response.
1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics.

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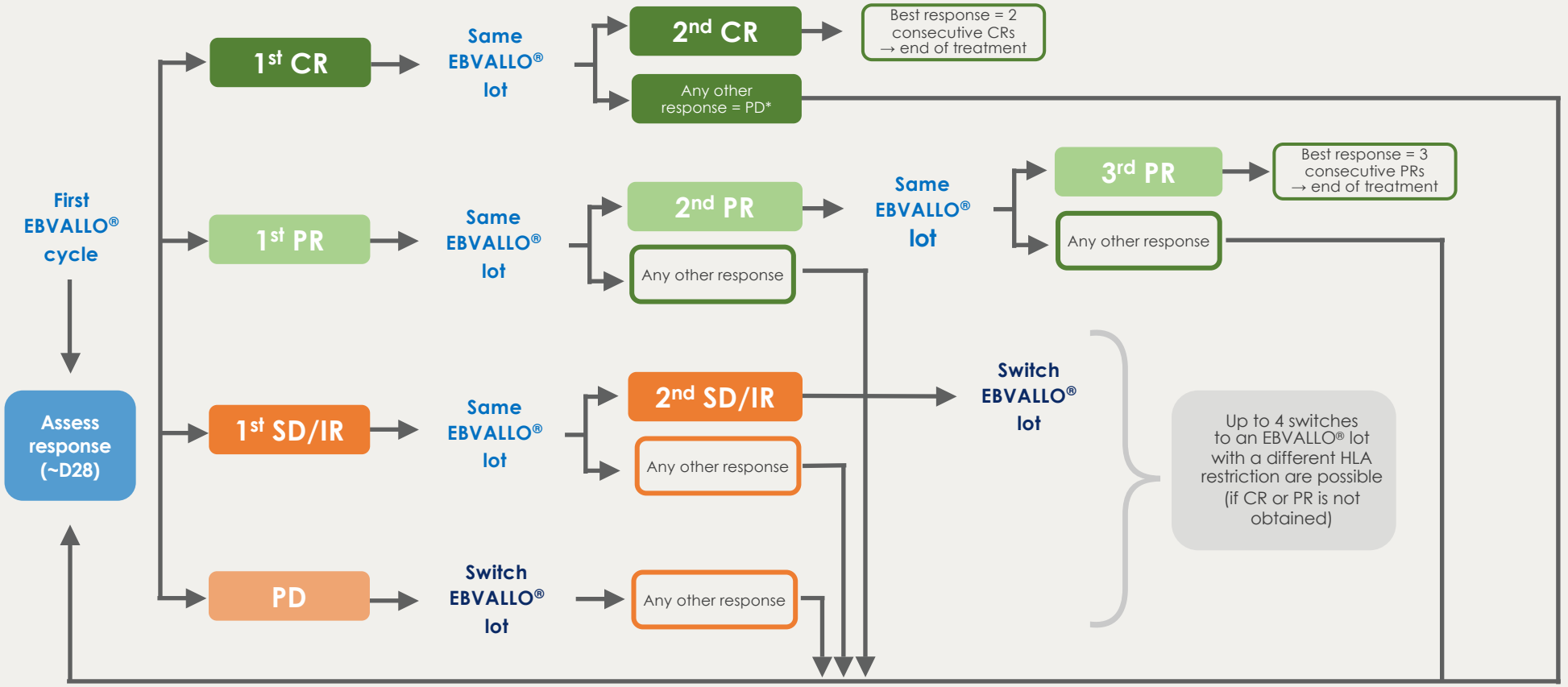
The number of cycles of EBVALLO® is determined by response to treatment[1]



*CR at the end of a cycle followed by PR or other response at any subsequent cycle is considered PD.[1]

CR, complete response; HLA, human leukocyte antigen; IR, indeterminate response; MoA, mechanism of action; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disease; SD, stable disease.

1. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics.

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ALLELE: Demographics and baseline patient characteristics

	Baseline patient characteristics[1,2]		
	HCT (n=14)	SOT (n=29)	All (n=43)
Median age, years (range)	51.9 (3.2–73.2)	44.4 (6.1–81.5)	48.5 (3.2–81.5)
Male, n (%)	8 (57.1)	16 (55.2)	24 (55.8)
ECOG score (age ≥16 years)*			
n	13	27	40
ECOG <2, n (%)	10 (76.9)	18 (66.7)	28 (70.0)
ECOG ≥2, n (%)	3 (23.1)	8 (29.6)	11 (27.5)
Missing, n (%)	0	1 (3.7)	1 (2.5)
PLTD-adapted prognostic index (age ≥16 years)†			
Low risk (%)	1 (7.7)	2 (7.4)	3 (7.5)
Intermediate risk (%)	6 (46.2)	13 (48.1)	19 (47.5)
High risk (%)	6 (46.2)	11 (40.7)	17 (42.5)
Unknown risk (%)	0	1 (3.7)	1 (2.5)

* Percentages for ECOG were based on the number of patients in the corresponding age group.[1]
† Disease risk for PTLD patients was assessed at baseline using the PTLD-adapted prognostic index (based on age, ECOG score and serum LDH level).[2]
Adapted from EBVALLO® EPAR 2022.

Data cut-off date: Nov 5, 2021.
ECOG, Eastern Cooperative Oncology Group; HCT, haematopoietic cell transplantation; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.
1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387; 2. EBVALLO® European Public Assessment Report (EPAR), 13 October 2022 (EMA/858618/2022).

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ALLELE: Demographics and baseline patient characteristics

	Baseline patient characteristics[1,2]		
	HCT (n=14)	SOT (n=29)	All (n=43)
Disease morphology and histology			
Diffuse large B-cell lymphoma (%)	10 (71.4)	19 (65.5)	29 (67.4)
Other (%)	3 (21.4)	8 (27.6)	11 (25.6)
Plasmablastic lymphoma (%)	1 (7.1)	2 (6.9)	3 (7.0)
Extra nodal disease (%)	9 (64.3)	24 (82.8)	33 (76.7)
Prior therapies			
Median no. of prior systemic therapies (range)	1.0 (1–4)	1.0 (1–5)	1.0 (1–5)
Ritixumab monotherapy, n (%)	14 (100)	23 (79.3)	37 (86.0)
Ritixumab monotherapy as 1L, n (%)	14 (100)	22 (75.9)	36 (83.7)
Chemotherapy-containing regimen,* n (%)	3 (21.4)	16 (55.2)	19 (44.2)

* Chemotherapy regimens could have also been combined with rituximab or other immunotherapy agents.

Adapted from EBVALLO® EPAR 2022.

43 patients (14 HCT, 29 SOT recipients) received at least one dose of study treatment and were included in the analysis[2]

Data cut-off date: Nov 5, 2021.

ECOG, Eastern Cooperative Oncology Group; HCT, haematopoietic cell transplantation; LDH, lactate dehydrogenase; SOT, solid organ transplantation

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

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ALLELE: Treatment information[1]

	HCT (n=14)	SOT (n=29)	All (N=43)
Median time from transplant to EBV+ PTLD diagnosis (range)	4.3 months (3.2–7.8)	13.2 months (7.2–103.2)	–
Median time from initial EBV+ PTLD diagnosis to first administration of EBVALLO® (range)	1.2 months (0.8–3.0)	6.6 months (3.5–13.0)	4.0 months (2.2–8.6)
Median cycles of EBVALLO® (range)	3.0 (2.0–4.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
Median number of doses administered (range)	9.0 (6–12)	6.0 (3.0–9.0)	6.0 (3.0–12.0)
Median treatment duration (range)	2.8 months (1.9–4.3)	1.9 months (0.5–3.4)	2.1 months (0.5–3.9)

Data cut-off date: Nov 5, 2021.
EBV+, Epstein Barr virus positive; HCT, haematopoietic cells transplant; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.
1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387.

LABORATOIRES
Pierre Fabre

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

	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)

* Secondary endpoints.[1]
† Median duration of response was estimated by the Kaplan–Meier method.[1]

Data cut-off date: Nov 5, 2021.
CI, confidence interval; IQR, interquartile range; HCT, haematopoietic cell transplant; NE, not estimable; SOT, solid organ transplantation.
1. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387.

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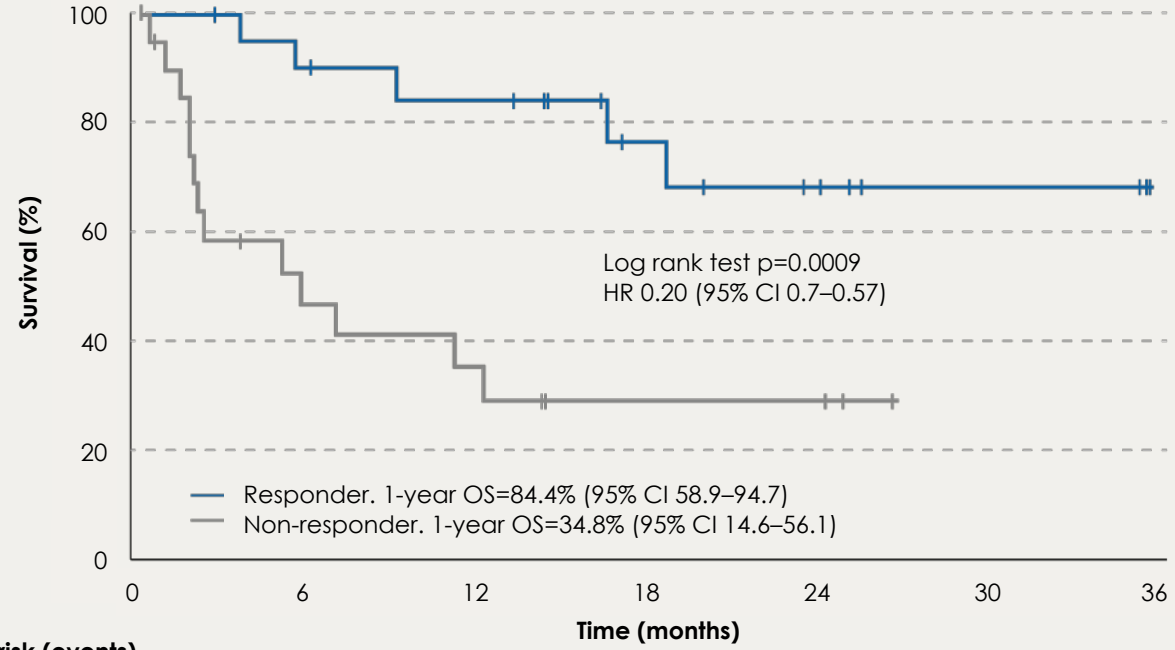
ALLELE: Patients responding to EBVALLO® had a longer overall survival than non-responders[1]

Kaplan–Meier curve of overall survival in patients with EBV+ PTLD post-HCT and SOT who received EBVALLO®[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)	

Adapted from Mahadeo KM, et al. 2024.

Patients responding to EBVALLO® had higher 1-year overall survival rate compared with non-responders **(84.4% vs. 34.8%)[1]**

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 positive; HCT, haematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

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

LABORATOIRES
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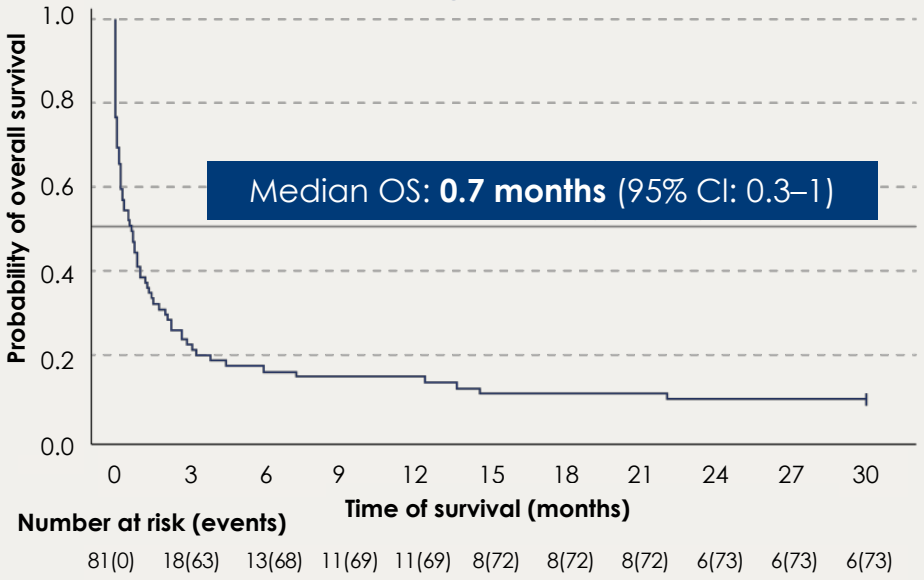
The prognosis for HCT and SOT recipients with R/R EBV+ PTLD was previously poor

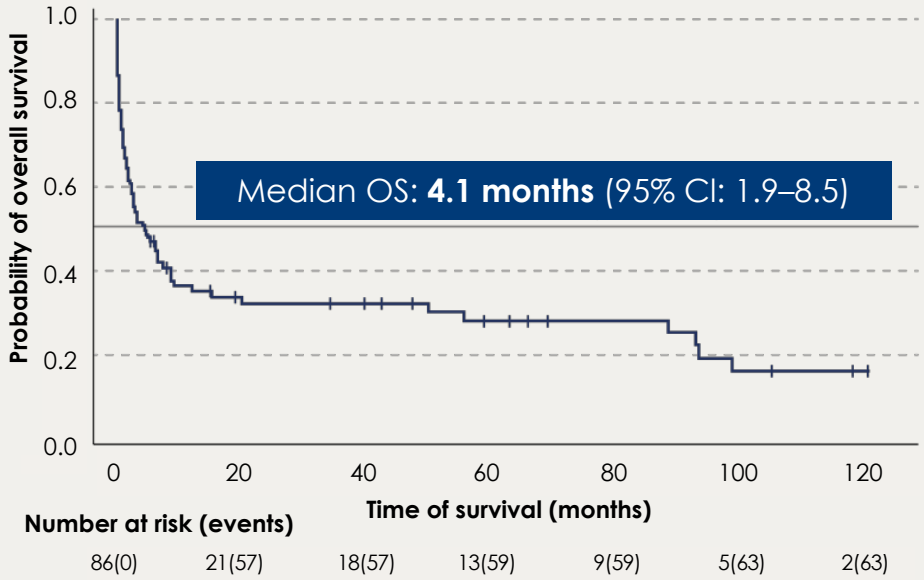
- A large multinational, multicentre* retrospective chart review study of EBV+ PTLD patients following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000–December 2018 and were refractory or relapsed at any point after such therapy[1,2]

OS in patients with R/R EBV+ PTLD following HCT (N=81)[1]



Adapted from Socié G, et al. 2022.

OS in patients with R/R EBV+ PTLD following SOT (N=86)[2]



Adapted from Dhamidharka V, et al. 2022.

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

CI, confidence interval; 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.

1. Socié G, et al. Bone Marrow Transplant. 2024;59:52–58; 2. Dharnidharka V, et al. HemaSphere. 2022;6(Abstract):997–998.

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ALLELE: EBVALLO® 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 EBVALLO® to 30 days after the last dose or treatment-related events that occurred on or after the first dose of EBVALLO®.[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 EBVALLO®
- 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 EBVALLO®

Data cut-off date: Nov 5, 2021.
For a full list of adverse events please consult your local EBVALLO® 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.

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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 EBVALLO®

For a full list of adverse events please consult your local EBVALLO® 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.

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

The EBVALLO® 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 EBVALLO® 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. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics.

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Changing the face of EBV+ PTLD with EBV-specific T-cell immunotherapy

The prognosis for HCT and SOT recipients with R/R EBV+ PTLD was **previously poor**[1,2]

EBVALLO® is now approved, available on demand and can be delivered to patients rapidly[3]

ORR was 51% among all patients in the Phase 3 ALLELE study[4]

Patients responding to EBVALLO® had a **longer overall survival** vs. non-responders (1-year OS rate of **84.4%** vs. 34.8% respectively)[4]

There has been **no evidence of the safety concerns** seen with other adoptive T-cell therapies relevant to this population with EBVALLO®[4]*

For a full list of adverse events please consult your local EBVALLO® Summary of Product Characteristics
*No reports of graft-versus-host disease, graft rejection, cytokine release syndrome, or neurotoxicity.
EBV+, Epstein-Barr virus positive; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant.
1. Socié G, et al. Bone Marrow Transplant. 2024;59:52–58; 2. Dharnidharka V, et al. HemaSphere. 2022;6(Abstract):997–998; 3. EBVALLO® (tabelecleucel) EU Summary of Product Characteristics; 4. Mahadeo KM, et al. Lancet Oncol. 2024;25(3):376–387;

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- This is a promotional event organised and funded by Pierre Fabre intended for Healthcare Professionals (HCPs) practicing within Europe
- The prescribing information for EBVALLO may vary depending on local approval in each country, Healthcare Professionals are recommended to consult their local prescribing information before prescribing this product
- The opinions expressed in the symposium represents the opinions of the speakers and do not necessarily represent the views of Pierre Fabre. The contents of this symposium are copyright of Pierre Fabre – Pierre Fabre 2024. All rights reserved
- For complete information, please refer to the EBVALLO Summary of Product Characteristics

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