Disease deck

Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ PTLD)

November 2024 | PF-0027

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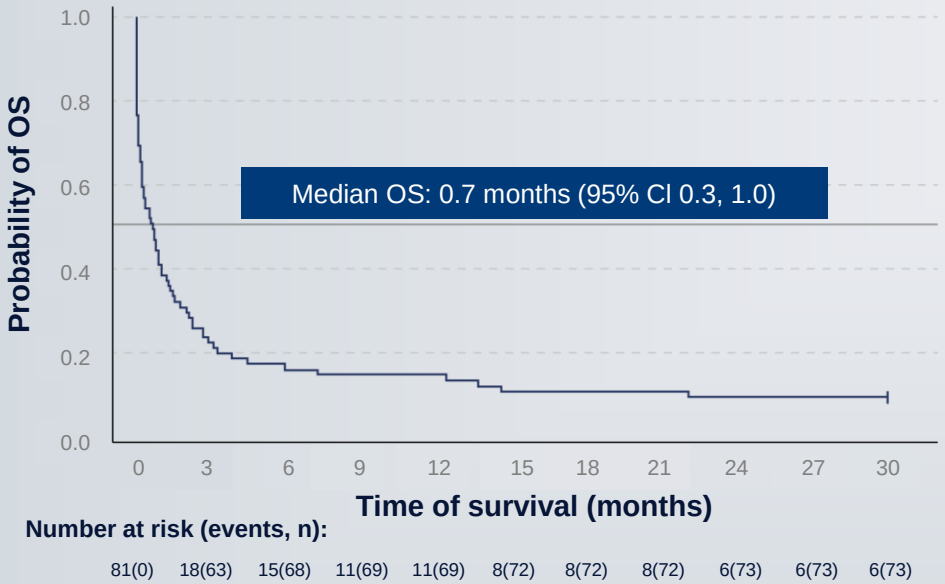
Relapsed or refractory EBV+ PTLD is a rare, life-threatening, and often fatal malignancy[1,2]

- EBV+ PTLD is a life-threatening and fatal complication of transplantation, occurring due to impaired T-cell immunity[1]
- In patients with EBV+ PTLD who fail initial treatment, disease progression is usually rapid, with devastating outcomes[1,2]

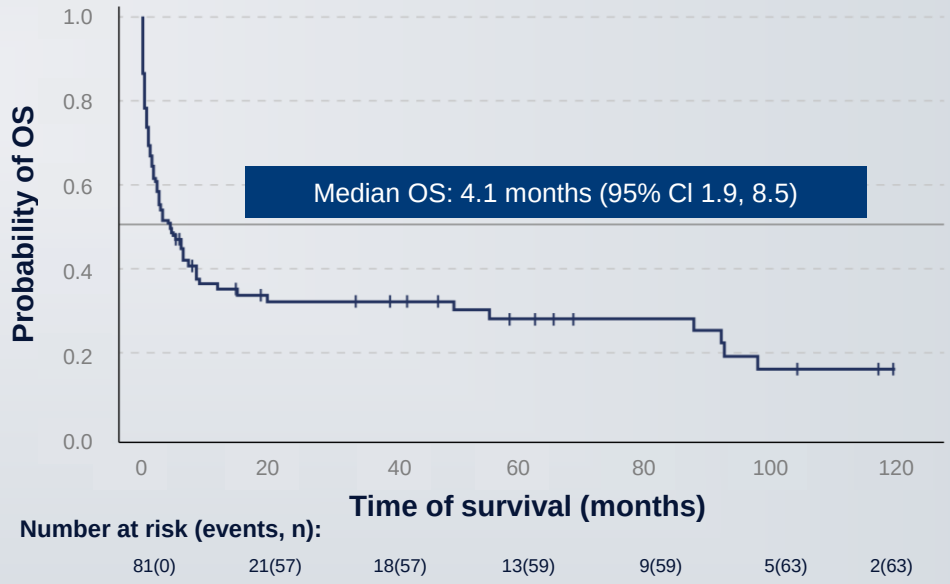
Overall survival in patients with R/R EBV+ PTLD following HCT (N=81)*[1]



Adapted from Socié G, et al. 2022.

**OS for patients with EBV+ PTLD following HCT who failed anti-CD20 Ab ± chemotherapy (N=81) from the date of failure to the end of follow-up.[1]*

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



Adapted from Dhamidharka V, et al. 2022.

†OS for patients with EBV+ PTLD following SOT who failed anti-CD20 Ab + chemotherapy (N=86) from the date of failure to the end of follow-up.[2]

Ab, antibody; CD, cluster of differentiation; CT, chemotherapy; EBV, Epstein-Barr virus; HCT, hematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disease; R/R, relapsed or 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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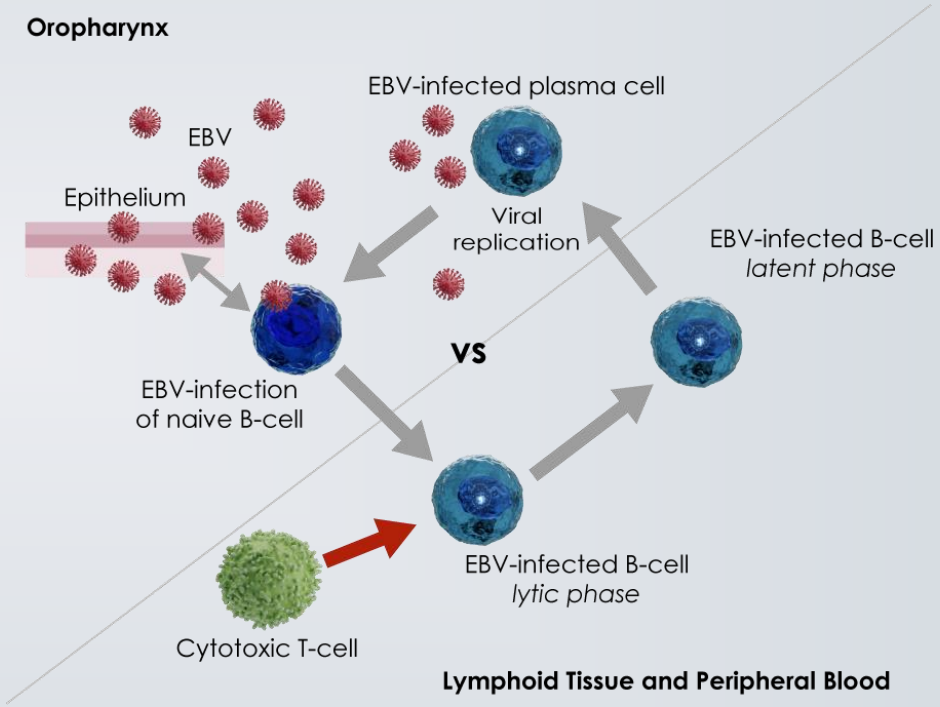
EBV infection is kept under control by intact T-cell immunity[1,2]

- EBV is one of the most common viruses in humans[3]
  - EBV is a gamma-herpes virus that is transmitted orally (via infected saliva)[3]
  - Globally, **approximately 90%** of adults and **50%** of children are infected[3]
- EBV primarily infects B-cells and subsequently establishes a **lifelong, latent infection** within memory B-cells, which is kept under control by intact T-cell immunity[1–3]
- **In times of suppressed T-cell immunity**, EBV is associated with more than a dozen malignancies, including **PTLD**[4]

EBV lifecycle[2]



Adapted from Nijland ML, et al. 2015.

EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disease.

1. Kimura H, et al. Rev Med Virol 2008;18(5):305–319; 2. Nijland ML, et al. Transplant Direct 2015;2(1):e48; 3. Bednarska K, et al. Br J Haematol 2024;204:415–433; 4. Crombie JL, LaCasce AS. Front Oncol 2019;9:109.

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Impaired T-cell immunity post-transplantation plays a significant role in the development of EBV+ PTLD[1,2]

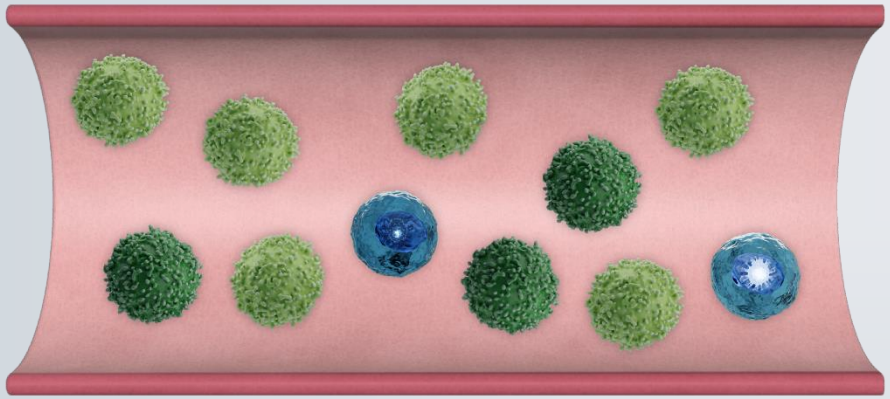
Immunocompetent individual

T-cells keep the EBV infection under control by killing infected B-cells[1,2]

Transplant patients

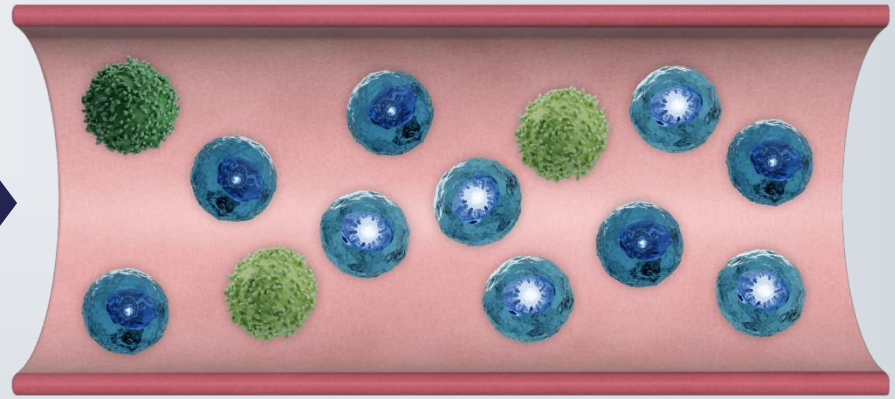
Due to impaired T-cell immunity, re-activated EBV can cause B-cells to transform and rapidly proliferate, causing a range of malignancies, such as PTLD[1,2]

Intact T-cell immunity



Immunosuppression

Impaired T-cell immunity



Key

- EBV-specific CD8+ CTL
- CD4+ helper T-cell
- B-cell with latent EBV infection
- B-cell with reactivated EBV infection

CD, cluster of differentiation; CTL, cytotoxic T-cell; EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disease.

1. Nijland ML, et al. Transplant Direct 2015;2(1):e48; 2. Cohen JI. N Engl J Med 200;343:481–492.

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Recipients of allogeneic HCT or SOT have an increased risk of EBV+ PTLD due to impaired T-cell immunity[1]

Key differences in the development of EBV+ PTLD in recipients of allogeneic HCT or SOT

Variable	Allogeneic HCT	SOT
Typical origin of infected cells[1]	Donor origin	Recipient origin
Duration of immunosuppression[1]	**Short term**	**Lifelong**
Frequency of PTLD[2–9]	1.1–1.7% (in the first year)[2,3]	Up to 9.1% (depending on the organ transplanted)*[4–9]
EBV-associated[10–12]	~100%[10–12]	~50%[10]
Estimated time of onset[13,14]	**Within the first year post-transplant[13]**	**At any time post-transplant** ~50% of cases are diagnosed more than 1 year from time of transplant[14]

*PTLD 5-year cumulative incidence by organ: kidney, 0.6%; liver, 1%; heart, 0.9%; lung, 1.7%; pancreas, 2.5%; and intestine, 9.1%.[4–9]
EBV, Epstein-Barr virus; HCT, hematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplantation.

1. Fujimoto A, et al. Cancers (Basel) 2020;12:328; 2. Dierickx D, et al. Leuk Lymphoma 2013;54(11):2433–2440; 3. García-Cadenas I, et al. Eur J Haematol 2019;102(6):465–471; 4. Hart A, et al. Am J Transplant 2021;21(S2):21–137; 5. Kwong AJ, et al. Am J Transplant 2021;21(S2):208–315; 6. Colvin M, et al. Am J Transplant 2021;21(S2):356–440; 7. Valapour M, et al. Am J Transplant 2021;21(S2):441–520; 8. Kandaswamy R, et al. Am J Transplant 2023;21(S2):138–207; 9. Horslen SP, et al. Am J Transplant 2021;21 Suppl 2:316–355; 10. Dierickx D, et al. N Engl J Med 2018;378:549–562; 11. Socié G, et al. Bone Marrow Transplant 2024;59:52–58; 12. Hjellbakk HK, et al. Centr Eur J Immunol 2020;45(2):233–236; 13. Tai R, et al. Br J Radiol 2015;88(1052):20140861; 14. Ghobrial IM, et al. Transplantation 2005;79(2):244–247.

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The risk of developing EBV+ PTLD post-allogeneic HCT is increased by pre- and post-transplant factors[1–4]

Pre-allogeneic HCT risk factors[1,4]

1) Patient age at the time of transplant

- Higher risk if aged <20 years
- Higher risk if aged ≥50 years

2) T-cell depletion

- *In vivo* (within the patient's body)
- *Ex vivo* (outside the body, before transplant)

3) EBV serology mismatch between donor and recipient

4) Use of cord blood for transplant

5) HLA mismatch between donor and recipient

6) Prior splenectomy

7) Multiple (>1) allogeneic HCTs

Post-allogeneic HCT risk factors[1,4]

1) Development of severe GvHD that is acute or chronic

2) High or increasing EBV load in the blood

3) Treatment with mesenchymal stem cells

EBV, Epstein-Barr virus; GvHD, graft versus host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease.

1. Lindsay J, et al. Curr Opin Infect Dis 2021;34:635–645; 2. Al-Mansour Z, et al. Curr Hemetol Malig Rep 2013;8(3):173–183; 3. Tai R, et all. Br J Radiol 2015;88(1052):20140861;
4. Ru Y, et al. Eur J Haematol 2018;101:283–290.

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The likelihood of developing EBV+ PTLD post-SOT is increased by pre- and post-transplant risk factors[1–4]

Pre-SOT risk factors[1,4]

1) Patient age at the time of transplant

- Increased risk if aged <10 years
- Increased risk if aged ≥60 years

2) Genetic factors related to the immune system:

- Cytokine gene polymorphisms (e.g. IL-10, IL-6, IFN-γ)
- Certain HLA types (e.g. HLA-A2, HLA-B5)
- HLA-DQ mismatches

3) EBV status

- EBV serology mismatch: donor EBV+, recipient EBV−
- EBV reactivation within 12 months post-transplant

Post-SOT risk factors[1,4]

1) Organ transplant type (from highest to lowest):

- Multiorgan > Intestine > Lung > Heart > Liver > Pancreas > Kidney

2) Immunosuppression:

- Higher degree of immunosuppression
- Longer duration of immunosuppressive therapy

3) Receipt of specific immunosuppressive agents:

- Anti-thymocyte globulin
- Calcineurin inhibitors

EBV, Epstein-Barr virus; GvHD, graft versus host disease; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplant.

1. Lindsay J, et al. Curr Opin Infect Dis 2021;34:635–645; 2. Al-Mansour Z, et al. Curr Hemetol Malig Rep 2013;8(3):173–183; 3. Tai R, et al. Br J Radiol 2015;88(1052):20140861;
4. Ru Y, et al. Eur J Haematol 2018;101:283–290.

The signs and symptoms of EBV+ PTLD are heterogeneous, and disease progression is rapid and aggressive[1–4]

Presentation:
From incidental, asymptomatic findings to fulminant presentation, including organ failure and spontaneous tumor lysis[1]

Target organs[2]

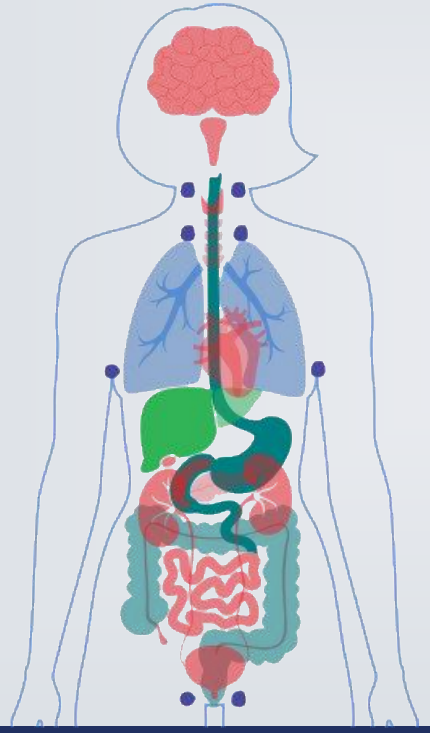
CNS

Lungs

GI tract

Lymph nodes

Liver



Symptoms[2,3]

B symptoms: fever, night sweats, weight loss, and lymphadenopathy

Rare symptoms: encephalitis/myelitis, pneumonitis, hepatitis, and hemophagocytic lymphohistiocytosis

EBV+ PTLD diagnosis[2]

Achieved via biopsy, alongside detection/ monitoring of EBV titer and imaging tests

Disease progression[3,4]

Rapid and aggressive

EBV+ PTLD requires early diagnosis and a targeted treatment plan[1–4]

CNS, central nervous system; EBV, Epstein-Barr virus; GI, gastrointestinal; PTLD, post-transplant lymphoproliferative disease.

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; 4. Abbas F, et al. World J Transplant 2020;10(2):29–46.

Summary: EBV+ PTLD is a serious concern in the management of transplant patients, as a direct result of impaired T-cell immunity[1,2]

EBV+ PTLD is a rare and **aggressive** hematologic malignancy that is **fatal** if left untreated[1,3]

- Overall **survival is low** in patients who have failed initial treatment[1,3]

EBV is one of the most common viruses in humans and establishes a **lifelong, latent infection** that is **controlled by intact T-cell immunity**[4,5]

Recipients of **SOT or allogeneic HCT** have an increased risk of PTLD due to **impaired T-cell immunity**[2,5]

Clinical presentation of EBV+ PTLD is **heterogeneous**, but it progresses **aggressively and rapidly**, and therefore requires early diagnosis and a targeted treatment plan[5,6]

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

1. Socié G, et al. Bone Marrow Transplant 2024;59:52–58; 2. Nijland ML, et al. Transplant Direct 2015;2(1):e48; 3. Dharnidharka V, et al. HemaSphere 2022;6(Abstract):997–998; 4. Bednarska K et al. Br J Haematol 2024;204:415–433; 5. Fujimoto A, et al. Cancers (Basel) 2020;12:328; 6. Abbas F, et al. World J Transplant 2020;10(2):29–46.

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Current clinical landscape

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NCCN recommendations for the treatment of EBV+ PTLD*[1]

First-line options**

Reduction in immunosuppression (RIS)

If possible, given monitoring requirements

AND

Anti-CD20 Ab

If used as monotherapy

OR

Chemo-immunotherapy

Mostly used in SOT. Avoided in HCT due to poor efficacy and risks

Partial response, persistent or progressive disease

Second-line options

Chemo-immunotherapy

OR

Clinical trial

OR

T-cell immunotherapy

NCCN Updated: 2024

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*Treatment options for EBV+ PTLD depend on the histologic subtype and should be individualized;[1] **Surgery is also an option for localized PTLD.[1]
Ab, antibody; CD, cluster of differentiation; EBV, Epstein-Barr virus; HCT, hematopoietic cell transplant; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplant.

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). B-Cell Lymphomas 2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480. Accessed November 2024.

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Reported response to anti-CD20 Ab ± chemotherapy is variable[1–5]

Response to anti-CD20 Ab ± sequential treatment with chemotherapy or anti-CD20 Ab + chemotherapy varies in patients with EBV+ PTLD[1]

- Response rate of ~55% with anti-CD20 Ab monotherapy[1]
- Overall, 50–70% of patients have a complete response to treatment with anti-CD20 Ab ± chemotherapy[2–5]

Patients with PTLD can experience chemotherapy-related toxicities[2–4]

- Approximately 60% and ~35–40% of patients experienced Grade 3/4 leukopenia and infection, respectively[2,3]
- Treatment-related mortality in patients who received chemotherapy following failure of anti-CD20 Ab has ranged from 7% to 13% in retrospective and prospective clinical trials[2–4]

Chemotherapy is not an option for ALL patients with EBV+ PTLD

Ab, antibody; CD, cluster of differentiation; EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disease.

1. Allen UD, et al. Clin Transplant 2019;33(9):e13652; 2. Trappe RU, et al. J Clin Oncol 2017;35(5):536–543; 3. Trappe R, et al. Lancet Oncol 2012;13:196–206; 4. Burns DM, et al. Transplantation 2020;104;2582–2590; 5. Jagadeesh D, et al. J Clin Oncol 2020;38(15):e20026.

With no FDA-approved treatment options for R/R EBV+ PTLD, there is a significant unmet need for new therapies

- Patients with R/R EBV+ PTLD have limited treatment options and a substantially worse prognosis, with very limited survival[1,2]

Low overall survival rates in patients with R/R EBV+ PTLD[1,2]

Median OS of

0.7 months

in patients with PTLD following **HCT** who failed anti-CD20 Ab ± chemotherapy (N=81)*[1]

**OS for patients with EBV+ PTLD following HCT who failed anti-CD20 Ab ± chemotherapy (N=81) from the date of failure to the end of follow-up.[1]*

Median OS of

4.1 months

in patients with PTLD following **SOT** who failed anti-CD20 Ab ± chemotherapy (N=86)†[2]

†OS for patients with EBV+ PTLD following SOT who failed anti-CD20 Ab + chemotherapy (N=86) from the date of failure to the end of follow-up.[2]

Ab, antibody; CD, cluster of differentiation; CT, chemotherapy; EBV, Epstein-Barr virus, FDA, US Food and Drugs Administration; HCT, hematopoietic cell transplant; OS, overall survival; PTLD, post-transplant lymphoproliferative disease; R/R, relapsed or 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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Adoptive T-cell immunotherapies under investigation

Different sources and applications for adoptive immunotherapy in EBV+ PTLD[1,2]

Transplantation cell type	Allogeneic HCT	SOT
Donor lymphocytes[1]	ORR: 72% - but with risk of GvHD	N/A
Autologous EBV-CTLs[1]	N/A	Use is limited due to ongoing IS
Donor-derived EBV-CTLs[1]	ORR: 68% - without significant toxicity	N/A
Third-party EBV-CTLs[2]	ORR: 68% - without significant toxicity	ORR: 54% - without significant toxicity
CAR T-cells (non-specific to EBV)[1]	Promising results – however rejection and GvHD triggered by cytokine release syndrome is a potential threat	

Adapted from Dierickx D, et al. 2022.

CAR, chimeric antigen receptor; CTL, cytotoxic T-cell; EBV, Epstein-Barr virus; GvHD, graft versus host disease; HCT, hematopoietic cell transplantation; IS, immunosuppression; N/A, not applicable; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplantation.

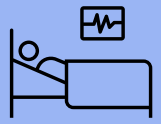
1. Dierickx D, et al. Curr Opin Oncol 2022;34:413–421; 2. Prockop S, et al. J Clin Invest 2020;130(2):733–747.

Patients with EBV+ PTLD have urgent unmet needs

The outcome of R/R EBV+ PTLD is often fatal, and it therefore requires swift clinical action upon diagnosis[1,2]

Impaired T-cell immunity post-SOT or -HCT plays a significant role in the development of EBV+ PTLD[3,4]

Current standard of care options include RIS and anti-CD20 Ab ± chemotherapy, but the toxicity profile of, and response to, this combination are often suboptimal[5–8]



As there are no FDA-approved treatment options for R/R EBV+ PTLD, there is a significant unmet need in these patients[1,2]

Ab, antibody; CD, cluster of differentiation; EBV, Epstein-Barr virus, FDA, US Food and Drug Administration; HCT, hematopoietic cell transplant; PTLD, post-transplant lymphoproliferative disease; RIS, reduction of immunosuppression; R/R, relapsed or 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; 3. Nijland ML, et al. Transplant Direct 2015;2(1):e48; 4. Cohen JI N Engl J Med 200;343:481–492; 5. Allen UD, et al. Clin Transplant 2019;33(9):e13652; 6. Trappe RU, et al. J Clin Oncol 2017;35(5):536–543; 7. Trappe R, et al. Lancet Oncol 2012;13:196–206; 8. Burns DM, et al. Transplantation 2020;104;2582–2590.

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Thank you

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Back-up slide

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PTLD is classified into distinct histologic subtypes by the WHO[1]

The WHO recognizes the following distinct histologic subtypes of PTLD:[1]

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

CHL, classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; NK, natural killer; PTLD, post-transplant lymphoproliferative disease; WHO, World Health Organization.

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

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