Hematology DIALOGUES LIVE

Epstein-Barr Virus-Positive Post-Transplant Lymphoproliferative Disorders: Addressing Unmet Needs with Emerging Therapies

Independent Satellite Symposium preceding the
Society of Hematologic Oncology 2024 Annual Meeting
Thursday, September 5, 2024 | 6:45 AM - 7:45 AM

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American Society for Transplantation and Cellular Therapy (ASTCT).

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Activity Overview

Target Audience

This activity is intended for hematologists, hematology-oncologists, pediatric hematologists, pediatricians, internists, and nurse practitioners (NPs), PAs, and nurses who provide care to individuals with EBV+ PTLD.

Educational Objectives

After completing this activity, the participant should be better able to:

- Summarize the epidemiology and burden of EBV+ PTLD
- Differentiate among current and emerging prognostic scoring systems for EBV+ PTLD in order to inform treatment decisions
- Evaluate the latest clinical evidence of emerging treatment options for EBV+ PTLD, based on safety, efficacy, mechanism of action, treatment- and disease-specific factors to determine optimal treatment strategies for patients with EBV+ PTLD

Agenda

Understanding EBV+ PTLD

- Epidemiology
- Burden
- Diagnosis
- *Experts React: Causes of the Increasing Incidence of EBV+ PTLD*

Prognostic Challenges

- Disease Specific Features
- Patient Specific Features
- Risk Factors for Poor Prognosis in SOT recipients
- Risk Factors for Poor Prognosis in allo-HCT recipients
- Current scoring systems and their limitations
- *Experts React: Estimating Survival Risk for Patients*

Game-Changing Emerging Agents for EBV+ PTLD

- Overall Treatment Concerns
- Chemotherapy
- Emerging EBV-Targeted Therapies: Key Clinical data
- Guidelines
- *Experts React: The Promise of New Options for EBV+ PTLD*

Q&A with Expert Faculty

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Accreditation Information

ILNA Coding

The program content has been reviewed by the Oncology Nursing Certification Corporation (ONCC) and is acceptable for recertification points in the following ILNA subject areas:
1.0 points: Care Continuum (OCN, CBCN, CPHON, AOCNP); Disease Related Biology (CPHON); Early Post-Transplant Management and Education (BMTCN); Foundations of Transplant (BMTCN); Late Post-Transplant Management and Education (BMTCN)
1.0 points: Oncologic Emergencies (OCN, CPHON, AOCNP); Oncology Nursing Practice (OCN); Pediatric Hematology and Oncology Nursing Practice (CPHON); Professional Practice/Performance (BMTCN, AOCNP); Quality of Life (BMTCN); Roles of the APRN (AOCNP); Symptom Management, Palliative Care, Supportive Care (OCN, CPHON, AOCNP); Transplant Process and Infusion (BMTCN); Treatment (OCN, CBCN, AOCNP, CPHON)
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- Review and manage your personal account.
- Search for accredited events based on the European Hematology Curriculum.

For further assistance please contact:
EBAH Office Koninginnegracht 12b, 2514 AA – The Hague, The Netherlands Phone: +31 (0)70 3020 099 Email: info@ebah.org

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This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

IPCE CREDIT™

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Kris M. Mahadeo, MD, MPH has a financial interest/relationship or affiliation in the form of:

Research Funding: Adaptimmune, Jazz, Syndax

The following relationships have ended within the last 24 months:

Consultant/Advisor (ended 2023): Atara, Jazz, Vertex

Planner/Presenter

Timothy Voorhees, MD, MSCR, has a financial interest/relationship or affiliation in the form of:

Speaker's Bureau: AbbVie, Genmab, Incyte, Kite, MorphoSys, Recordati, Viracta

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Guest Speaker

Sarah Featherston, RN, CPN, BMTCN has a financial interest/relationship or affiliation in the form of:

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Hematology DIALOGUES LIVE

Understanding EBV+ PTLD

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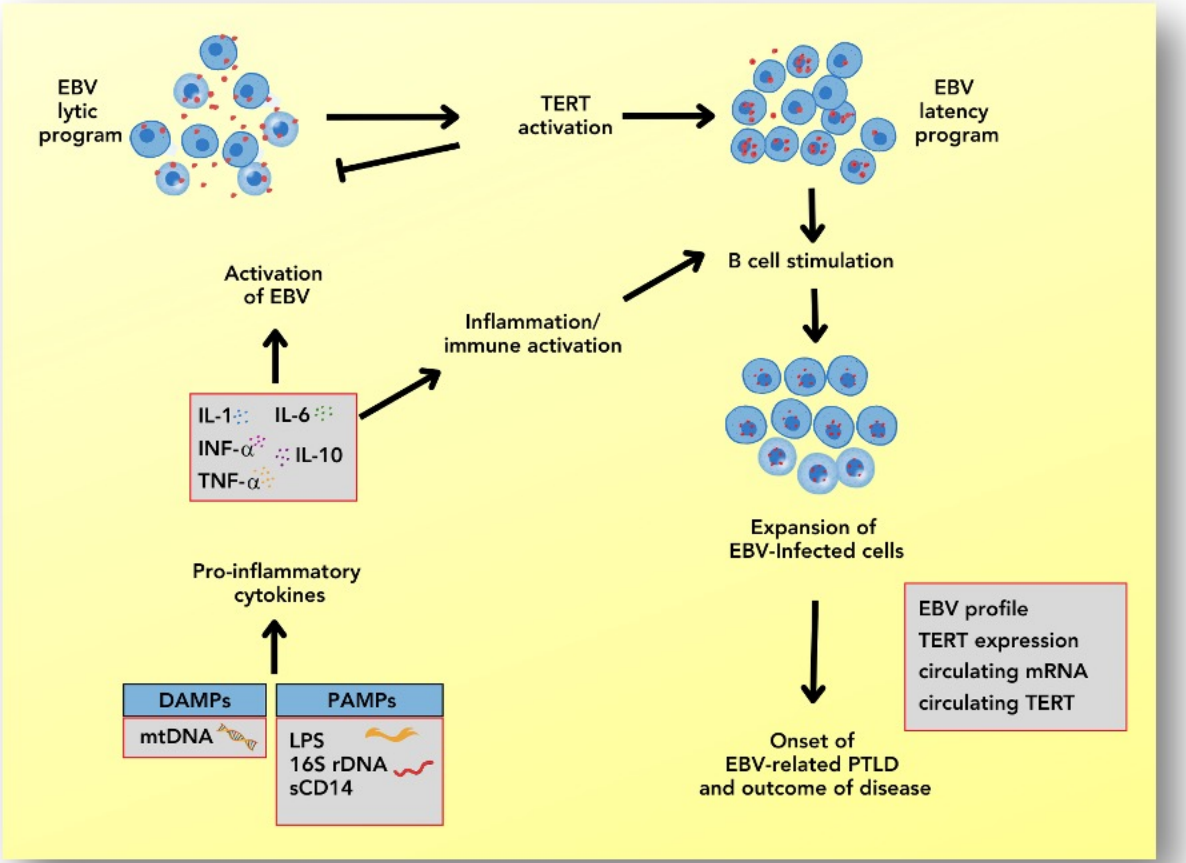
Epidemiology of EBV in PTLD

- PTLD is a heterogeneous group of lymphomas that may arise after SOT or allo-HCT causing immunosuppression
  - EBV+ PTLD is more frequently observed after allo-HCT
  - PTLD can be life-threatening if untreated
- EBV is highly prevalent worldwide
  - Most early PTLDs are EBV+ and result from the loss of immune surveillance
- PTLD ranks as the second most common malignancy after skin cancers among heart transplant recipients
  - It has had a significant impact on overall mortality with a 5-year survival rate of 20% prior to rituximab treatment



Allo-HCT, allogeneic hematopoietic cell transplant; SEER, Surveillance, Epidemiology, and End Results; SOT, solid organ transplant.

Nijland ML, et al *Transplant Direct*. 2015;2(1):e48; Crespo-Leiro MG, et al. *Am J Transplant*. 2008;8:1031–1039; Ullah A, et al. *Cureus*. 2023;15(5):e39777; Petrara MR, et al. *Cancer Lett*. 2015;369(1):37-44.

Epidemiology of EBV in PTLD

- PTLDs exist on a spectrum
  - Early (non-destructive) vs polymorphic vs monomorphic (60% to 80%)
- EBV accounts for nearly all cases of PTLD following allo-HCT and 47% to 68% of cases following SOT
  - EBV+ PTLD is an extremely uncommon condition
  - It occurs in approximately 1% to 2% of cases within the initial year following allo-HCT and up to 10% of de novo malignancies post-SOT
- In 2021, over 140 000 solid organs were transplanted globally
  - Incidence of PTLD is estimated at 2% to 20% depending on organ type
- In 2022, 8 527 allo-HCTs were performed in the US, leading to approximately 150 new cases of PTLD

Crespo-Leiro MG, et al. *Am J Transplant*. 2008;8:1031–1039; Garcia-Cadenas I, et al. *Eur J Haematol*. 2019;102(6):465-471.

PTLD Risk Factors

PTLDs are predominantly B-cell disorders, with diffuse large B-cell lymphoma being the most common, often extra-nodal, with variable clinical presentations determined by pathologic subtype

- Risk factors include:
  - EBV serology mismatch
    - EBV-negative recipient and EBV+ donor
  - Type of transplant
    - Highest for patients who have multi-organ transplant, as well as bowel, heart, and lung transplants
  - Age
  - Immunosuppression

Socié G, et al. *Bone Marrow Transplant*. 2024;59(1):52-58.

PTLD Disease Burden

- PTLD in an allo-HCT recipient develops earlier than in patients who received SOT, has a more aggressive course, and results in poorer survival
- In both SOT and allo-HCT recipients, the incidence of EBV+ PTLD is relatively low (approximately 250 per 100 000 transplants) but can lead to a significantly high rate of mortality
  - Five-year survival rates after liver and kidney transplants are 64% and 70%, respectively
    - Heart and lung recipients have a five-year survival rate of more than 50%
- PTLD develops within 2 to 4 months after allo-HCT
  - Most cases appear within the first year after transplant, coinciding with immune system recovery

Uhlin M, et al. *Haematologica*. 2014;99:346–52; Cimino FM, Snyder KA. *Am Fam Physician*. 2016;93(3):203-210.

PTLD Incidence

- The incidence of EBV+ PTLD has increased in the past 20 years, likely due to the increased number of organ transplants and immunosuppressive therapies
  - Over the past two decades, transplant registries have observed an increasing incidence of PTLD
- US OPTN/UNOS database covering adult transplantation from 1999 to 2008 revealed varying incidences of PTLD across organ systems:
  - Highest in lung recipients (5.72 per 1,000 person-years(PY))
  - Intermediate in liver (2.44/1 000 PY) and heart recipients (2.24/1 000 PY)
  - Lowest in kidney recipients (1.58/1 000 PY)

OPTN, Organ Procurement Transplant Network; UNOS, United Network for Organ Sharing.
Sampaio MS, et al.. *Transplantation*. 2012;94(10):990-998; Kotton CN, et al. *Am J Transplant*. 2017;17(6):1439-1446.

Diagnosis

- Due to its heterogeneity and nonspecific clinical presentation, diagnosing PTLD is challenging
- Clinical diagnosis must account for the following:
  - Rejection of allograft organ
  - Opportunistic infections
  - Common infectious etiology
- Histopathology and radiology are needed for diagnosis, and SOT and allo-HCT recipients who develop PTLD may have a higher EBV viral load than those who do not

Dojcinov SD, Quintanilla-Martinez L. *Am J Clin Pathol*. 2023 Jan 4;159(1):14-33.

Hematology DIALOGUES LIVE

Prognostic Challenges

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Assessing Patient Prognosis

- WHO classifies PTLD into four categories:
  - Early lesions
  - Polymorphic PTLD
  - Monomorphic PTLD
  - Classical Hodgkin lymphoma
- Treatment aim is to cure PTLD and maintain transplanted organ function
- Prognosis and treatment selection are impacted by the following factors:
  - Disease-specific (SOT vs allo-HCT, underlying pathophysiology, time from transplant)
  - Patient-specific factors (age, EBV serostatus, reaction to immunotherapy)

WHO, World Health Organization.
Chaganti S, et al. *Adv Ther*. 2023;40(3):1267-1281.

Prognostic Factors for SOT Recipients

- The international prognostic index for SOT recipients includes:
  - Age > 60 years
  - Ann Arbor stage ≥ III
  - ECOG PS ≥ 2
  - Elevated lactate dehydrogenase
  - > 1 extra-nodal site of involvement
- Current scoring systems do not include/consider:
  - Type of transplant, which has an impact on survival and disease progression
  - Inability to tolerate RIS and lack of response to rituximab, which is indicative of a poor prognosis

ECOG, Eastern Cooperative Oncology Group; PS, performance status; RIS, reduction in immunosuppression.
Caillard S, et al. *J Clin Oncol*. 2013;31(10):1302-1309; Quintanilla-Martinez L, et al. *Virchows Arch*. 2023;482(1):227-244.

Prognostic Factors for Allo-HCT Recipients

- The most common risk factors for developing EBV+ PTLD among allo-HCT recipients, include:
  - Prior HCT
  - Post-transplant EBV DNAemia
  - T-cell depletion ex vivo or in vivo
  - Histocompatibility or EBV serology mismatch between the donor and recipient
  - Use of cord blood
- Inferior responses to first-line rituximab therapy are the result of:
  - Older age
  - Extra-nodal disease
  - Acute GVHD
  - Inability to tolerate RIS
- Factors associated with a poor response to EBV-specific CTLs after prior rituximab may include:
  - Prior receipt of multi-agent chemotherapy
  - Extra-nodal disease
  - > 3 sites of disease

CTL, cytotoxic T lymphocytes.
Socié G, et al. *Bone Marrow Transplant*. 2024;59(1):52-58. O'Reilly M, Peggs KS. *Transplantation*. 2020 Oct;104(10):1972-1973.

American Society of Transplantation Infectious Diseases Community of Practice

- Support preemptive strategies targeting early EBV+ PTLD in EBV- seronegative recipients, involving peripheral blood EBV DNA measurement using standardized assays, coupled with RIS to reduce viral load
- Treatment recommendations include a sequential approach tailored to CD20-positive PTLD, employing RIS, rituximab, and cytotoxic chemotherapy based on treatment response
- Limitations:
  - Last updated in 2019
  - PTLD diagnosis should be based on WHO pathology classification from tissue biopsy, but optimal staging procedures are uncertain

Allen UD, et al. *Clin Transplant*. 2019;33(9):e13652.

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias

- Lymphoid proliferations in post-transplant patients are PTLDs or attributable to other causes such as specific infections, non-specific inflammation, or organ rejection
- Presence of a few EBV+ cells does not confirm PTLD, as scattered EBV+ cells can occur in lymphoid proliferations even in immunocompetent individuals
  - EBV+ PTLD cases typically exhibit latency pattern III
- Subclassification is determined after PTLD confirmation
  - Excisional biopsy is recommended for diagnosis, with re-biopsy of recurrent lesions advised to exclude evolution or alternative diagnoses

Allen UD, et al. *Clin Transplant*. 2019;33(9):e13652; Shah N, Eyre TA, et al. *Br J Haematol*. 2021;193(4):727-740.

Hematology DIALOGUES LIVE

Game-Changing Emerging Agents for EBV+ PTLD

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Gaps in Treatment for EBV+ PTLD

- Currently, no FDA approved medications treat EBV+ PTLD
- Differs from typical non-Hodgkin lymphoma treatment
- Lifelong immunosuppression in allo-HCT and SOT recipients comes with increased risks, like infection or allograft rejection
- Continual monitoring for GVHD

Nijland ML, et al. *Transplant Direct*. 2015;2(1):e48; Crespo-Leiro MG, et al. *Am J Transplant*. 2008;8:1031–1039; Ullah A, et al. *Cureus*. 2023;15(5):e39777.

NCCN Clinical Guidelines for EBV+ PTLD Following HCT

Learning Point

PTLD Subtype	First-Line Therapy	Initial Response	Follow-Up/Second-Line Therapy
Non-destructive lesions (ICC)/ Hyperplasia (WHO5)	Reduction of immunosuppression	Complete response	Manage immunosuppression and monitor EBV PCR, and graft organ function
		Partial response, persistent or progressive disease	Rituximab and monitor EBV PCR
Polymorphic PTLD (B-cell type) (ICC/WHO5) — Systemic	RI, if possible and: • Rituximab alone or • Chemoimmunotherapy	Complete Response	Monitor EBV PCR and: • Observation or • Continue RI, if possible ± maintenance rituximab, and graft organ functioning monitoring
Polymorphic PTLD (B-cell type) (ICC/WHO5) — Localized	RI, if possible and: • ISRT ± rituximab or • Surgery ± rituximab or • Rituximab alone	Partial response, persistent or progressive disease	Chemoimmunotherapy or Clinical trial or EBV-specific cytotoxic T-cell immunity (if EBV driven)
Monomorphic PTLD (B-cell type)	RI, if possible and: • Rituximab alone or • Chemoimmunotherapy	Complete response	See appropriate histologic subtype for follow-up
		Partial response, persistent or progressive disease	If RI was initial therapy, then rituximab or chemoimmunotherapy or If rituximab monotherapy was initial therapy, then chemoimmunotherapy or consider rituximab for patients with partial response and IPI 0-2 or If chemoimmunotherapy was initial therapy, see BCEL-7 or Clinical trial or EBV-specific cytotoxic T-cell immunity (if EBV-driven)

HCT, hematopoietic cell transplant; ICC, International Consensus Classification; ISRT, Involved site radiation therapy; PCR, polymerase chain reaction; RI, reduction of immunosuppression; WHO5, World Health Organization 5th Edition.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas - August 26, 2024. Version 3.2024. Accessed August 30, 2024.

NCCN Clinical Guidelines for EBV+ PTLD Following HCT

SUGGESTED TREATMENT REGIMENS

(in alphabetical order)

An FDA-approved biosimilar is an appropriate substitute for rituximab

Monomorphic PTLD (B-Cell Type) and Polymorphic PTLD (B-Cell Type)

Sequential chemoimmunotherapy

- Rituximab 375 mg/m^2 weekly × 4 weeks
  - Restage with PET/CT scan
    - If PET/CT scan negative (5-PS: 1 - 3), rituximab 375 mg/m^2 every 3 weeks × 4 cycles
    - If PET/CT scan positive (5-PS: 4 - 5) RCHOP-21 every 3 weeks + G-CSF × 4 cycles[†]

Concurrent chemoimmunotherapy

- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- For patients who are frail who cannot tolerate anthracycline, no specific regimen has been identified but options my include:
  - RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
  - RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
  - RCVP (rituximab, cyclophosphamide, vincristine, prednisone)

[†]If 5-PS: 5 because of new sites of disease or clear progression, treat as refractory disease

Primary CNS PTLD (B-Cell Type)

High-dose methotrexate + rituximab

CT, computed tomography; G-CSF, granulocyte colony-stimulating factor; PET, positron emission tomography; RCHOP, rituximab-cyclophosphamide-hydroxydaunorubicin-vincristine-presnisone.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas - August 26, 2024. Version 3.2024. Accessed August 30, 2024.

Patient Considerations in Alignment with Clinical Recommendations

- Factors that should be considered for this patient population:
  - Severity of the underlying condition necessitating transplantation
  - Complexities of the transplant process itself
  - Potential risks to the transplanted organ,
  - A subset of patients with EBV+ PTLD may not be suitable for chemotherapy
- Recommendations include avoiding chemotherapy for patients with the following characteristics:
  - Impaired organ or bone marrow function
  - A high ECOG score
  - History of HCT
  - Not responding to chemotherapy

Chaganti S, et al. *Adv Ther*. 2023;40(3):1267-1281.

IPTA and ECIL-6: Prevention of EBV Disease and PTLD Management in Pediatric Populations

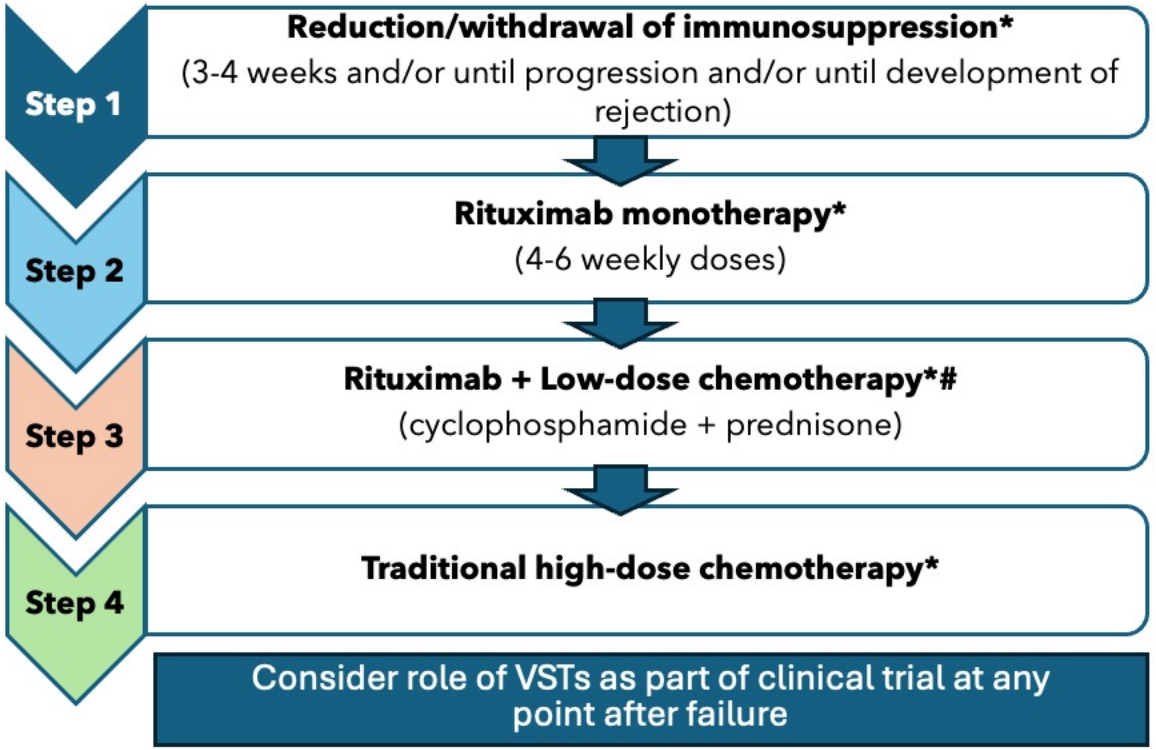
Guideline Endorsed Recommendations for the Prevention of EBV Disease and PTLD

	SOT[a1]	HCT[b2]
Prophylaxis		
Chemoprophylaxis - Antivirals	Not Recommended (weak/moderate to prevent EBV infection) (strong/moderate to prevent EBV disease)	Not recommended (DII)
Immunoprophylaxis		
Vaccines	Unavailable	
IVIG	Not recommended (weak/moderate)	Not recommended (DIII)
Anti-CD20	Not recommended (strong/low)	Marginally recommended (CII)
VSTs	Not recommended	Marginally recommended (CII)
Preemptive therapy		
Reduction of immunosuppression	Recommended (strong/moderate for liver) (weak/low for other organs)	Recommended when combined with anti-CD20 (AII)
Chemoprophylaxis – Antivirals	Not recommended (weak/low)	Not recommended (DIII)
Immunoprophylaxis		
Anti-CD20	Not recommended (weak/very low)	Recommended, alongside RIS whenever possible (AII)
VSTs	Not recommended (weak/low)	Marginally recommended (CII)

ECIL-6, European Conference on Infections in Leukemia; IVIG, intravenous immunoglobulin; VSTs, virus-specific T cells.
[a]Grading recommendations for SOT: (x/y); x = strength of recommendation; y = quality of evidence.
[b]Grading recommendations for HCT: A = strong; B = moderate; C = marginal; D = against; I = at least 1 RCT; II = at least from one clinical trial; III = expert opinion, descriptive studies.
Yamada M, et al. *J Pediatric Infect Dis Soc*. 2024;13(Supplement_1):S31-S38.

IPTA and ECIL-6 Recommendations for EBV Disease in Pediatric SOT and HCT Recipients

International Pediatric Transplant Association PTLD Consensus Conference proposed stepwise approach to the treatment of EBV+ PTLD in children after SOT



Recommendation for Therapy of EBV+ PTLD in HCT According to ECIL-6 Guidelines

First-line therapy in EBV+ -PTLD	Grade of recommendation
1. Rituximab	AIIu
2. Reduction of immunosuppressive therapy (if possible) combined with rituximab	AIIu
3. EBV-specific cytotoxic T lymphocytes (generated from HCT or third-party donor) if available	CIIu
Second-line therapy in EBV-PTLD	
1. EBV-specific-CTLs or donor lymphocyte infusion	BIII
Third-line in EBV+ PTLD	
1. Chemotherapy ± rituximab after failure of other methods	CIIh
CNS EBV disease	
Therapeutic options in EBV+ PTLD in central nervous system include:	
1. Rituximab ± chemotherapy	BIIh
2. Rituximab systemic or intrathecal monotherapy	CIII
3. Anti-EBV T-cell therapy	CIII
4. Radiotherapy	CIII
Strategies that are NOT recommended for treatment of EBV+ PTLD: Surgery, IVIG, interferon, and antiviral agents are not recommended for therapy of PTLD	DIII

IPTA, International Pediatric Transplant Association.
*Potential exceptions to standard algorithm include: Burkitt PTLD, Hodgkin PTLD, T/NK cell lymphomas (monomorphic type), Central Nervous System PTLD, and plasmacytoma.
Grading recommendations for HCT: A = strong; B = moderate; C = marginal; D = against; I = at least 1 RCT; II = at least from one clinical trial; III = expert opinion, descriptive studies, h = historical controls. u = uncontrolled clinical trials.
Yamada M, et al. *J Pediatric Infect Dis Soc*. 2024;13(Supplement_1):S31-S38.

OS for Patients with EBV+ PTLD

- Although success rates vary, up to 50% of EBV+ PTLD cases are R/R to first-line rituximab therapy
- Factors contributing to a poor response include:
  - Acute GVHD requiring immunosuppressive medications
  - Involvement of extra-nodal sites
  - Intolerance to RIS
  - Use of bone marrow grafts
- The 3-year OS for allo-HCT recipients with EBV+ PTLD treated with rituximab-containing therapies ranges from 20% to 48%, with patients having multiple risk factors experiencing the lowest OS rates
- There is a pressing clinical need for effective alternative treatments for patients with EBV+ PTLD after allo-HCT when initial therapies fail

OS, overall survival; R/R, relapsed/refractory.

Garcia-Cadenas I, et al. *Eur J Haematol*. 2019;102:465–471; Uhlin M, et al. *Haematologica*. 2014;99:346–352; Fox CP, et al. *Bone Marrow Transplant*. 2014;49:280–286; Styczynski J, et al. *Clin Infect Dis*. 2013;57:794–802; Fujimoto A, et al. *Cancers*. 2020;12:328; Hoegh-Petersen M, et al. *Bone Marrow Transplant*. 2011;46:1104–1112.

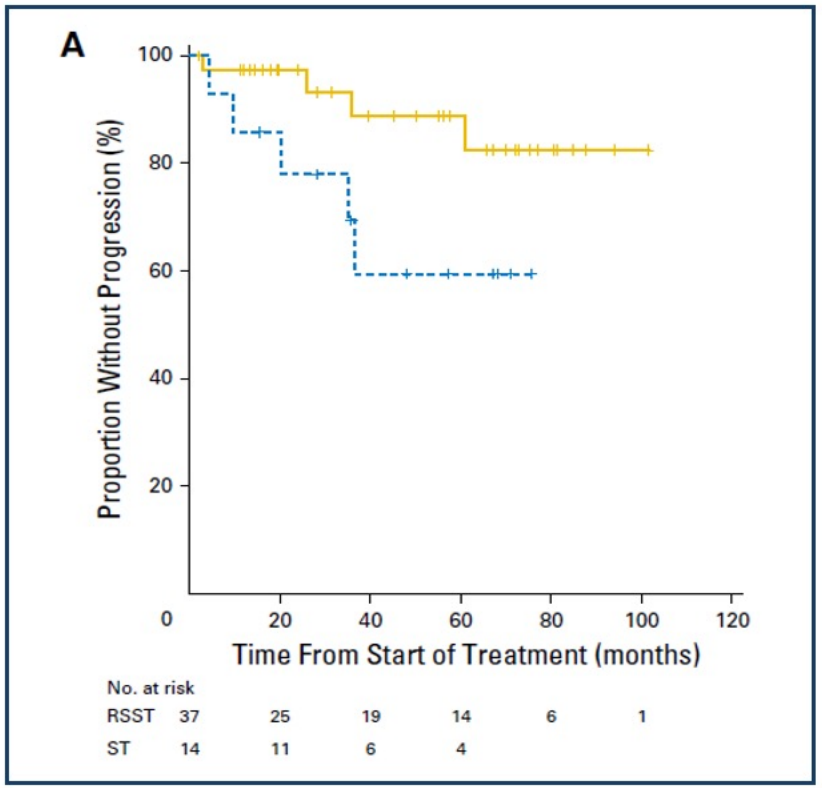
OS for Patients with EBV+ PTLD

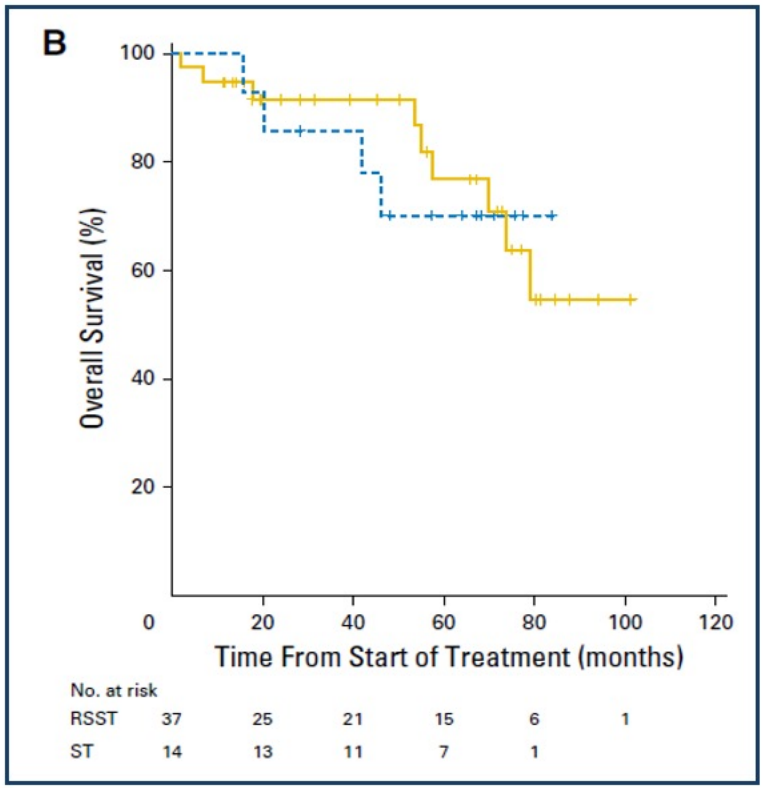
- Current guidelines for managing R/R EBV+ PTLD post-HCT are based on limited evidence
- Outcomes following failure of rituximab with or without chemotherapy are generally poor, with a median OS of only 33 days
- Moreover, chemotherapy is typically ineffective and associated with a high treatment-related mortality rate in patients with R/R EBV+ PTLD post-HCT, further constraining treatment options following rituximab failure

Fox CP, et al. *Bone Marrow Transplant*. 2014;49:280–286; Styczynski J, et al. *Clin Infect Dis*. 2013;57:794–802.

PTLD-1 Trial

Phase 2 trial assessing safety and efficacy of rituximab for treatment-naïve patients with EBV+ PTLD post-SOT (N = 152)





Patients experienced grade 3 or 4

- Leukopenia: 57/91 (63%) (95% CI, 52% to 72%)
- Infections: 52/151 (34%) (95% CI, 27% to 42%)
  - Febrile neutropenia (24 patients) was the most common

Median time of follow-up: 4.5 years

Patients in complete response after rituximab induction (low-risk group)

Time to progression and overall survival in the RSST cohort (n = 37; solid line) and the ST cohort (n = 14; dashed line)

CI, confidence interval; RSST; risk-stratified sequential treatment; ST, sequential treatment.
Trappe RU, et al. *J Clin Oncol*. 2017;35(5):536–543.

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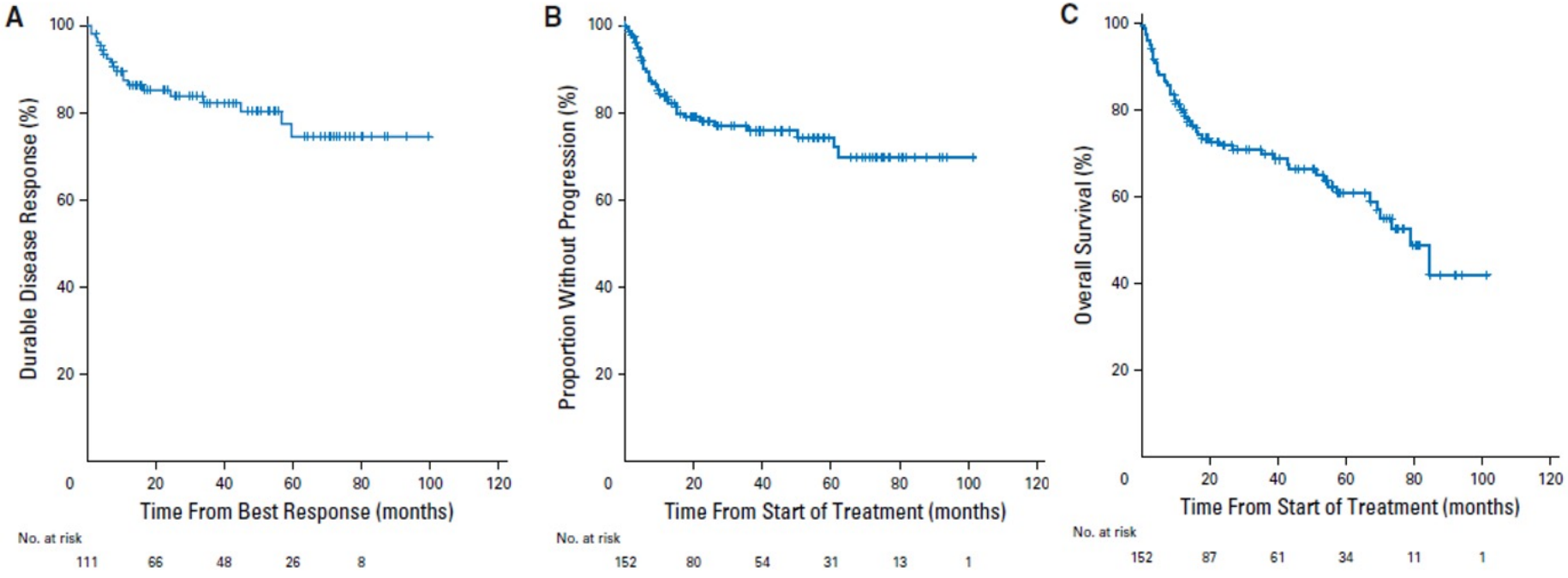
Phase 2 trial assessing safety and efficacy of rituximab for treatment-naïve patients with EBV+ PTLD post-SOT (N = 152)

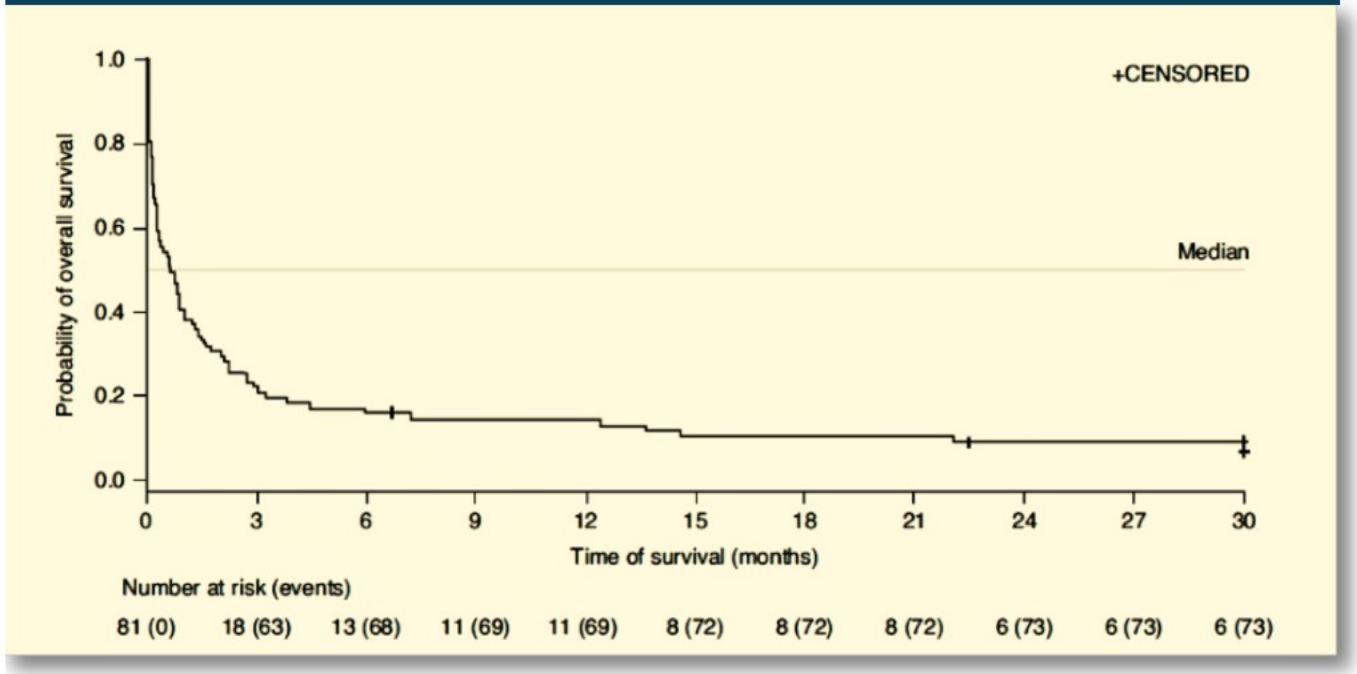
Median time of follow-up: 4.5 years



(A) Response duration (patients in complete response or partial response). (B) Time to progression (all patients). (C) Overall survival (all patients).
Trappe RU, et al. *J Clin Oncol*. 2017;35(5):536-543.

Outcomes for patients with EBV+ PTLD post-allo-HCT after failure of rituximab-containing therapy

OS from date of R/R to rituximab ± chemotherapy



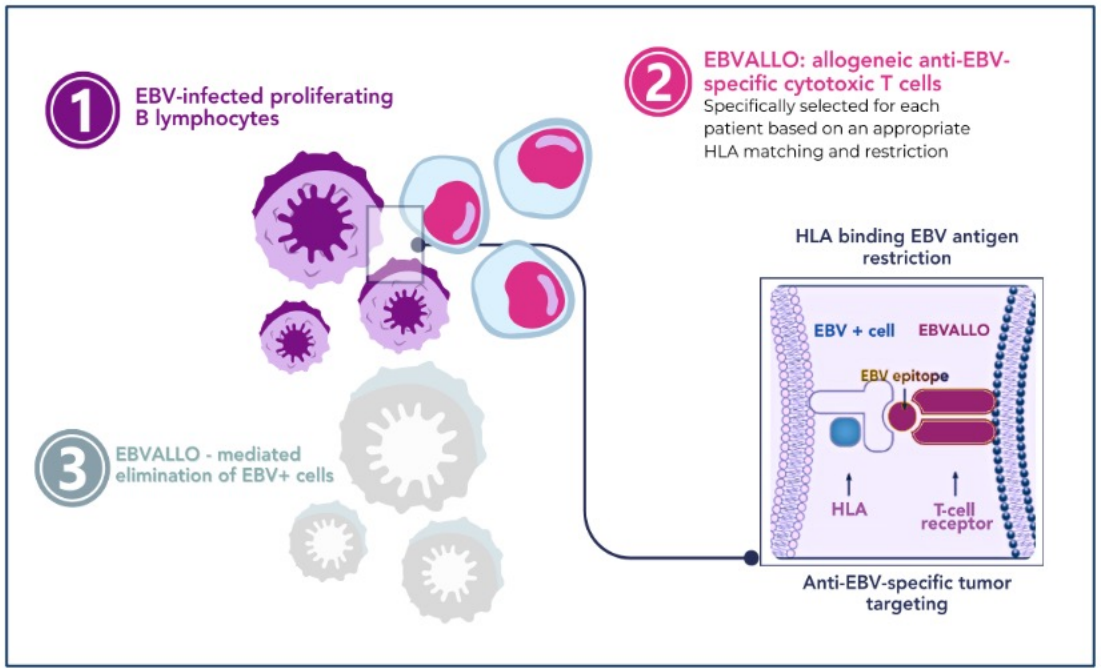
	R/R to rituximab±chemotherapy (N = 81)
Median follow-up, months (minimum - maximum)	0.7 (0.03 - 107.1)
Median OS,[a] months (95% CI)	0.7 (0.3 - 1.0)
OS rate,[a] % (95% CI)	
3 months	22.2 (13.9 - 31.8)
6 months	16.0 (9.1 - 24.8)
12 months	14.7 (8.0 - 23.3)
24 months	9.4 (4.2 - 17.0)

	R/R to rituximab ± chemotherapy (N = 81)
Total deaths	74 (91.4)
Cause of death n, (%)	
PTLD	42 (56.8)
GVHD	10 (13.5)
Treatment-related mortality	8 (10.8)
Sepsis infection	5 (6.8)
Relapsed primary disease leading to HCT	3 (4.1)
Organ rejection/failure	3 (4.1)
Unknown	2 (2.7)
Graft failure	1 (1.4)

OS is from the R/R date to the end of follow-up.
Socié G, et al. *Bone Marrow Transplant*. 2024;59(1):52-58.

ALLELE Trial

- Patients with biopsy-proven EBV+ R/R PTLD treated with intravenous tabelecleucel (N = 63)
- 14 patients had prior allo-HCT, and 29 had SOT



	HSCT group (n = 14)	SOT group (n = 29)	All (n = 43)
Objective response	7 (50%, 23 - 77)	15 (52%, 33 - 71)	22 (51%, 36 - 67)
Best overall response			
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%)

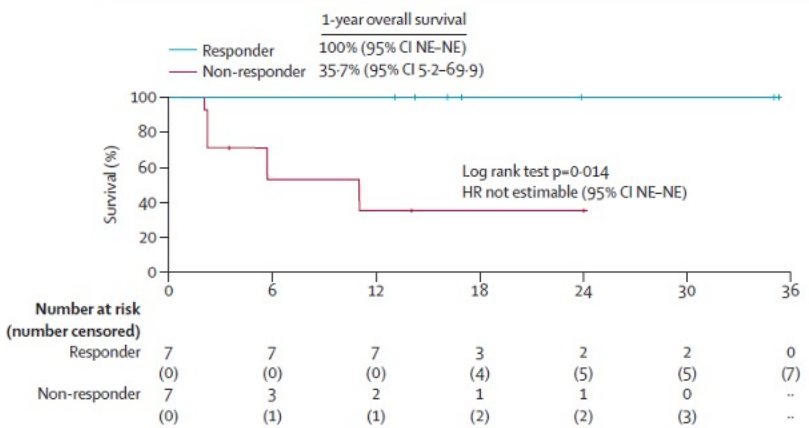
Data are n (%, 95% CI) or n (%). Due to rounding, columns may not add to 100%. Response assessed per Lugano Classification with LYRIC modification by independent oncologic response adjudication in the full analysis set (consists of all patients who received at least one dose of tabelecleucel).
HSCT, hematopoietic stem cell transplant.
Mahadeo KM, et al. *Lancet Oncol*. 2024;25(3):376-387; EBVALLO. EU Prescription Information. 2024.

ALLELE Trial

Learning Point

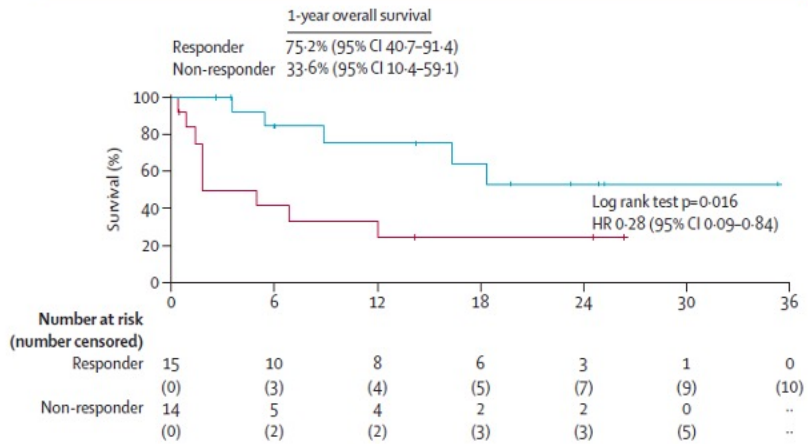
Survival in patients with EBV+ PTLD following HSCT or SOT who received tabelecleucel

OS in patients with EBV+ PTLD following HSCT



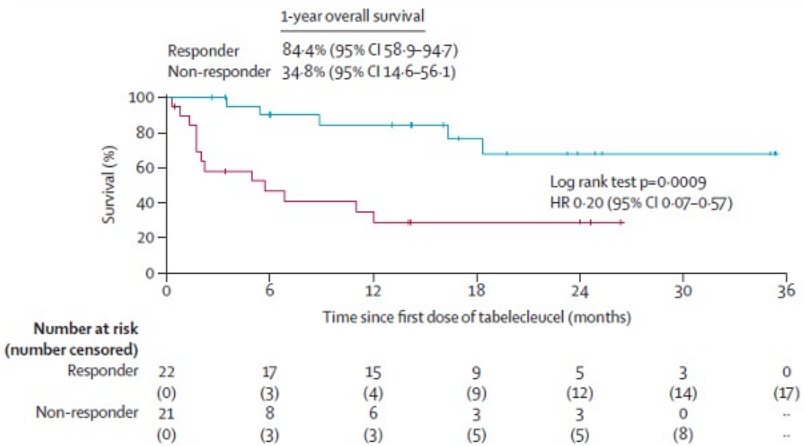
Median time of follow-up was 14.1 months (IQR 5.7 - 23.9)

OS in patients with EBV+ PTLD following SOT



Median time of follow-up was 6.0 months (IQR 1.8 - 18.4)

OS in patients with EBV+ PTLD disease overall



Median time of follow-up was 11.0 months (IQR 2.6 - 19.8)

IQR, interquartile range.
Mahadeo KM, et al. *Lancet Oncol*. 2024;25(3):376-387.

ALLELE Trial

Learning Point

	HSCT group (n = 14)					SOT group (n = 29)				
	Grade 1 - 2	Grade 3	Grade 4	Grade 5	Total	Grade 1 - 2	Grade 3	Grade 4	Grade 5	Total
Disease progression	0	3 (21)	1 (7)	1 (7)	5 (36)	6 (21)	8 (28)	0	2 (7)	16 (55)
Pyrexia	5 (36)	0	0	0	5 (36)	7 (24)	1 (3)	0	0	8 (28)
Diarrhea	4 (29)	0	0	0	4 (29)	8 (28)	0	0	0	8 (28)
Fatigue	3 (21)	1 (7)	0	0	4 (29)	3 (10)	2 (7)	0	0	5 (17)
Nausea	4 (29)	0	0	0	4 (29)	3 (10)	2 (7)	0	0	5 (17)
Neutrophil count decreased	1 (7)	2 (14)	2 (14)	0	5 (36)	0	2 (7)	2 (7)	0	4 (14)
Vomiting	3 (21)	0	0	0	3 (21)	2 (7)	4 (14)	0	0	6 (21)
Constipation	1 (7)	1 (7)	0	0	2 (14)	4 (14)	0	0	0	4 (14)
Decreased appetite	2 (14)	1 (7)	0	0	3 (21)	3 (10)	0	0	0	3 (10)
Hypotension	1 (7)	0	0	0	1 (7)	3 (10)	2 (7)	0	0	5 (17)
Abdominal pain	2 (14)	0	0	0	2 (14)	2 (7)	1 (3)	0	0	3 (10)
Acute kidney injury	0	0	0	0	0	1 (3)	3 (10)	1 (3)	0	5 (17)
Anemia	0	1 (7)	0	0	1 (7)	2 (7)	2 (7)	0	0	4 (14)
Dehydration	2 (14)	1 (7)	0	0	3 (21)	1 (3)	1 (3)	0	0	2 (7)
Dyspnea	2 (14)	0	0	0	2 (14)	3 (10)	0	0	0	3 (10)
Hypokalemia	2 (14)	1 (7)	0	0	3 (21)	2 (7)	0	0	0	2 (7)
Hypomagnesemia	2 (14)	0	0	0	2 (14)	3 (10)	0	0	0	3 (10)
Sepsis	0	0	3 (21)	0	3 (21)	0	2 (7)	0	0	2 (7)

TEAE, treatment-emergent adverse events. Data are n (%). TEAEs occurring in more than 10% of patients in the overall patient population.
Mahadeo KM, et al. *Lancet Oncol*. 2024;25(3):376-387.

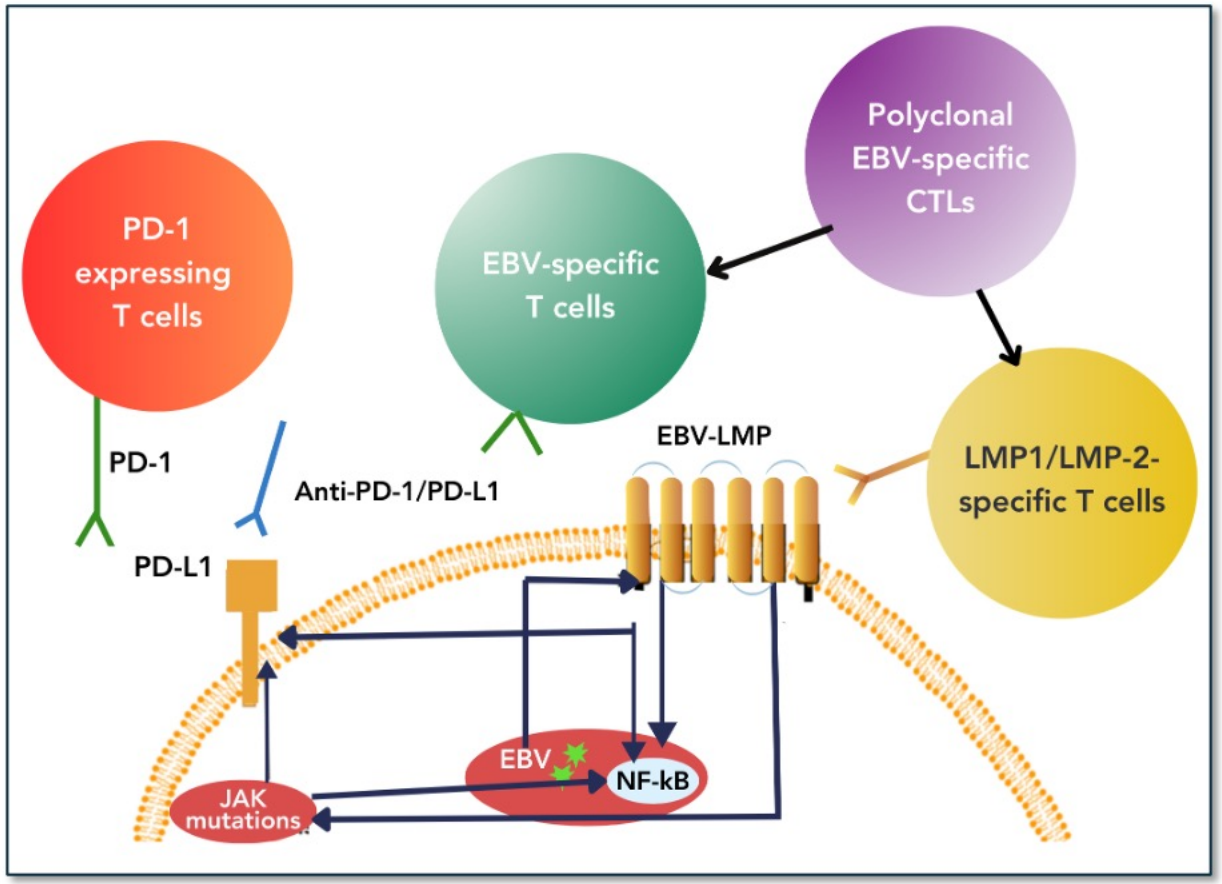
ALLELE Trial: TEAE Summary

- Serious TEAEs were reported in 23 (53%) of 43 patients and fatal TEAEs in five (12%)
- No fatal TEAE was treatment-related
- There were no reports of tumor flare reaction, CRS, ICANS, transmission of infectious diseases, marrow rejection, or infusion reactions
- No events of GVHD or SOT rejection were reported as related to tabelecleucel

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
Fox CP, et al. *Bone Marrow Transplant*. 2014;49:280-286; Styczynski J, et al. *Clin Infect Dis*. 2013;57:794–802.

Future of Treatment for EBV+ PTLD

- Tablecluecel is under review as monotherapy for treatment of adult and pediatric patients older than 2 years with EBV+ PTLD who have received at least one prior therapy
- EBV-CTLs are included in the current NCCN guidelines for treatment of EBV+ PTLD, particularly for R/R EBV+ PTLD
- Studies assessing tabelecleucel in combination with immune checkpoint inhibitors and with antibody drug conjugates are also underway



CTL, cytotoxic T lymphocytes; NCCN, National Comprehensive Cancer Network.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas - August 26, 2024. Version 3.2024. Accessed August 30, 2024; Lv K, et al. *Front Oncol*. 2022 Apr 19;12:838817.

Key Takeaways

- **Key Takeaway #1**: Thoughtful review of disease epidemiology and diagnosis of EBV+ PTLD is essential when identifying patients to improve overall outcomes
- **Key Takeaway #2**: Consideration of the challenges and complexities of prognosis to better inform treatment decisions
- **Key Takeaway #3**: As data for EBV+ PTLD continues to evolve, education on the latest evidence and guidance for treating patients is imperative