Analisi del sottogruppo pediatrico nello studio di fase 3 ALLELE su tabelecleucel per pazienti con PTLD EBV positiva dopo trapianto allogenico o di organo solido recidivata o refrattaria a rituximab ± chemioterapia

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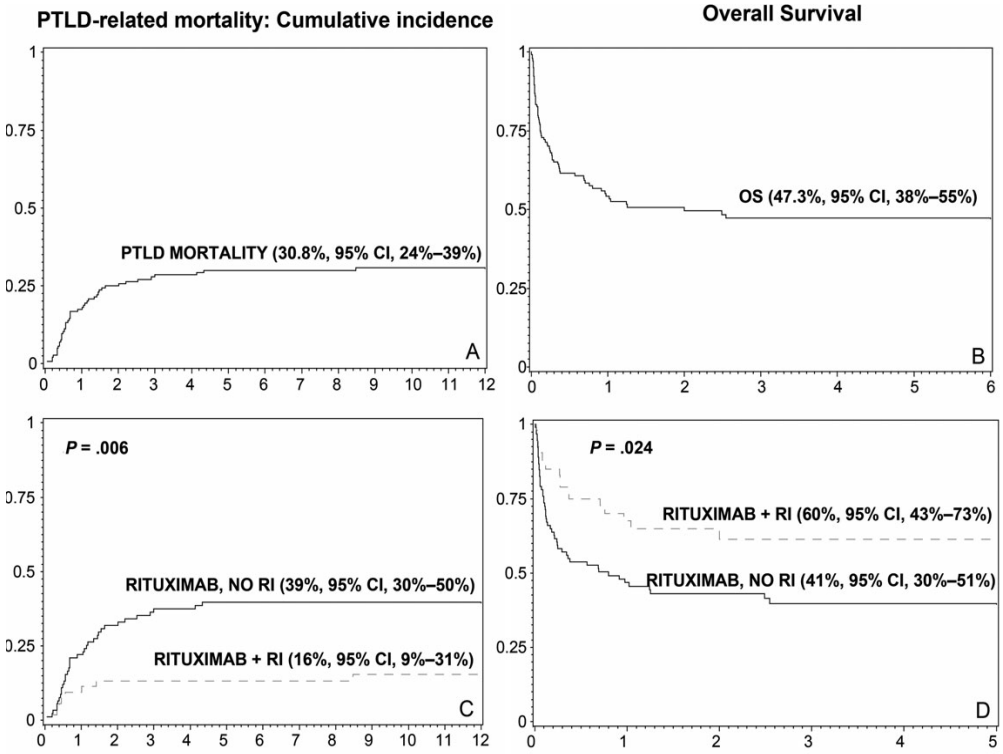


AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP MEDICI
LECCE, 12-14 ottobre 2026
HILTON GARDEN INN

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS						X	
ALEXION						X	
VERTEX						X	
PIERRE FABRE					X		



- ✓ Overall EBV-related PTLD frequency of 3.22%
- ✓ In total, 69.4% patients survived PTLD
- ✓ The 5-years overall survival in patients who developed CNS-PTLDs was 22% and 5-year treatment-related mortality was 78%

Transplant Cell Ther. 2021 Mar;27(3):261
Styczynski et al. EBMT ; CID 2016

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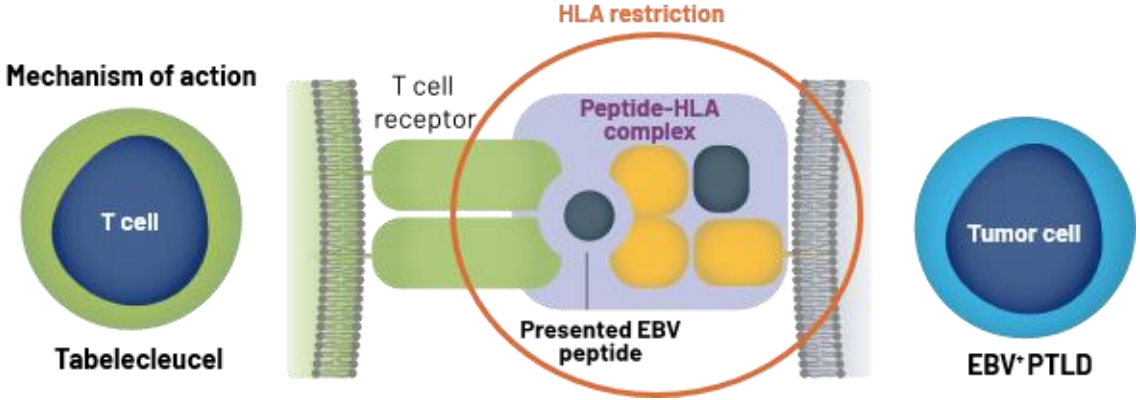
Hematologic Malignancy, poster #5488

67th ASH Annual Meeting, December 6–9, 2025, Orlando, Florida

Background and Aim

- ALLELE is a multicenter, open label, phase 3 trial assessing the safety and efficacy of tabelecleucel in patients with relapsed or refractory EBV+ PTLD after HCT or SOT and prior treatment with rituximab ± chemotherapy.
- Results from 75 patients enrolled in the ALLELE trial were presented previously.[1]
- Here we report results from 12 pediatric patients who have participated in ALLELE.

Tabelecleucel is an off-the-shelf, non-genetically modified, allogeneic, EBV-specific T cell immunotherapy that targets and eliminates EBV-infected cells in an HLA-restricted manner.



Manufacturing: Derived from unrelated third-party donors and cryo-preserved in a bio-bank adapted to cover multiple HLA profiles.

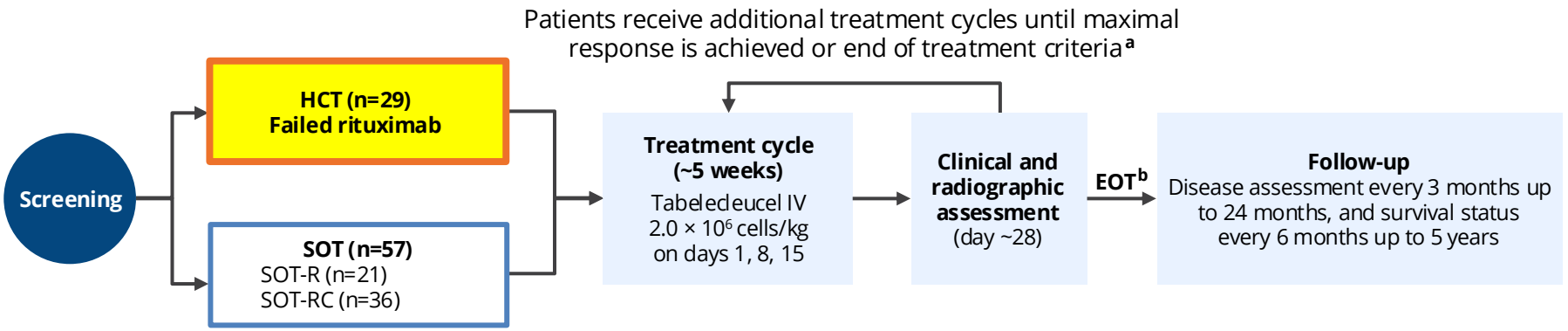
Product selection: Based on the characterization of **HLA restriction** and donor: recipient compatibility.

Administration: No lymphodepletion or pre-medication, 1-hour post-injection monitoring, inpatient or outpatient administration.

1. Ghobadi A, et al. *Blood*. 2024;144;70–71, ASH Annual Meeting.

EBV+ PTLD, Epstein-Barr virus-associated post-transplant lymphoproliferative disease; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; SOT, solid organ transplant.

ALLELE Study Design[1]



Key eligibility criteria
- Prior allogeneic HCT or SOT
- Biopsy-proven EBV+ PTLD
- Previous rituximab or rituximab-CT failure
- ECOG PS ≤3

Primary endpoint
- ORR

Key secondary endpoints:
- TTR and time to best response
- OS in responders vs non-responders
- PFS in responders
- Rates of allograft loss/rejection episodes (SOT)

[a] In case of non-response, patients may receive tabelecleucel using a T cell line with different HLA restrictions (switch).
[b] EOT, end of treatment (maximal response, unacceptable toxicity, start of non-protocol therapy, or failure of up to 2 [SOT patients] or 4 [HCT patients] different HLA restrictions).

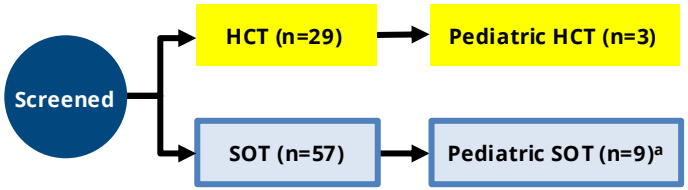
Patient numbers are from the overall study population as of September 10, 2024, with results reported in Nikiforow S. et al, 67th ASH Annual Meeting, 2025, poster #1934.

1. Protocol version V5.0

CT, chemotherapy; EBV+ PTLD, Epstein-Barr virus-associated post-transplant lymphoproliferative disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOT, solid organ transplant; SOT-R, SOT and failed rituximab; SOT-RC, SOT and failed rituximab and chemotherapy; TTR, time to response.

Patients (data cutoff, Sept 2024)

- 86 patients (29 HCT, 57 SOT), ranging in age from 2.7–81.5 years were enrolled and treated with tabelecleucel.
- Of these patients, **12 were <17 years of age** at informed consent (3 HCT, 9 SOT).



[a] Transplant types were heart (n=5), kidney (n=1), liver (n=1), and multivisceral (n=2).

- All patients had extranodal disease; 8 had lymph node disease.
- Patients received a median of 2 tabelecleucel cycles.

Table 1. Baseline characteristics

	HCT (n=3)	SOT (n=9)	Total (N=12)
Age, median (range), y	7.0 (3.2–16.8)	10.6 (2.7–16.7)	8.8 (2.7–16.8)
Age group, n (%)			
2–<6 y	1 (33.3)	1 (11.1)	2 (16.7)
6–<12 y	1 (33.3)	4 (44.4)	5 (41.7)
12–<17 y	1 (33.3)	4 (44.4)	5 (41.7)
Lansky score in patients ≤16 years of age, median (range)	85 (80–90)	70 (40–90)	70 (40–90)
PTLD morphology, n (%)			
Diffuse large B cell lymphoma	1 (33.3)	5 (55.6)	6 (50.0)
Other	2 (66.7)	4 (44.4)	6 (50.0)
Median (range) time, mo			
From transplant to EBV+ PTLD diagnosis	3.6 (3.3–4.0)	7.2 (2.4–133.2)	–
From EBV+ PTLD diagnosis to 1st tabelecleucel infusion	1.0 (0.6–2.0)	4.1 (1.4–43.8)	3.0 (0.6–43.8)

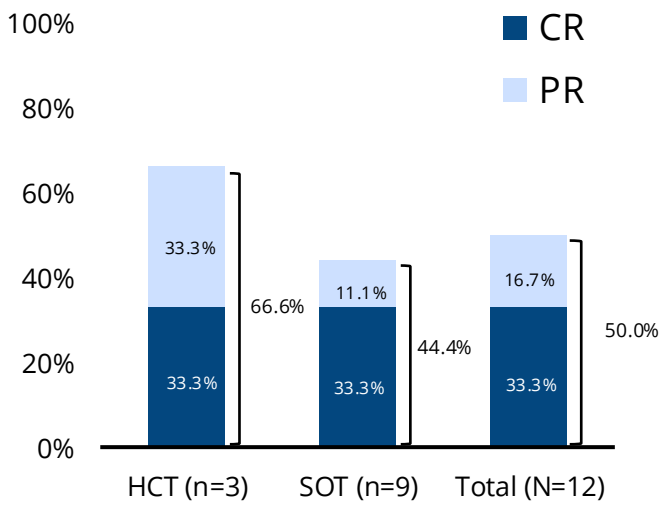
EBV+ PTLD, Epstein-Barr virus-associated post-transplant lymphoproliferative disease; HCT, hematopoietic cell transplant; SOT, solid organ transplant.

Table 2. Treatment response outcomes

	HCT (n=3)	SOT (n=9)	Total (N=12)
ORR, n responders, (%)[a]	**2 (66.7)**	**4 (44.4)**	**6 (50.0)**
Best objective response, n (%)			
CR	1 (33.3)	3 (33.3)	4 (33.3)
PR	1 (33.3)	1 (11.1)	2 (16.7)
Progressive disease	0 (0.0)	5 (55.6)	5 (41.7)
Not evaluable	1 (33.3)	0 (0.0)	1 (8.3)
Median (range) time, mo[b]			
TTR	1.1 (1.0–1.1)	2.9 (0.9–4.7)	1.6 (0.9–4.7)
Time to best response	1.1 (1.0–1.1)	4.2 (0.9–7.3)	2.4 (0.9–7.3)

[a] Assessed per Lugano classification with LYRIC modification by IORA.
[b] Calculated in responders only.

Figure 1. Objective response rate



- Median (range) follow-up time was 5.2 months (1.1–52.7).
- Of the 6 responders, 2 had a durable response of >6 months, and 3 were censored at data cutoff with no disease progression or death.
- Of all 12 patients, 6 were still alive at cutoff, including 5 treatment responders and 1 non-responder.

CR, complete response; HCT, hematopoietic cell transplant; IORA, independent oncologic response adjudication; LYRIC, Lymphoma Response to Immunomodulatory therapy Criteria; ORR, objective response rate; PR, partial response; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplant; TTR, time to response.

Safety

- 6 patients developed TESAEs; 4 TESAEs (in 2 patients) were considered treatment-related.
- No fatal SAEs were deemed related to tabelecleucel.
- 1 SOT patient was reported with grade 1 fever considered as a sign of possible treatment-related CRS with no sign of severity.
- No other reported treatment-emergent identified and potential risks including AEs of special interest:
  - tumor flare
  - IRRs
  - ICANS
  - GvHD
  - transmission of infection
  - bone marrow/solid organ transplant rejection.

Table 3. Summary of TEAEs

	HCT (n=3)	SOT (n=9)	Total (N=12)
TEAEs, n (%)			
Any	3 (100.0)	8 (88.9)	11 (91.7)
SAE	**1 (33.3)**	**5 (55.6)**	**6 (50.0)**
Fatal SAE	1 (33.3)	1 (11.1)	2 (16.7)
Treatment-related TEAEs, n (%)			
Any	1 (33.3)	6 (66.7)	7 (58.3)
SAE[a]	**0 (0.0)**	**2 (22.2)**	**2 (16.7)**
Fatal SAE	0 (0.0)	0 (0.0)	0 (0.0)

[a] Treatment-related SAEs were pyrexia (n=2), acute kidney injury (n=1), and angina pectoris (n=1).

- This safety profile is consistent with that reported in the overall study population.

AE, adverse event; CRS, cytokine release syndrome; GvHD, graft-vs-host disease; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IRRs, infusion related reactions; SAE, serious adverse event; SOT, solid organ transplant; TEAE, treatment emergent adverse event; TESAE, treatment emergent SAE.

Conclusions

- This analysis of 12 pediatric patients from the ALLELE trial suggests that the risk/benefit profile in the pediatric subgroup is consistent with that reported in the overall study population.
- The ORR in the pediatric subgroup of 50% (6/12 patients) is consistent with the ORR in the overall study population of 47.7% (41/86 patients).
- The safety profile of tabelecleucel was favorable and no new safety findings were identified for the pediatric population.

- **These results support the use of tabelecleucel in pediatric patients with R/R EBV+ PTLD who have poor survival and very limited treatment options.**

EBV+ PTLD, Epstein-Barr virus-associated post-transplant lymphoproliferative disease; ORR; objective response rate; R/R, relapsed or refractory.

Patient Profile & Transplant Regimen

Patient Baseline

Age & Sex **12 Years Old, Female**

Primary Diagnosis **Sickle Cell Disease (SSD)**

Transplant Type: **Haploidentical HCT**

Conditioning & Prophylaxis

Conditioning Protocol **Treosulfan-based**

GVHD Prophylaxis **Post-transplant Cyclophosphamide (PTCy)**

CMV Serostatus (D/R) **+ / + (Positive / Positive)**

EBV Serostatus (D/R) **+ / - (Positive / Negative)**

Combination of Treosulfan-based conditioning and PTCy aims to optimize engraftment while controlling severe GVHD risks in pediatric haploidentical HCT for SSD.

Engraftment & Chimerism Outcomes

+34 Neutrophil Engraftment

+19 Platelet Engraftment

Chimerism Analysis

Full Donor Status

100% Donor

Complication at +4 Months Post-HCT

Routine viral load surveillance via qPCR revealed significant **Epstein-Barr Virus (EBV) reactivation** at 4 months (+120 days) post-transplant.

VIRAL LOAD QUANTITATION

18,488

copies / mL

Clinical Presentation & CNS Spread

Initial Manifestation (13-20/01)

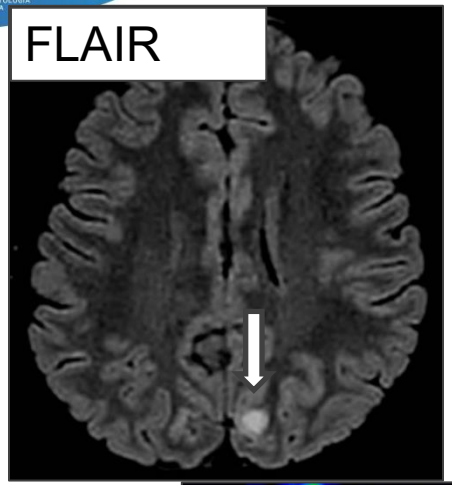
- Persistent fever accompanied by nausea, diarrhea, and exudative pharyngitis with tonsillar hypertrophy.
- Widespread lymphadenopathy (cervical, axillary, mediastinal, and abdominal).
- High EBV blood DNA copy count indicating acute reactivation/ proliferation.

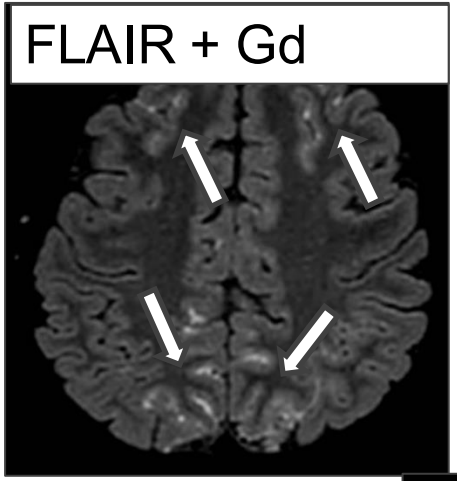
Gastrointestinal Bleeding (26/01)

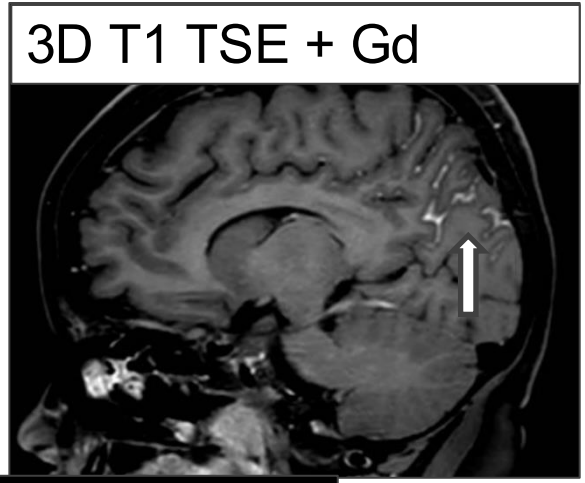
- Onset of lower GI hemorrhage (rectal bleeding) secondary to EBV intestinal lymphatic tissue invasion.
- Prompt initiation of Somatostatin and NovoSeven (rFVIIa) for hemostasis.

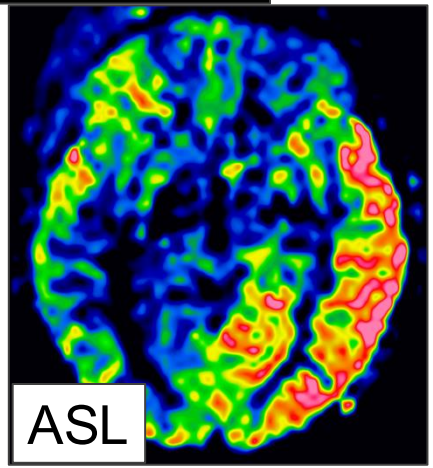
CNS Complications (28/01)

- Acute neurological decline (GCS 9, lethargy, drooling, rightward gaze & head deviation).
- Urgent brain CT/MRI revealed leptomeningeal enhancement & pericritical perfusion abnormalities.
- Lumbar puncture confirmed EBV-PTLD with CNS invasion; required transient mechanical ventilation.


FLAIR


FLAIR + Gd


3D T1 TSE + Gd


ASL


DWI

Multimodal Therapy & Progression



B-Cell Depletion & Chemo

- ✓ Full discontinuation of base immunosuppression (Cyclosporine).
- ✓ Targeted monoclonal antibody therapy: 2 doses of Rituximab (375 mg/m²) (23/01) .
- ✓ Low-dose cytoreductive Cyclophosphamide (5 mg/kg × 2) and systemic Methylprednisolone.

Intrathecal & Neuro Care

- ✓ Targeted intrathecal chemotherapy via medicated LP (Methotrexate + Methylprednisolone) (28/01).
- ✓ Seizure prophylaxis with Levetiracetam; EEG showed slow theta-delta activity without epileptiform discharges.
- ✓ Successful respiratory weaning from mechanical ventilation to HFNC, then room air.

3rd-Party VST Immunotherapy

- ✓ Indicated due to negative maternal EBV secretion test and high clinical severity.
- ✓ **Administered 3 infusions of 3rd-party anti-EBV Virus-Specific T-cells (Feb 2, Feb 9, Feb 16).**
- ✓ Excellent tolerability leading to a progressive drop in viral load and clinical resolution.



Rapid improvement of clinical neurological status

Improvement of neuroradiological picture : 28 days after 1° infusion

Actually (8 months after CTL and 1 yr after HCT): good clinical condition

(ruxolitinib for cGVHD)

PTLD After Hematopoietic Stem Cell Transplantation
Treatment Overview

PTLD (Post-Transplant Lymphoproliferative Disorder) is a spectrum of lymphoid proliferations, usually EBV-driven, that can occur after HSCT. Treatment aims to control the disease, preserve the graft, and minimize toxicity.

1. Initial Steps

- **Confirm diagnosis** (histology, EBV status, staging).
- **Reduce immunosuppression** (if feasible and safe).
- **Monitor EBV viral load** (useful for risk stratification and response).
- **Treat associated infections** (e.g., EBV, CMV, other viruses).

2. Treatment According to Disease Extent

Localized / Early Disease
(e.g., single site, low tumor burden)

- **Reduction of immunosuppression**
- **Rituximab** (anti-CD20) (first-line, especially for B-cell PTLD)
- **Consider local therapy** (surgery or radiotherapy) in selected cases.

Goal: achieve disease control with minimal toxicity.

Multifocal / Advanced Disease
(e.g., multiple sites, high tumor burden, or extranodal involvement)

- **Rituximab-based therapy** (single agent or combination)
- **Chemotherapy** (e.g., R-CHOP, R-CVP, or other regimens depending on histology and patient condition)
- **Consider antiviral therapy** (e.g., ganciclovir) in EBV-positive cases (evidence limited).

Goal: induce remission and control progression.

Refractory / Relapsed Disease
(after initial therapy or high-risk features)

- **Alternative immunotherapy** (e.g., obinutuzumab, ibrutinib in selected cases)
- **Adoptive immunotherapy** (e.g., EBV-specific cytotoxic T cells)
- **Allogeneic DLI** (in selected patients with suitable disease control and graft function)
- **Clinical trials** (novel agents, targeted therapies).

Goal: achieve durable response while managing graft-versus-host disease (GVHD) risk.

Key Considerations

- Balance disease control with risk of GVHD and graft rejection.
- Adjust therapy based on histology (B-cell vs T-cell), EBV status, and patient fitness.
- Close monitoring for infections and treatment-related toxicities.

Follow-up

- Regular clinical evaluation and imaging.
- Monitor **EBV viral load** (especially in high-risk patients).
- Long-term surveillance for relapse and late effects.

Early recognition and a tailored, stepwise approach improve outcomes in PTLD after HSCT.



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TRAPIANTO DI CELLULE EMOPOIETICHE