CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Starhotels Anderson
24 maggio 2024

I DISORDINI LINFOPROLIFERATIVI POST-TRAPIANTO

Dott.ssa Francesca Gaia Rossi
Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico di Milano

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda						x	
Janssen						x	
Incyte						x	

Definition and Epidemiology

- Post-transplant lymphoproliferative disorders (PTLDs) are heterogeneous, rare and potentially life-threatening group of lymphoproliferative disorders occuring in the setting of immunosoppression following hematopoietic stem cell transplant (HSCT) and solid organ transplantation (SOT)
- Italy: 4000 SOT/years
- Lymphoma accounts for 21% of all neoplasia after SOT as compared to 5% in immunocompetent individuals
- Incidence ranges between 1% to 20% after SOT and between 1% to 10% after HSCT
- Mortality after PTLD is up to 50% because of treatment failure or complications of chemotherapy

Risk factors

TABLE 1 | Major risk factors in the development of PTLD.

Risk factors for PTLD		
Infectious etiologies	EBV, especially when EBV(–) recipients received a transplant graft from EBV(+) donor. Mismatch for CMV, HCV, and HHV-8, especially when they coincided with EBV infection.	(5, 12)
Age and race	Ages <10 and >60 years. Race: White transplant patients > Blacks.	(13, 14)
Immunosuppressive therapy	The degree, duration, and type of immunosuppression (in particular, anti-thymocyte globulin, calcineurin inhibitors, anti-CD3, tacrolimus, and cyclosporine)	(15, 16)
HSCT/SOT-related factor	SOT types (multi-organ and intestinal transplants have an increasing risk than have lung transplants > heart transplants > liver transplants > pancreatic transplants > kidney transplants). HLA mismatch in HSCT (haploidentical transplants have an increasing risk than have unrelated donor > umbilical cord transplant > HLA-identical related). Type of GVHD prophylaxis, T-cell depletion has the highest risk. Severity of GVHD transplant.	(16–19)
Genetic factors	Polymorphisms in cytokine genes. Recipient HLA, donor polymorphisms.	(20, 21)

EBV, Epstein–Barr virus; CMV, cytomegalovirus; HCV, hepatitis C; HHV, human herpesvirus; HSCT, hematopoietic stem cell transplant; HLA, human leukocyte antigen; GVHD, graft-vs.-host disease; SOT, solid organ transplant.

Risk factors according to the type of transplant

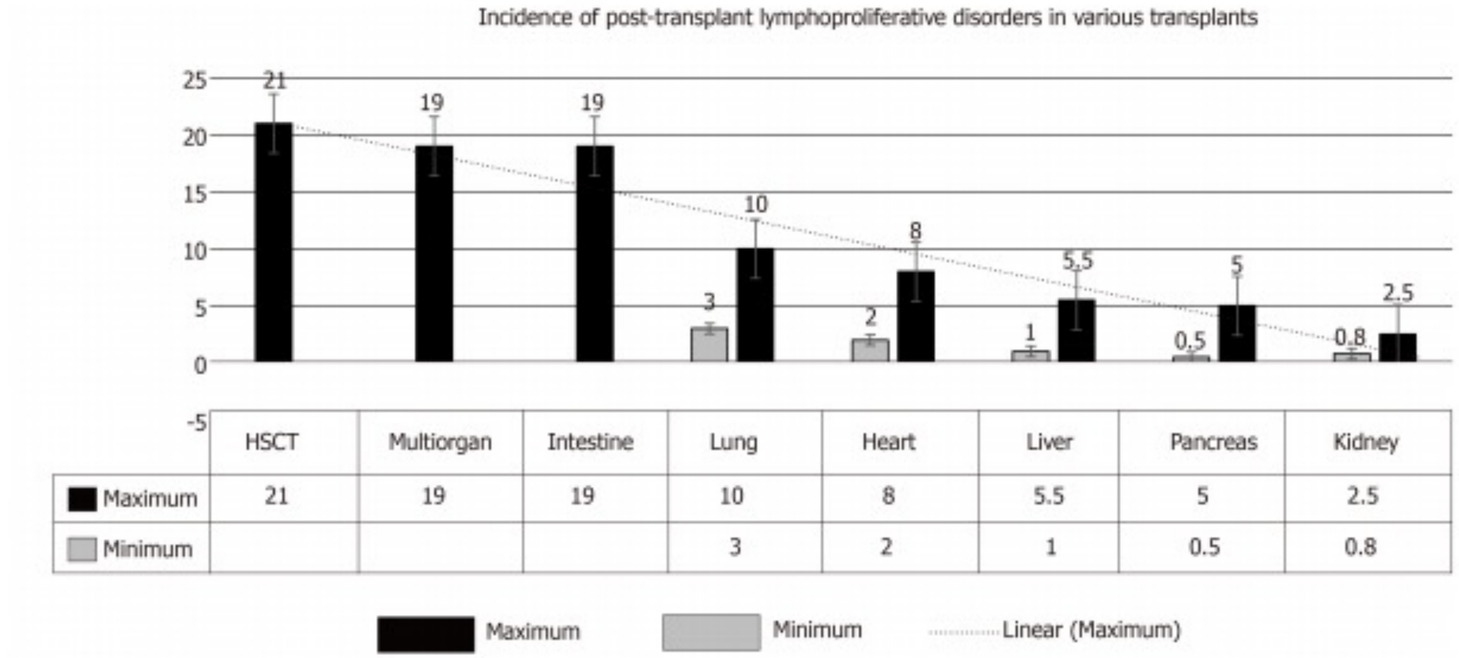


Figure 1 The range increased incidence of post-transplant lymphoproliferative disorders in various transplants. Incidence in intestinal transplant and in multi-organ transplants it is < 20%, while in hematopoietic stem-cell transplant it is > 20% with selective T-cell depletion[4]. HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant.

Bimodal curve of incidence:

- **initial spike** (about 30% of cases) in the first year, mostly driven by EBV first infection or riactivation
- **Late wave/plateau** which can be both EBV+ but more often EBV –

Risk factors in HSCT

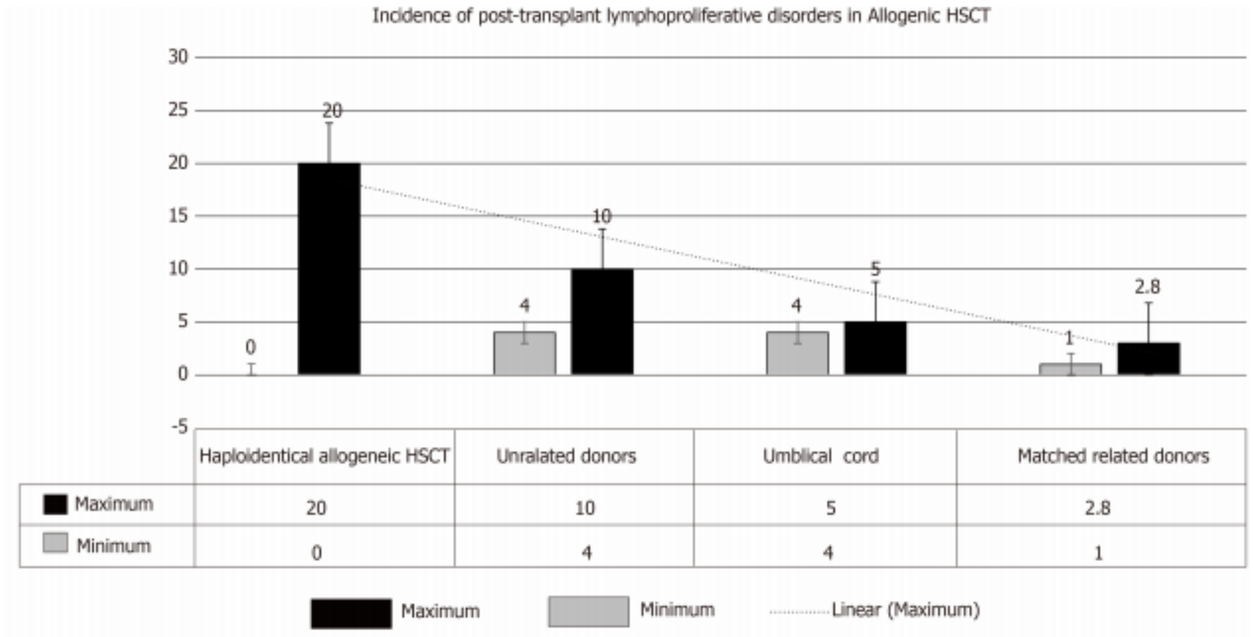


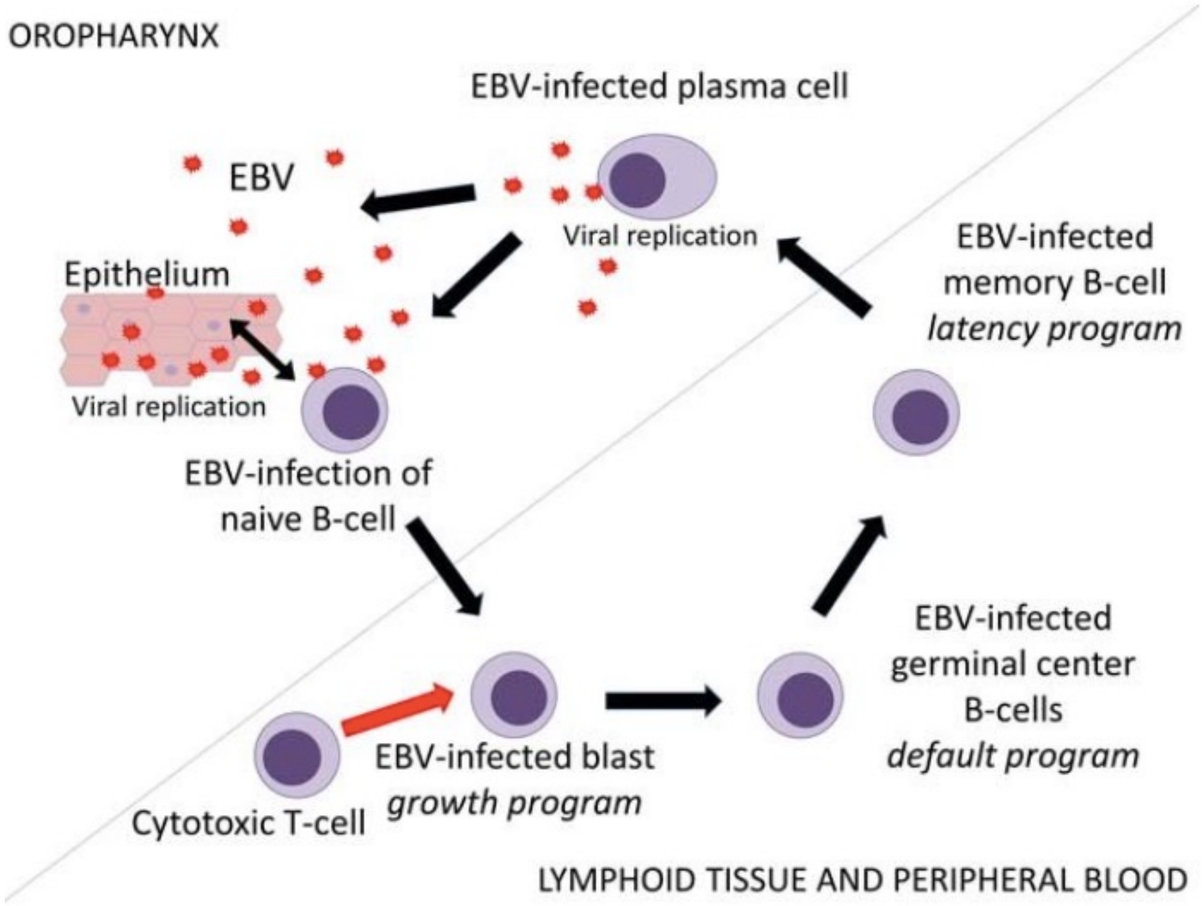
Figure 2 Incidence of post-transplant lymphoproliferative disorders after allogenic hematopoietic stem-cell transplant. An additional risk factor in hematopoietic stem-cell transplantation is: recipient age of > 50 yr[4]. HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant.

Incidence influenced by:

- Source of stem cell: haplo >20% in case of T-cell depletion; MUD 4-10%; cord 4-5%; matched related donor 1-3%
- Development or treatment of GVHD
- T cell depletion of donor marrow (ATG)
- CMV infection → consequent reduction of cellular immunity
- age of recipient > 50 yr

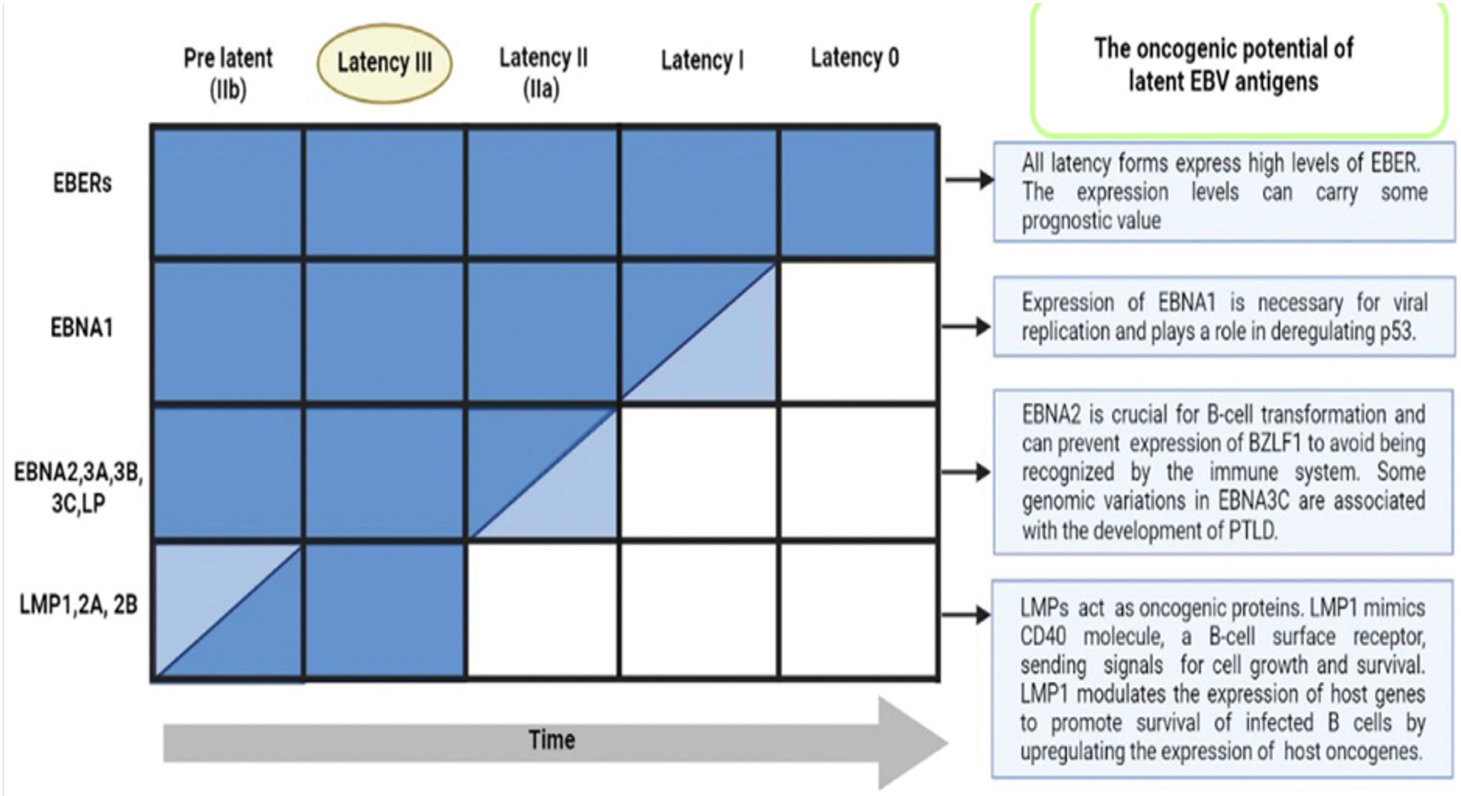
Almost all cases occur in the first 6-12 months and are **universally EBV+**. Late cases only in pts with GVHD treated with immunosuppressive therapy

Role of EBV in PTLD EBV+ pathogenesis



Disregulation of latency stage of infection or uncontrolled lytic phase can lead to the development of EBV-associated malignancies like PTLD

Role of EBV in PTLD pathogenesis



In PTLD EBV is in latent stage III, where it expresses all 9 viral proteins, high expression levels of EBV-encoded small RNAs (EBERs) and MicroRNAs.

EBV is latent in recipient or donor lymphocyte in the graft

All latent EBV antigens can have oncogenic potential when T-cell surveillance is decreased

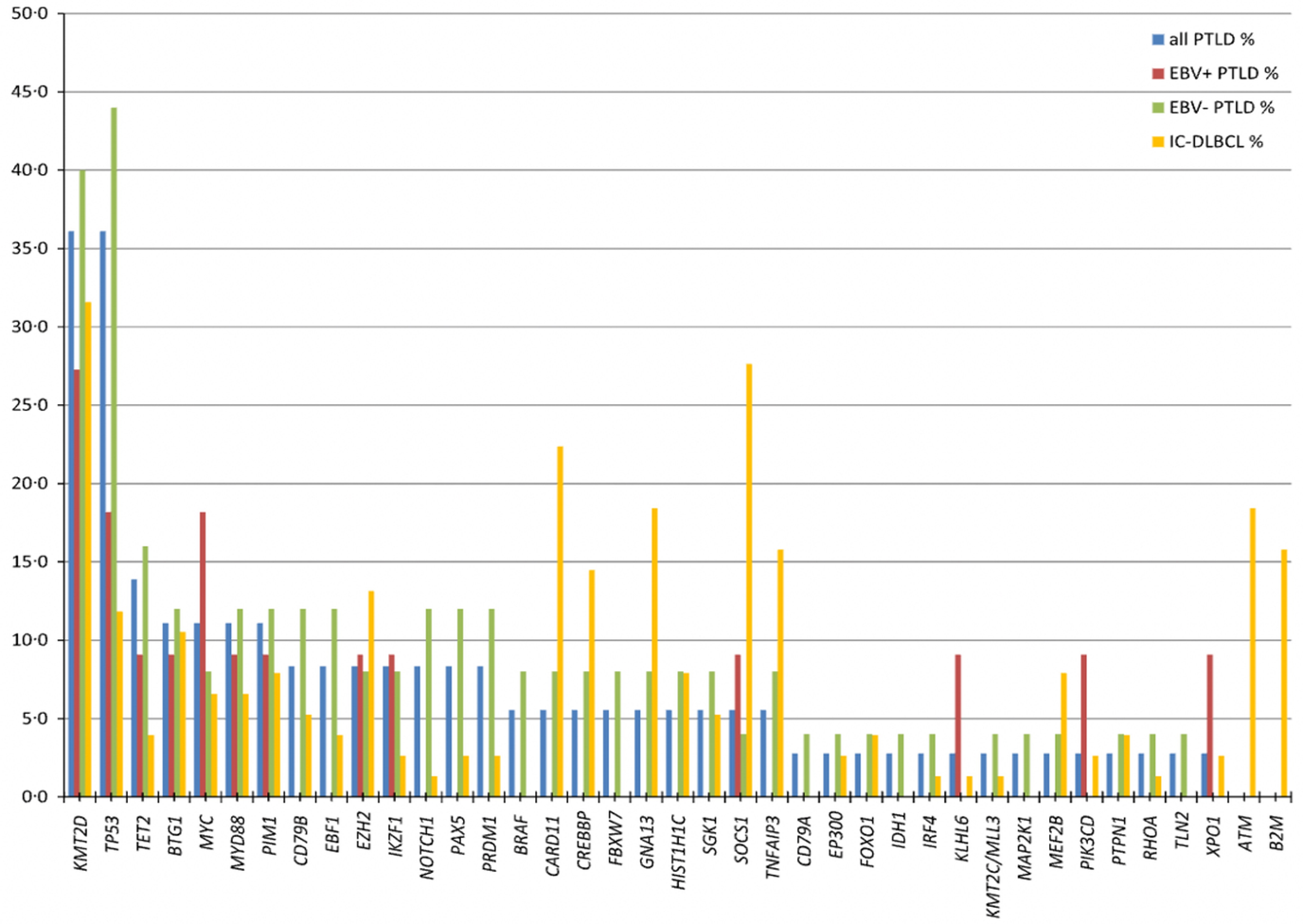
Dierickx et al, Curr Opin Oncol 2022

Pathogenesis of EBV- PTLD

Pathogenesis unclear, only hypotesis:

- accelerated immunoscence
- hit-and-run EBV infection
- CMV co-infection
- Long term immunosoppression

GEP profile non GCB



Morscio et al, Am J Transplant, 2013

Genomic characterization of EBV+ and EBV- PTLD

Genomic approach	EBV(+)/EBV(–) PTLD	References
CGH	The most common copy number aberration in EBV(+) PTLD is the gain/amplification of 9p24,	(36)
FISH	whereas in EBV(–) PTLD, it includes gain of 3/3q and 18q, loss of 6q23/TNFAIP3, and loss of	(26)
WGP	9p21/CDKN2A	(27)
SNP	TP53 mutations were more frequent in EBV(–) PTLD than EBV(+) PTLD and IC-DLBC.	(31)
NGS	Compared with EBV(+) PTLD, EBV(–) PTLD and IC-DLBC have more frequent gene mutations	(29)
	associated with the NF-κB pathway.	(37)
	EBV(+) PTLD has a constitutive activation of the PI3K/Akt/mTOR pathway.	
TRANSCRIPTIONAL APPROACH		
GEP	EBV(–) and EBV(+) PTLD demonstrated different GFP especially gene involved in inflammation	(38)
MicroRNA expression	and immune response pathway profile.	(30)
	EBV(+) PTLD has a suppressed expression of microRNA-194.	(31)
		(33)

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; WGP, whole-genome prediction; SNP, single-nucleotide polymorphism; NGS, next-generation sequencing; IC-DLBC, immunocompetent diffuse large B cell; GEP, gene expression profiling; NF-κB, nuclear factor-κB.

Ferla et al, Frontiers Oncol 2020

PTLD Classification

- **WHO 2022** → PTLD are included in Lymphoid proliferations/lymphomas with immunodeficiency/disregulation, manteining subclassification based on histological diagnosis, associated virus and setting of immunodeficiency/dysregulation
- **ICC Classification** → traditional hystological approach

WHO 2016	WHO 2022	ICC
Lymphoid proliferations / lymphomas with immune deficiency or dysregulation		
Nondestructive PTLD	Hyperplasias arising in immune deficiency / dysregulation	Plasmacytic hyperplasia PTLD
		Florid follicular hyperplasia PTLD
		Infectious mononucleosis PTLD
Polymorphic PTLD	Polymorphic lymphoproliferative disorders arising in immune deficiency / dysregulation (new term that includes various etiologies)	Polymorphic PTLD
Other iatrogenic immunodeficiency associated lymphoproliferative disorders		Other iatrogenic immunodeficiency associated lymphoproliferative disorders
Monomorphic PTLD	Lymphomas arising in immune deficiency / dysregulation (new umbrella term that includes monomorphic PTLD, lymphomas associated with HIV infection, etc.)	Monomorphic PTLD
Classic Hodgkin lymphoma PTLD		Classic Hodgkin lymphoma PTLD
Lymphomas associated with HIV infection		
Lymphoproliferative diseases associated with primary immune disorders	Inborn error of immunity associated lymphoid proliferations and lymphomas	

Note: asterisk (*) denotes a provisional entity

PTLD Classification

Characteristic	Nondestructive PTLD†	Polymorphic PTLD	Monomorphic PTLD	Hodgkin's Lymphoma–like PTLD
Underlying architecture	Nondestructive	Destructive	Destructive	Destructive
Composition	Plasma cells, small lymphocytes, immunoblasts	Complete spectrum of B-cell maturation	Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD	Fulfills specific criteria for classic Hodgkin's lymphoma
Immunohistochemical features	No diagnostic value	Mixture of B cells and T cells	Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type)	CD20–, CD30+; most cases CD15+
EBV association	Almost 100%	>90%	Both EBV-positive and EBV-negative	>90%
Clonality	No in most cases	Variable	Yes	Yes
Molecular genetic findings	None	Variable (BCL6 somatic hypermutations)	Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients)	No information available
Clinical features	Mostly early PTLD	Variable	Both early and late PTLD	Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT

Clinical manifestations

- Heterogeneous presentation, from asymptomatic disease to rapidly progressive multi organ failure and death
- High incidence of extranodal localization (GI tract 20-30%, graft 10-15%, CNS 5-20%)
- Early PTLD more often EBV+ and graft localization, late PTLD more frequently monomorphic, rare graft localization. No differences in risk factors and response to treatment
- Histological biopsy for diagnosis, with EBV identification through in situ hybridization

Diagnostic workup

Diagnostic workup like other lymphomas: TC whole body, PET, bone marrow biopsy, brain RMN, liquor examination, endoscopy

NB: instead lymphomas in immunocompetent host, PTLD has no validate response PET criteria

Differential diagnosis

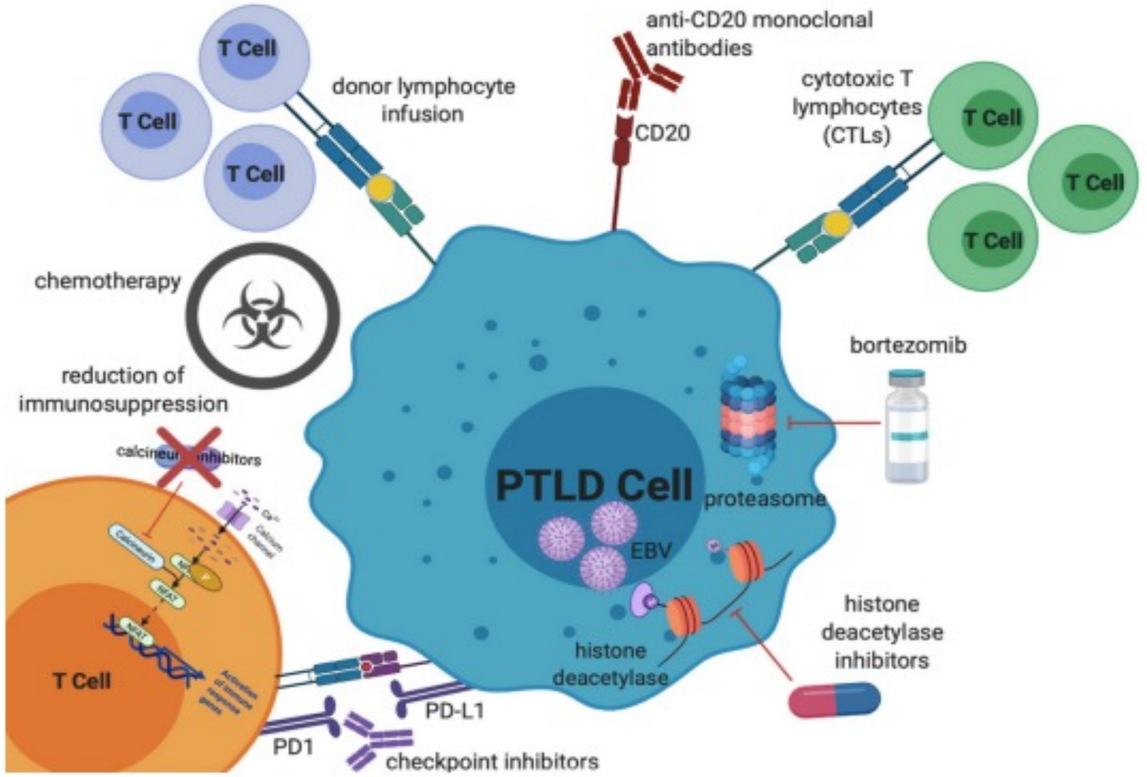
- Allograft rejection (especially when lymphoma is in the graft)
- Sepsis
- EBV primary infection or latent infection. Notably EBV sierology post SOT or HSCT can be false positive or false negative; EBV PCR has high specificity but not high sensitivity
- EBV disease: symptoms related to mononucleosis, chronic riactivation, hepatitis, interstitial pneumonia, meningoencephalytits

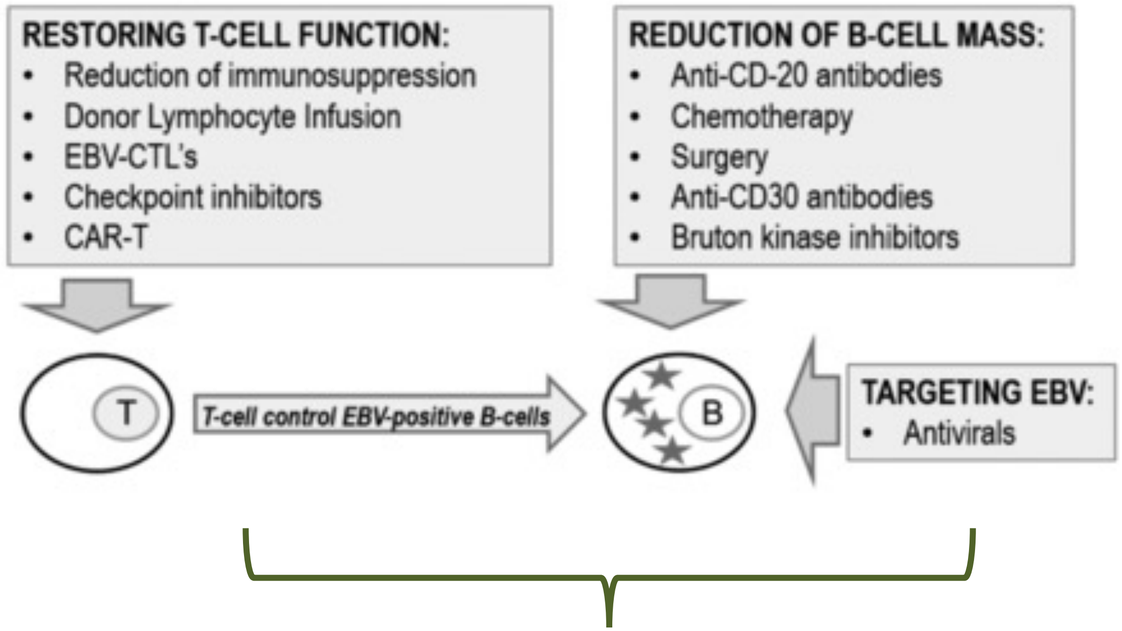
Prevent before cure: risk evaluation based on EBV DNA monitoring

- Guidelines published by the American Society of Transplantation Infectious Disease Community of Practice in 2019 strongly recommend the use of EBV DNAemia as monitoring tool, particularly in high-risk settings for PTLD development
- EBV DNAemia remains the most reliable test currently available, misured by RT-PCR
- Lack of consensus about 1) blood compartment to monitor (plasma/serum, PBMCs, whole blood), 2) clinical significance of EBV DNAemia 3) cutoff values to detrmine the risk of incipient PTLD development
- EBV DNAemia most useful post HSCT, high predictor of PTLD, especially in T-cell depleted BMT, but not diagnostic for PTLD

Compartment	EBV DNA state	Suggested cut-off	Ref
PBMC	Transcriptionally silent latenly infected resting memory B cells (low genome copy) Highly atypical B cells (high genome copy number)	1000 to 10000 copies/10exp5PBMC	Wagner et al 2001 Kanakry et al 2016 Kimura et al 2008
Plasma/serum	Encapsidated virus and free DNA in acute infection (lytic phase) Free DNA only in EBV-associated malignancies	1000 to 10000 EBV copies/mL	Van Esser et al 2001 Kanakri et al 2016 Wagner et al 2001 Bingler et al 2008
White blood	PBMCs + serum/plasma	10000 EBV copies/mL 211.6 IU/mL	Bingler et al 2008 Chang et al 2022

Goals of Treatment





- Prevent and control allograft rejecton
- Mitigate the toxicity of treatment and the increased susceptibility to infections

Shahid S and Prockop S, Cancer Drug Resist 2021

Styczynski J et al, Anticancer Res 2022

Table 2. Clinical trials focusing on PTLD

Clinical trial identifier	Title of the study	Role in PTLD	Target population
NCT03266653	EBV-specific cytotoxic T-lymphocytes (CTLs) for refractory EBV infection	Preventive	Children and adults
NCT05183490	R-MVST cells for treatment of viral infections	Preventive	Adults
NCT04989491	Evaluation of the efficacy of a treatment by one single dose of rituximab (375mg/m^2) in the prevention of the EBV primary infection and posttransplant lymphoproliferative disorder in adult EBV seronegative patients who received an EBV seropositive kidney allograft (REPLY)	Preventive	Adults
NCT04507477	Ex-vivo delivery of rituximab to prevent PTLD in EBV mismatch lung transplant recipients: a pilot trial	Preventive	Adults
NCT02580539	A study of the safety and efficacy of EBV specific T-cell lines (EBV-TCL-01)	Preventive or frontline	Adults
NCT02900976	Rituximab and LMP-specific T-cells in treating pediatric solid organ recipients with EBV-positive, CD20-positive posttransplant lymphoproliferative disorder	Frontline	Children and adults
NCT04337827	Rituximab and acalabrutinib in newly diagnosed B-cell posttransplant lymphoproliferative disorder	Frontline	Adults
NCT04554914	A study to evaluate tabeledeucel in participants with EBV–associated diseases	Frontline	Children and adults
NCT05786040	Tafasitamab and rituximab for front-line treatment of posttransplant lymphoproliferative disorder	Frontline	Adults
NCT01192464	EBV CTLs expressing CD30 chimeric receptors for CD30$^+$ lymphoma (CARCD30)	Frontline or relapsed	Children and adults
NCT03131934	Immunotherapy with tacrolimus resistant EBV CTL for lymphoproliferative disease after solid organ transplant (ITREC)	Frontline or relapsed	Children and adults
NCT05011058	An open-label, phase 2 trial of nanatinostat in combination with valganciclovir in patients with EBV$^+$ relapsed/refractory lymphomas (NAVAL-1)	Relapsed	Adults
NCT03394365	Tabelecleucel for solid organ or allogeneic hematopoietic cell transplant participants with EBV-associated posttransplant lymphoproliferative disease (EBV$^+$ PTLD) after failure of rituximab or rituximab and chemotherapy (ALLELE)	Relapsed	Children and adults
NCT04664179	EBV-specific T-lymphocytes for treatment of EBV$^+$ lymphoma (CILESTE)	Relapsed	Children and adults
NCT04925544	Clinical trial of a novel small molecule EBNA1 inhibitor, VK 2019, in patients with EBV$^+$ nasopharyngeal cancer (NPC) and other EBV-associated cancers, with pharmacokinetic and pharmacodynamic correlative studies	Relapsed	Adults
NCT05714748	Application of mRNA immunotherapy technology in EBV-related refractory malignant tumors	Relapsed	Adults
NCT02287311	Most closely matched 3rd party rapidly generated LMP, BARF1 and EBNA1 specific CTL, EBV$^+$ lymphoma (MABEL)	Relapsed	Children and adults

Preemptive treatment

Frontline treatment

Relapsed/refractory treatment

Amengual J and Pro B, et al, Blood 2023

Frontline Treatment flowchart

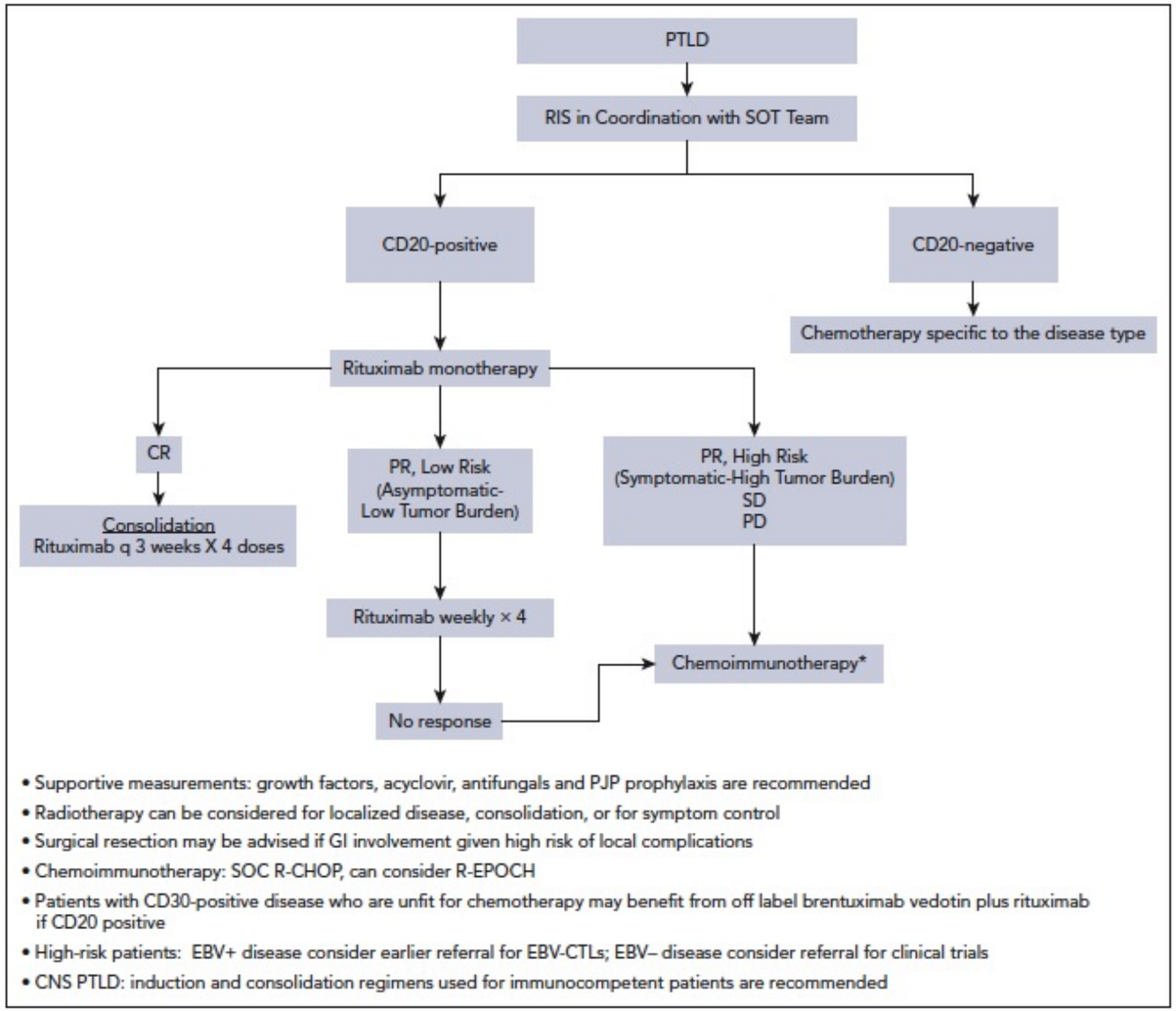


Figure 1. Algorithm for management of PTLD in a frontline setting. GI, gastrointestinal; PJP, *Pneumocystis jirovecii pneumonia*; q, every; SD, stable disease; SOC, standard of care.

Amengual J and Pro B, et al, Blood 2023

No available guidelines

First step is **always** Reduction of ImmuneSoppression **(RIS)**
Variable response rates, effective especially in polymorphic PTLD and early lesion

STOP MMF/AZATIOPRINE and **REDUCTION OF 30-50% of CALCINEURIN INHIBITORS** (ciclosporine or tacrolimus), adjusting dose of steroids → Rivalutation after 2-4 weeks from RIS, monitoring any signs of rejection

Second step → Rituximab monotherapy 375 mg/mq weekly for 4 weeks. CR 50% pts, fast response to treatment but 25% relapse within 1 year

Third step → Chemoimmunotherapy only for pts non responder to RIS/Rituximab

Upfront chemoimmunotherapy (i.e. CHOP/COMP, R-HDMTX, R+TIT) **only for specific histology (TCL, HL, Burkitt, PCNSL)**

First line Treatment: outcomes and critical issues

MAJOR CRITICAL ISSUES of RIS: GRAFT REJECTION (above all in heart transplantation)

- *Reshef, AJT 2011*: 67 pts treated with RIS (25 polymorphic, 42 monomorfic); **ORR 45% (37% CR**, 4 pts no need for second line treatment); **relapse rate 17% of pts in CR**; **45% allograft rejection** with RIS

- Prospective study (*Swinnen, Transplantation 2001*) in SOT only 6% ORR, all PR, **38% rejection rate** during RIS

MAJOR CRITICAL ISSUES of CHEMOTHERAPY WITHOUT RITUXIMAB: TRM

- *Choquet, Hematologica 2007:* 26 pts (85% monomorfici, 38% EBV+, high percentage of advanced stage and increased LD) treated with CHOP21 : CR 50% + PR 15% ; 40% di pz in CR, no relapse. Median PFS 42 mesi, OS 13.9 mesi. **TRM 31%**

Frontline Treatment: Rituximab monotherapy

A Prospective Phase 2 Trials with Rituximab Monotherapy

Study	No. of Patients	Overall Response Rate (complete response rate) %	Survival
Oertel et al.[58]	17	59 (53)	Overall survival at 3 yr, 56%
Blaes et al.[59]	11	64 (55)	Mean overall survival, 14 mo
Choquet et al.[60]	43	44 (28)	Overall survival at 1 yr, 67%
González-Barca et al.[61]	38	79 (34→60.5)	Overall survival at 27.5 mo, 47%
Trappe et al.[63]	70	60 (20)	Part of sequential treatment
Trappe et al.[41]	152	NR (25)	Overall survival at 3 yr, 91% (only low-risk patients treated with rituximab only)

BETTER OUTCOME: Early PTLD, young age, single site lesion

WORSE OUTCOME: CNS disease, bone marrow involvment, Late PTLD, Non B cell disease

PTLD-1 TRIAL *(Trappe et al, Lancet Oncology 2012)*

- Landmark study that estabilished the **role of sequential treatment**
- Phase 2 prospective trial, accrued 70 pts (96% monomorphic, 56% EBVneg, 76% age > 1 year)
- Schedule: 4 weekly doses of rituximab monotherapy 375 mg/mq ev, followed by 4 cycles of CHOP administered every 21 days
- **ORR 60%, CR 20% after Rituximab monotherapy**; **ORR 90% (CR 68%) after CHT,** 74% disease-free survival at last FU
- **TRM 11%, > in pts non responder to Rituximab monotherapy**
- **Response to Rituximab in monotherapy important prognostic factor for OS**
- **Advanced Age and ECOG>2 most important baseline characteristics predicting outcomes**

	Response to rituximab		Response to sequential treatment	
	n/N (%)	p value	n/N (%)	p value
Overall	42/70 (60%)		53/59 (90%)	
Age		0·36		0·34
<60 years	36/62 (58%)		46/52 (88%)	
≥60 years	6/8 (75%)		7/7 (100%)	
Sex		0·92		0·95
Male	28/47 (60%)		36/40 (90%)	
Female	14/23 (61%)		17/19 (89%)	
Transplant type		0·043		0·0075
Kidney	17/29 (59%)		26/26 (100%)	
Liver	7/16 (44%)		11/13 (85%)	
Heart	12/14 (86%)		12/13 (92%)	
Lung	4/4 (100%)		2/3 (67%)	
Kidney and pancreas	2/4 (50%)		2/3(67%)	
Heart and lung	0/2		0/1	
Bone marrow	0/1		Died before staging	
Time from transplantation to PTLD		0·50		0·48
≤1 year	9/17 (53%)		11/13 (85%)	
>1 year	33/53 (62%)		42/46 (91%)	
Histology		0·53		0·92
Polymorphic	2/3 (67%)		2/2 (100%)	
Monomorphic	40/67 (60%)		51/57 (89%)	
Burkitt's	1/2 (50%)		2/2 (100%)	
DLBCL	32/57 (56%)		42/47 (89%)	
Plasmacytoma-like	2/2 (100%)		2/2 (100%)	
Other B cell	5/6 (83%)		5/6 (83%)	
EBV association		0·42		0·051
Yes	16/29 (55%)		18/22 (82%)	
No	24/37 (65%)		33/34 (97%)	
Ann Arbor stage*		0·50		0·49
I	6/9 (67%)		8/9 (89%)	
II	6/9 (67%)		8/8 (100%)	
III	6/10 (60%)		8/9 (89%)	
IV	24/42 (57%)		29/33 (88%)	
Lactate dehydrogenase concentration		0·26		0·46
Within normal range	12/17 (71%)		16/17 (94%)	
Raised	28/51 (55%)		35/40 (88%)	
Extranodal disease†	33/54 (61%)	0·63	40/54 (74%)	0·47
Gastrointestinal involvement	9/17 (53%)		13/15 (86%)	
Liver	6/12 (50%)		7/8 (88%)	
Renal	2/3 (67%)		2/2 (100%)	
Pulmonary involvement	7/10 (70%)		4/6 (67%)	
Bone marrow involvement	5/7 (71%)		4/6 (67%)	
Graft	5/10 (50%)		3/4 (75%)	

PTLD-1 TRIAL *(Trappe et al, Lancet Oncology 2012)*

Durable disease response (%)

TTP (%)

OS (%)

PFS (%)

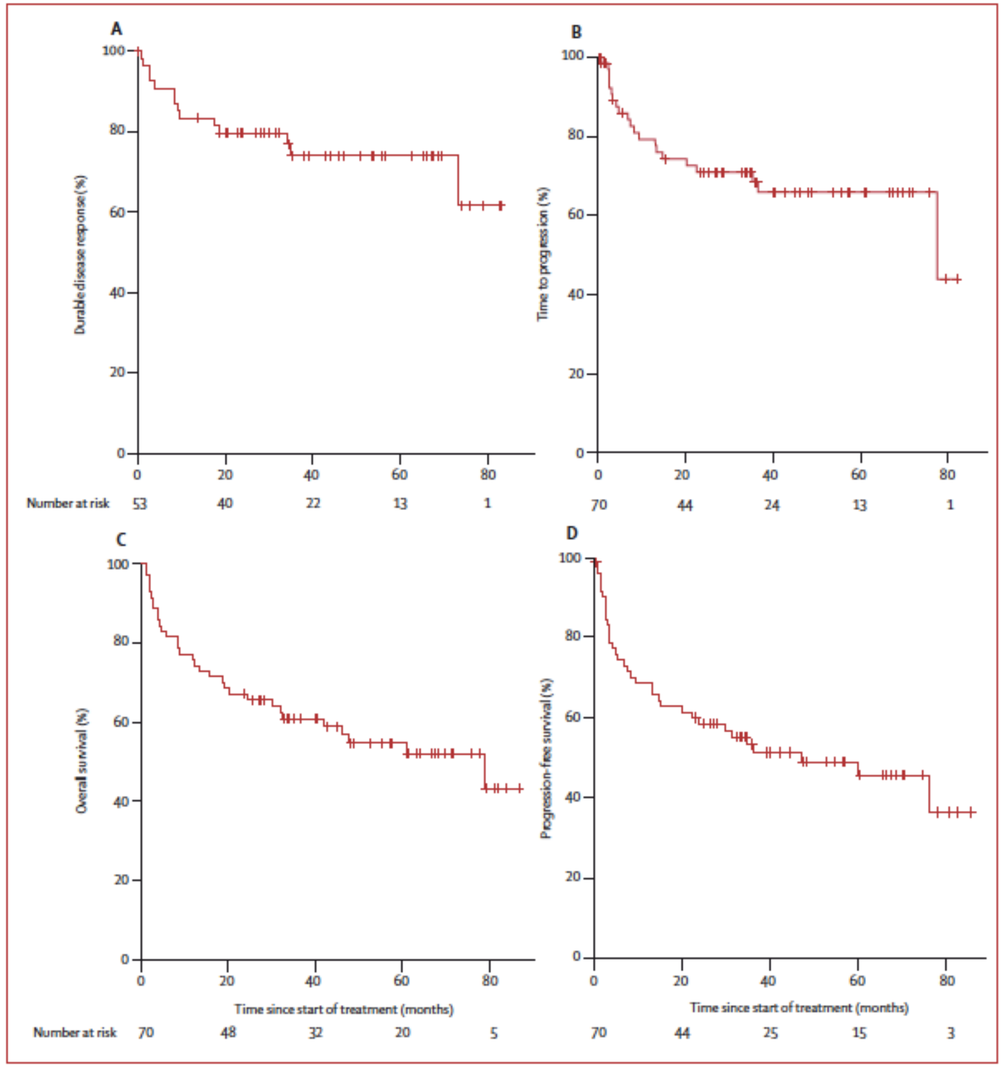
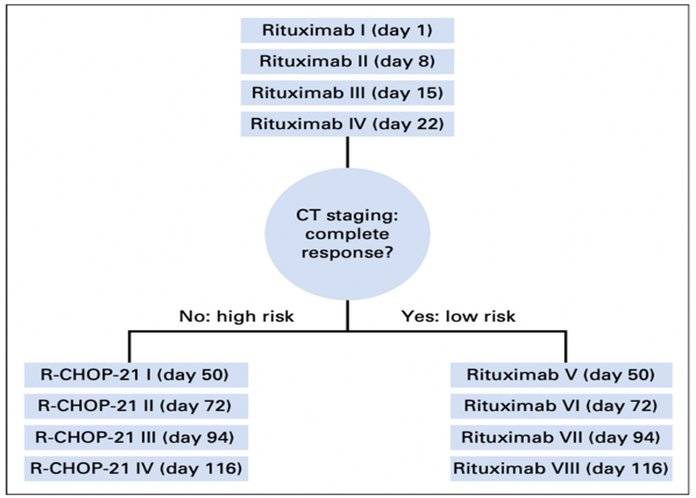
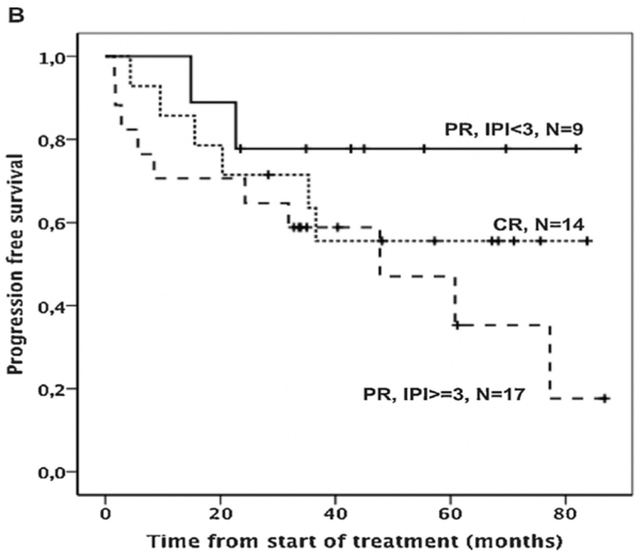


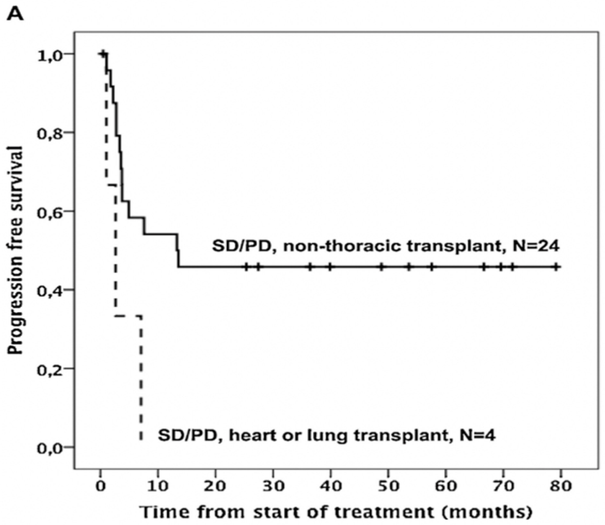
Figure 2: **Response duration, time to progression, overall survival, and progression-free survival**
Median time of follow-up was 5·1 years (IQR 1·62–5·93). Out of the final three deaths during the study period, only one was due to PTLD relapse, whereas two were not disease-related. (A) Durable disease response (patients in complete remission or partial remission). (B) Time to progression (all patients). (C) Overall survival. (D) Progression-free survival.

PTLD-1 TRIAL Risk Adapted *(Trappe RU et al, Am J transplant 2015)*

- Subsequent study evaluating a **risk-stratified sequential approach**
- 152 pts (85% monomorfic, 79% late-onset, 53% EBV-neg, IPI>3 38%)
- **pts in CR after Rituximab induction (Low-Risk Pts) → Excellent outcome,** four consolidation cycles
- **Pts who did not achieve CR (High Risk Pts) → escalated to R-CHOP** (75% of all pts enrolled)
- **ORR 88%, CR 70% (25% CR after R monotherapy), median OS 6.6 yrs Median TTP not reached** (75% at 3 yrs, 89% in the low-risk group)
- **TRM 8%**
- **Multivariate analysis → response to R and baseline IPI (<3 or ≥3) both highly significant prognostic factors**
- **Heart or lung transplant correlate with PFS and OS**
- **No differences between EBV+ e EBV- disease**

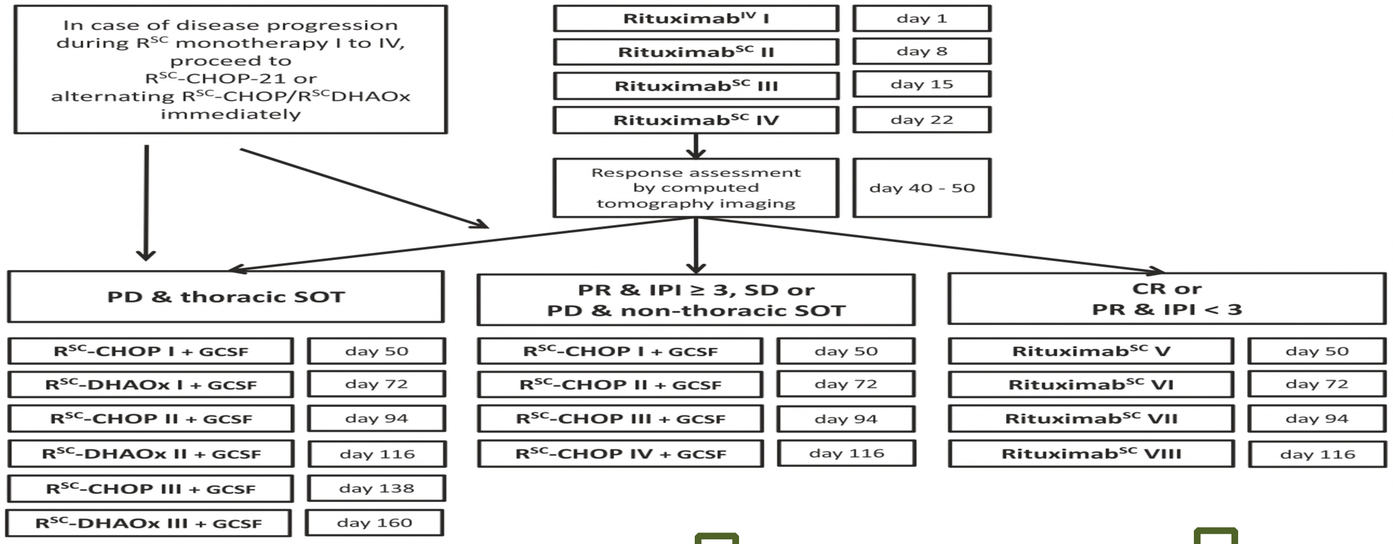






PTLD-2 TRIAL *(Zimmerman et al, Leukemia 2022)*

- Prospective multicentre phase II trial tested **safety and efficacy of subcutaneous R in PTLD after SOT**
- 58 pts enrolled (30% over 60yrs, monomorphic 97%, late-PTLD 78%, 38% EBV+, 73% advanced stage, 38% IPI>2, 22% ECOG 2)
- Rare histology were all high risk and 8/15 lung transplantation
- **median PFS 3.8 yrs, median OS 5.1 yrs**
- **TRM 7%.** Haematological toxicities (37% leucopenia G3/4 e trombocitopenia), 42% infections G3/4, renal toxicities, GI bleeding



Very-high risk group (only 5/9 pts evaluable):

ORR 60% (CR 40%)

2 ys PFS 11%, OS 7.4 months

TRM 25% (G3/4 infections =63%)

High Risk

ORR 100% (CR 41%)

3-ys PFS 54% OS 59%

TRM 8% (G3/4 infections =50%; haematological toxicities

Low Risk

ORR 95% (CR 52%)

3-ys PFS 85% OS 100%

no TRM, only some G3/4 infections

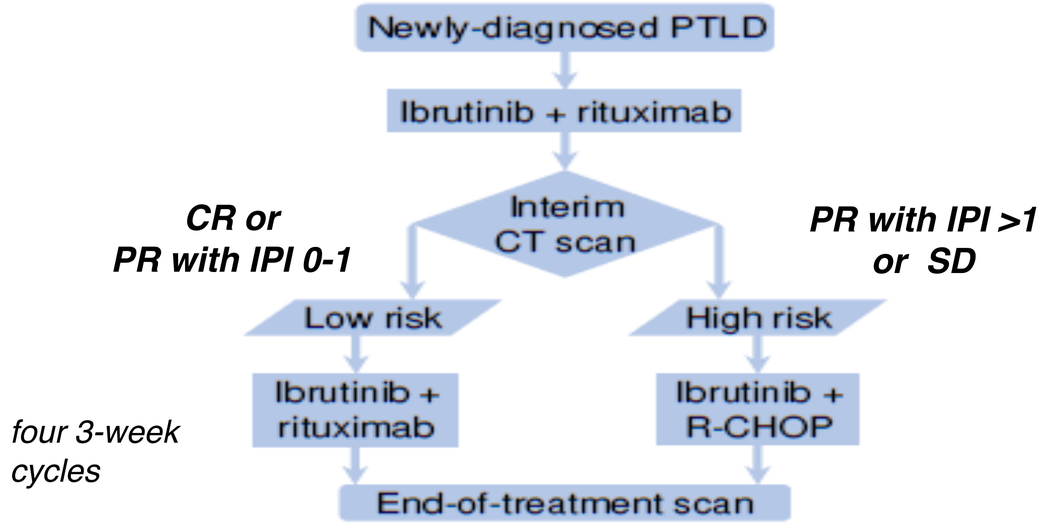
TIDAL TRIAL

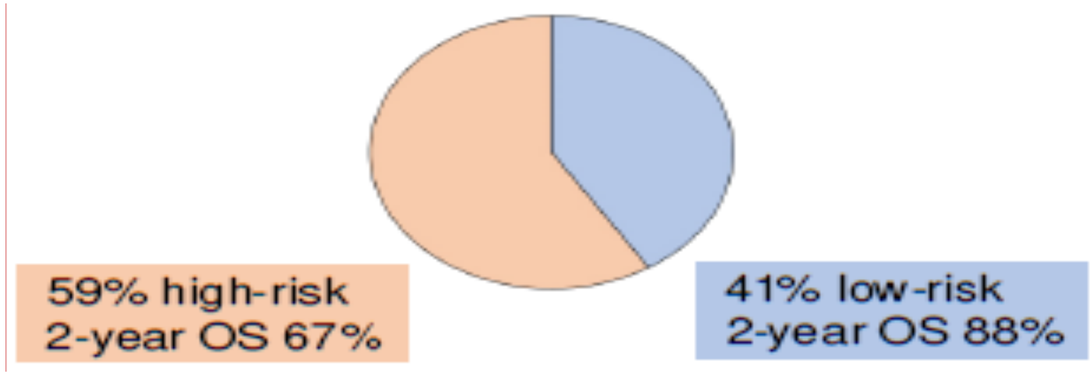
Prospective single arm phase 2 trial investigating activity and tolerability of ibrutinib combined with risk stratified therapy for first line treatment

Schedule: 49 days of Ibrutinib 560 mg once daily plus 4 doses of weekly rituximab

39 patients included:

- CR 29% after first induction
- ORR 67% (CR 56%) at end of treatment
  - ORR 81 % (CR 75%) in the low-risk arm
  - ORR 57% (CR 43%) in the high-risk arm
- 2-years PFS 56% and OS 75%
- PRIMARY ENDPOINT: CR on interim scan → NOT REACHED





Chaganti, Blood 2024

Brentuximab-Rituximab phase I/II trial *(Pearse et al, Leuk Lymphoma 2021)*

- Investigate efficacy of Bv+R once weekly for 4 weeks, followed by manteinance
- Schedule:
  - Pts in PD after induction therapy → CT
  - Pts in CR/PR/SD → manteinance with Bv+R for 12 months
- 20 pts enrolled (55% monomorfich, all with IPI>2, 35% ECOG 2)
- **ORR 75% con CR 60%**
- Median time to response: 28 days
- **HIGH rate of Toxicities**: 40% neutropenia, 30% hypertension, 25% infections, 15% peripheral neuropathy

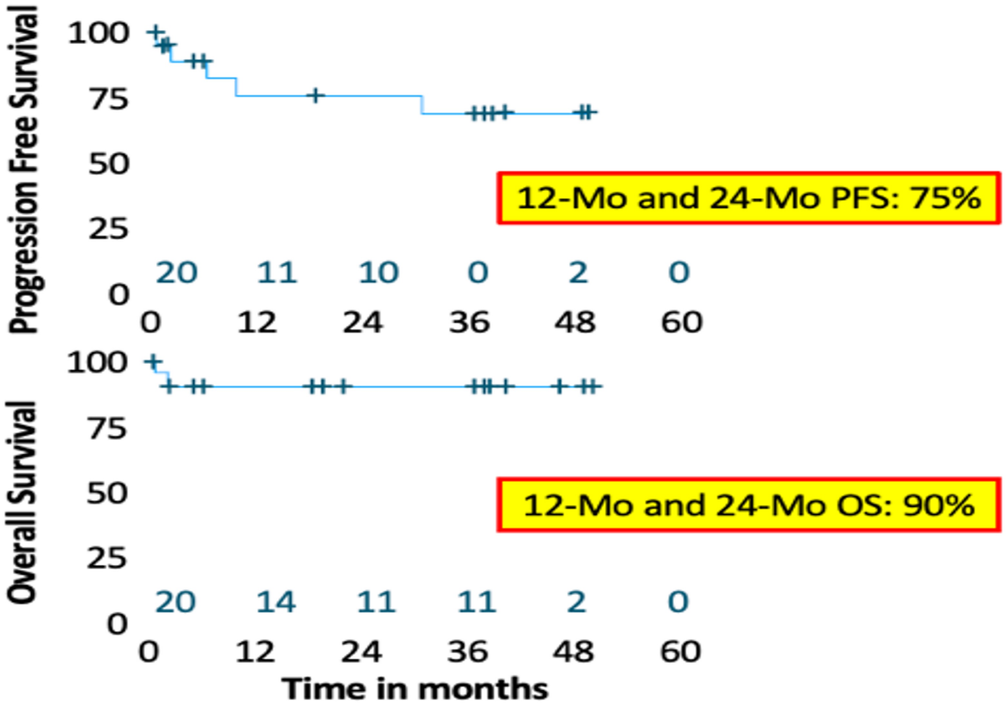


Table 3. Management of rare subtypes of PTLD

PTLD subtype	Associated pathology	Treatment options	Additional considerations
Hodgkin PTLD	Most are EBV-related Large Reed Stemberg cells may be positive for CD20 and CD79a; however CD15 is frequently negative	Hodgkin-like treatments • ABVD • Brentuximab-AVD use with caution due to increased risk of infectious complications • Rituximab may be considered for CD20$^+$ disease	Worse prognosis than non-SOT–related cHL Use of checkpoint blockade associated with organ rejection and death (use with extreme caution)
Primary CNS lymphoma	May present as mPTLD or pPTLD, and these entities do not correlate with prognosis Three subtypes: • Sporadic PCNS-LBCL–like: MYD88 and CD79B mutations are common • Systemic RAS–driven type: extra-CNS involvement • EBV-driven CNS-limited type: no oncogenic alterations	Rituximab plus high-dose methotrexate (>1.5 g/m^2) Rituximab plus high-dose cytarabine (1 g/m^2) Whole brain radiotherapy	Occurs most frequently after kidney SOT Kidney transplant is not an absolute contraindication for methotrexate
Plasmablastoid DLBCL	100% MUM1/IRF4$^+$ 82% CD138$^+$ 64% CD30$^+$ 55% EBER$^+$ Most have MYC and chromosome 17/TP53 derangements	In addition to treatment paradigm outlined in Figure 1, the addition of these may be considered: • Brentuximab vedotin if CD30$^+$ • Daratumumab if CD138$^+$ • Bortezomib	Occasionally occurs after nonplasmablastoid PTLD
T-cell PTLD	Can present as any of the mature T-cell lymphoma subtypes Most common subtypes: • Hepatosplenic T-cell lymphoma • Primary cutaneous ALCL • PTCL-NOS • ALK- ALCL	Treat based on recommendations for each disease entity	Rare, ~5% Often occurs as late event

Amengual J and Pro B, et al, Blood 2023

Second line Treatment

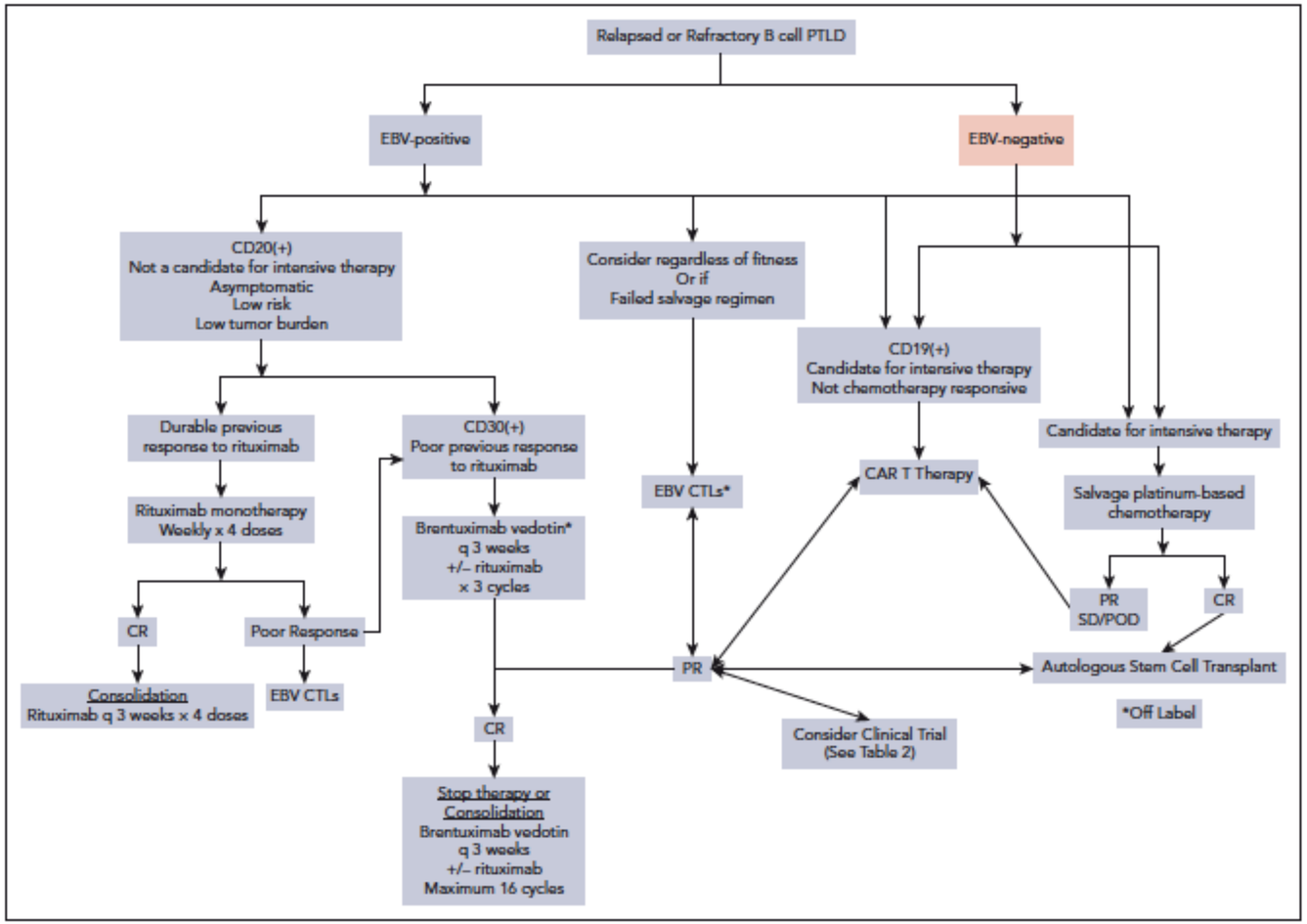


Figure 3. Algorithm for management of relapsed/refractory PTLD. POD, progression of disease.

Amengual J and Pro B, et al, Blood 2023

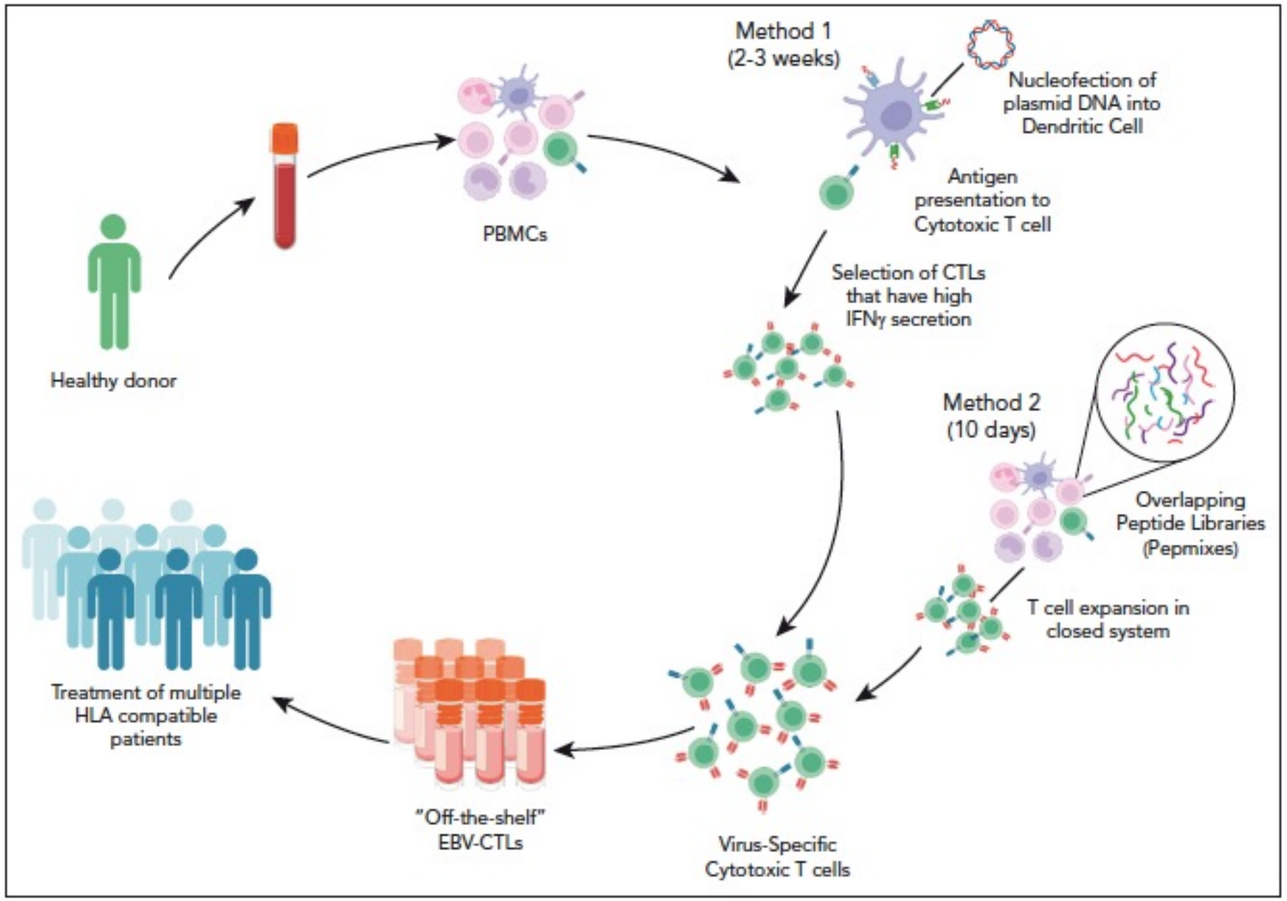
- Challenging treatment, hystorical poor outcomes.
- Retrospective multicentre review of 86 pts R/R to R+CT: median OS 4.1 mo, median FU 12.9 mo, 73.3% died (65% PTLD, 15.9% TRM, organ rejection or failure 3.2%)
- Antiviral therapy not effective alone
- Emerging role of EBV CTLs
- PD1/PD1 L expressed in PTLD but Checkpoint inhibitors increased rate of rejection (41%) or graft loss
- Adoptive immunotherapy to treat EBV infection
  - Manufacturing ex-vivo-expanded virus specific T cells by exposing donor lymphoblastoid cells to a laboratory EBV strain (HSCT setting)
  - Banks of HLA tped EBV stimulated T cells from healthy donors
- CART: only 41 case reports in 2023, limited experience. Limited DOR shortened by continuous IS

EBV specific cytotoxic T lymphocytes (EBV-CTLs)

TABLE 2 Summary of the major aspects of different types of EBV-cytotoxic T lymphocytes (EBV-CTLs).

Type of EBV-CTL	Key points
Autologous	• Can be given in SOT PTLD that arises from recipient, however, often third-party products are given due to the challenges encountered with autologous forms • Associated risk of graft rejection is minimal • Manufacture is time consuming (3–4 months) • Often SOT patients are on immunosuppressants, which could impair the activity of autologous EBV-CTLs • Prior use of chemoimmunotherapy could impair activity of EBV-CTLs • Production is challenging if recipient is EBV seronegative • Current data shows that autologous products are less efficient in clearing EBV viremia
HLA-matched derived from primary donor	• Manufacture is time consuming • Mostly used in HSCT PTLD • Not possible in patients who received umbilical cord transplant • Mostly not an option in SOT where graft is obtained from a cadaver • Associated with low risk of GvHD post-HSCT • HLA-matched
Off-the-shelf third-party products	• Used in both HSCT and SOT PTLD • Most used form due to rapid access • Associated risk of GvHD post-HSCT is low even with partially HLA-matched products • Compared to autologous products, activity is less affected by prior use of immunosuppressants and chemoimmunotherapy • Need to ensure that partially HLA-matched EBV-CTLs are restricted by an HLA allele shared by the patient's disease for better efficacy

EBV specific cytotoxic T lymphocytes (EBV-CTL)



Amengual J and Pro B, et al, Blood 2023

PROS

→ faster access and availability

→ target therapy

CONS

→Induction of alloreactivity

→High cost

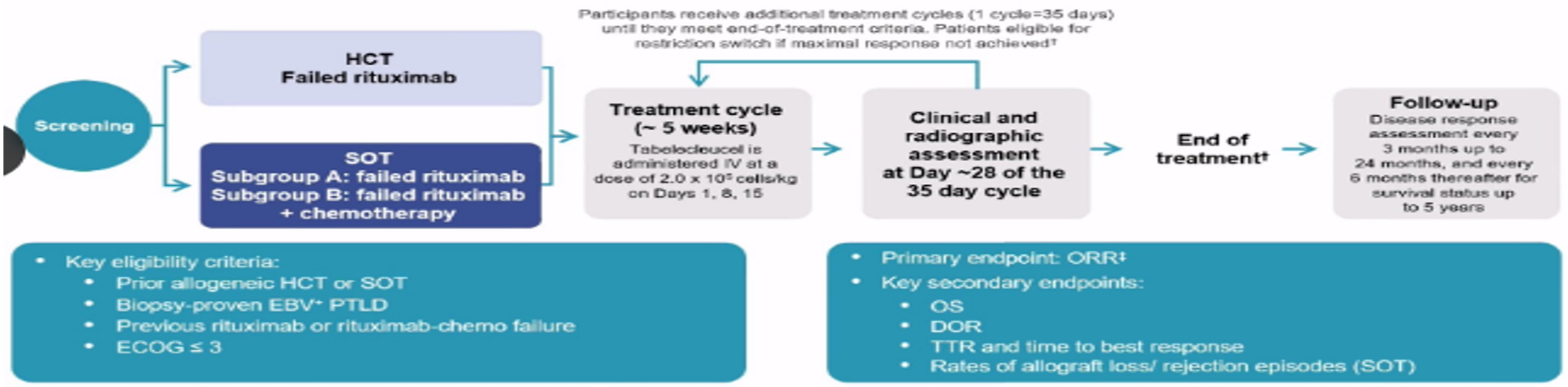
→Lack of persistence

Tab-cel manufacturing → PBMCs from unrelated EBV+ donor → separation of T cell donor from B-cell → B cell transformed in EBV+ Antigen Presenting Cells → expansion of EBV+ cytotoxyc T-cells (EBV-CTLs) HLA-typed → almost 95% of HLA variants

ALLELE Trial

- Multicentre open-label global phase III study with tabelecleucel (Tab-cel), an off-the-shelf allogeneic EBV-specific T-cell immunotherapy, for EBV+ PTLD following HSCT or SOT (Mahadeo et al, Blood 2022)

- No genetic alteractions in T-cells

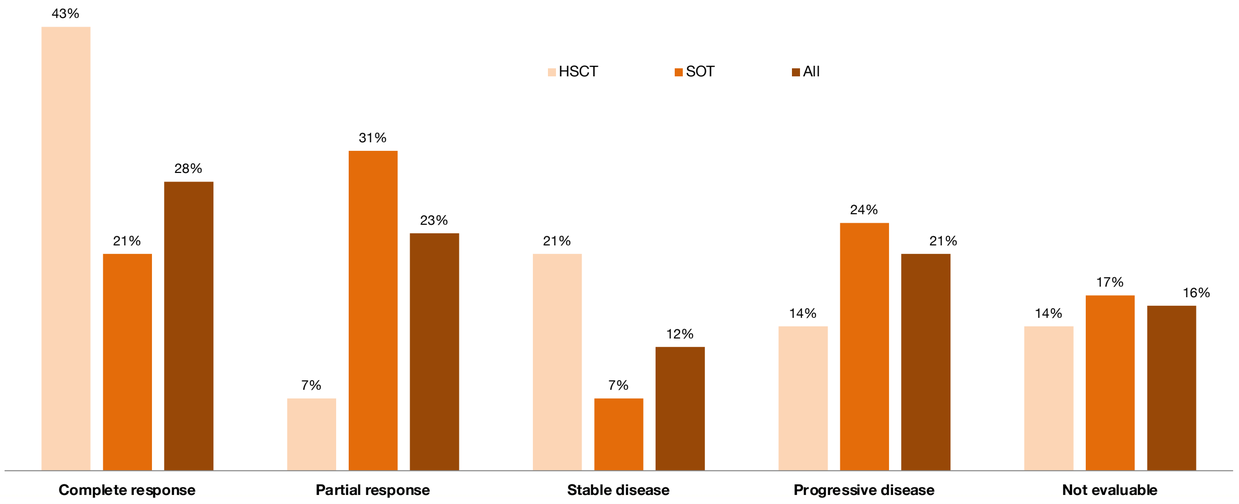


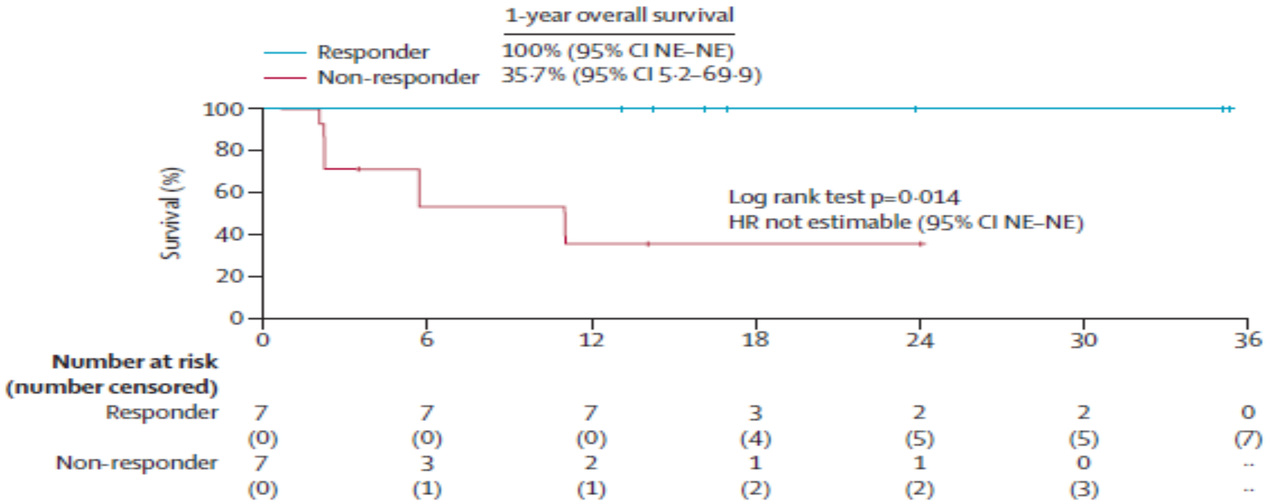
	Haematopoietic stem-cell transplant group (n=14)	Solid organ transplant group (n=29)	All (n=43)
Age, years	51·9 (21·9–65·1)	44·4 (23·8–67·0)	48·5 (21·9–65·4)
Sex			
Male	8 (57%)	16 (55%)	24 (56%)
Female	6 (43%)	13 (45%)	19 (44%)
Race			
Asian	1 (7%)	1 (3%)	2 (5%)
Black or African American	0	1 (3%)	1 (2%)
Native Hawaiian or Other Pacific Islander	0	1 (3%)	1 (2%)
White	12 (86%)	24 (83%)	36 (84%)
Other	1 (7%)	2 (7%)	3 (7%)
ECOG score (age ≥16 years)	1·0 (0–1·0)	1·0 (0–2·0)	1·0 (0–2·0)
ECOG ≥2 (age ≥16 years)*	3 (23%)	8 (30%)	11 (28%)
Lansky score (age <16 years)	90 (n=1)	40, 90 (n=2)	40, 90, 90 (n=3)
Post-transplant lymphoproliferative disease-adapted prognostic index (age ≥16 years)*			
Low	1 (8%)	2 (7%)	3 (8%)
Intermediate	6 (46%)	13 (48%)	19 (48%)
High	6 (46%)	11 (41%)	17 (43%)
Unknown	0	1 (4%)	1 (3%)
Disease morphology and histology			
Diffuse large B-cell lymphoma	10 (71%)	19 (66%)	29 (67%)
Plasmablastic lymphoma	1 (7%)	2 (7%)	3 (7%)
Other†	3 (21%)	8 (28%)	11 (26%)
Transplant organ type			
Kidney	NA	10 (34%)	NA
Heart	NA	6 (21%)	NA
Lung	NA	5 (17%)	NA
Liver	NA	1 (3%)	NA
Multivisceral	NA	7 (24%)	NA
Extranodal disease at screening	9 (64%)	24 (83%)	33 (77%)
Number of previous lines of systemic treatment	1 (1–1)	1 (1–2)	1 (1–2)
Previous rituximab monotherapy‡§	14 (100%)	23 (79%)	37 (86%)
Previous chemotherapy in combination with rituximab§	1 (7%)	13 (45%)	14 (33%)
Previous immunotherapy (other than rituximab)	1 (7%)	1 (3%)	2 (5%)
Previous immunotherapy in combination with chemotherapy	1 (7%)	0	1 (2%)
Previous immunotherapy alone	0	1 (3%)	1 (2%)
Time from transplant to diagnosis	4·3 months (3·2–7·8)	1·1 years (0·6–8·6)	NA
Time from initial EBV-positive diagnosis to first dose of tabelecleucel, months	1·2 (0·8–3·0)	6·6 (3·5–13·0)	4·0 (2·2–8·6)
Time from enrolment to first dose of tabelecleucel, days	7·0 (5·0–9·0)	8·0 (5·0–9·0)	7·0 (5·0–9·0)

43 pts who failed R or RCT
Median number of cycles of Tabcel → 2
(3 for HTSC and 2 for SOT)

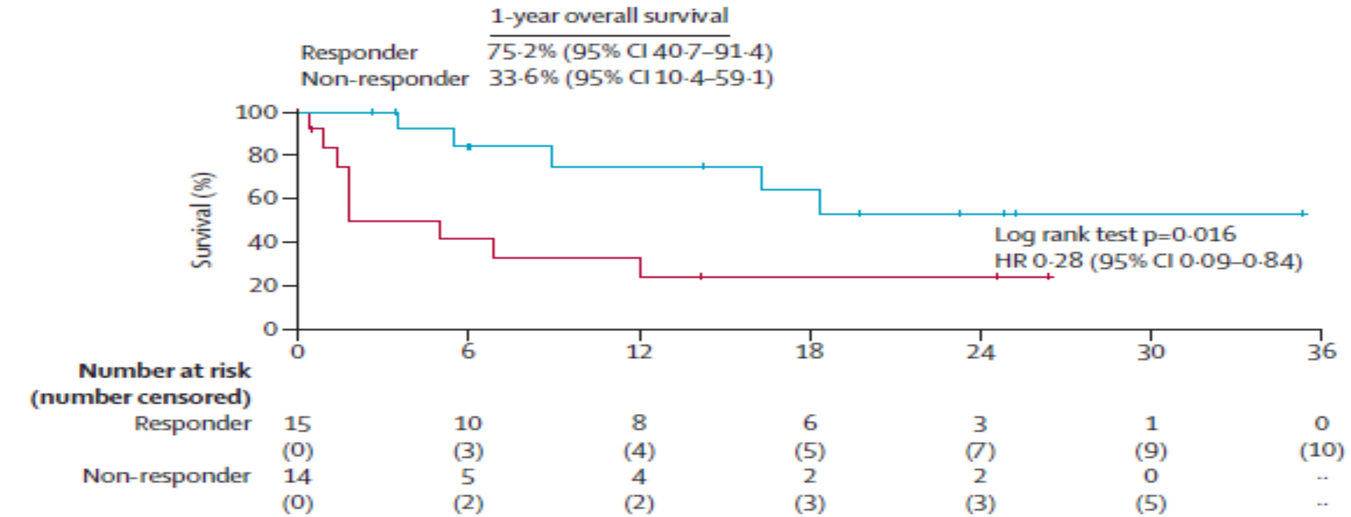
ORR 51.2%,
Median F-U 14 months
CR in 12 pts
Median OS 18.4 months
Median DOR 23 months
Median time to response 1 month
1 year OS 56% in SOT population, significative improvement compared with storical data

NO TRM, No evidence of allograft rejection




1-year overall survival
Responder 100% (95% CI NE–NE)
Non-responder 35·7% (95% CI 5·2–69·9)
Survival (%)
Log rank test p=0·014
HR not estimable (95% CI NE–NE)
Number at risk (number censored)
Responder 7 (0) 7 (0) 7 (0) 3 (4) 2 (5) 2 (5) 0 (7)
Non-responder 7 (0) 3 (1) 2 (1) 1 (2) 1 (2) 0 (3) .. ..

HSCT


1-year overall survival
Responder 75·2% (95% CI 40·7–91·4)
Non-responder 33·6% (95% CI 10·4–59·1)
Survival (%)
Log rank test p=0·016
HR 0·28 (95% CI 0·09–0·84)
Number at risk (number censored)
Responder 15 (0) 10 (3) 8 (4) 6 (5) 3 (7) 1 (9) 0 (10)
Non-responder 14 (0) 5 (2) 4 (2) 2 (3) 2 (3) 0 (5) .. ..

SOT

CAR-T in PTLD

Limited literature, only 41 cases of PTLD treated with CAR-T in 2023

Challanges:

- allograft rejection
- limited DOR due to the need to continuous IS therapy

McKennan, BJH 2023: real-world experience, 22 pts R/R SOT associated PTLD (20 DLBCL-NOS, 1 MCL, 1 HGBCL), 5% EBV+, 91% advanced stage, 64% IPI>2

- Prior SOT: kidney (n=14), liver (n=3), heart (n=3), intestinal, lung and kidney followed by pancreas (n=1 each)
- Before CAR-T: bridging therapy in 55%, 64% stop IS. Median IS restart after 3 months (1-14)
- CRS 82% (5% G3, 5% G4), ICANS 73% (27% G3, 9% G4), 2 treatment-related deaths
- >ORR 64% (CR 55%)
- >2-ys PFS 35% e OS 58%
- 14% after CAR-T allograft rejection

Antiviral Treatment- NAVAL-1 Trial

Global pivotal phase 2 trial, multicentric, open-label, single arm basket study

Inclusion criteria: >18 aa, EBV+ R/R lymphoma following 1 or more systemic therapies, no other therapies available ; not elegible to HD-CT withallo/AutoSCT or CAR-T; no CNS involvement, adeguate hepatic and hematological fuction

Aims → evaluate safety nad efficacy of the all oral combination of nanatinostat (class I HDAC inhibitor) with valganciclovir in R/R EBV+ lymohoma pts (PTCL, PTLD, DLBCL)

Rationale:

- EBV in latent form is not susceptible to yhe cytotoxic activity of ganciclovir
- Nanatinostat induces EBV lytic activation and express of the EBV BGLF4 proteine kinase → this in turn activates ganciclovir via phosphorylation → ganciclovir-induced inhibition of viral and cellular DNA synthesis and apoptosis
- Well tolerated, common Aes: nausea (38%) thrombocytopenia (436%), neutropenia (34%), anemia (34%), fatigue (26%), inappetence (22%)

43 pts evaluable, ORR 40% (CR 19%), median DoR 10,4 months

Open Trial

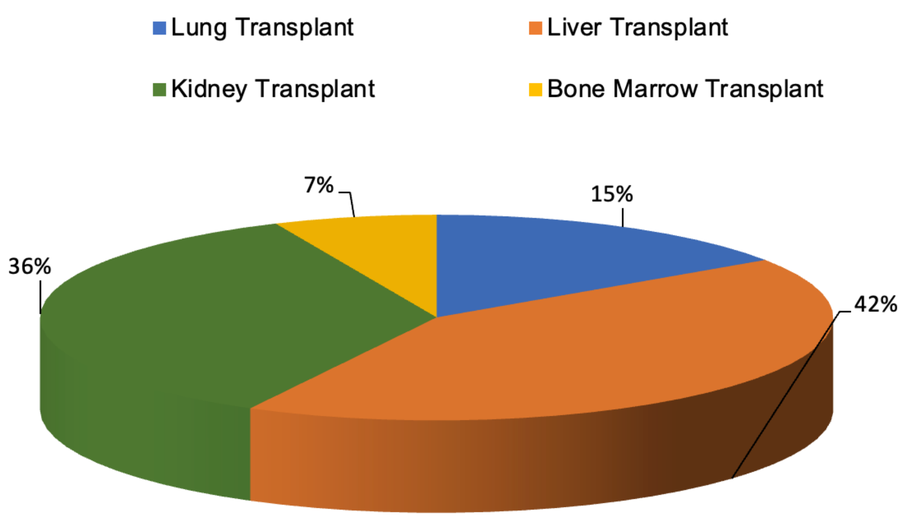
Agent	Sponsor	Age	NCT number
Rituximab and Acalabrutinib (BTK inhibitor)	Cleveland Clinic	18 and older	NCT04337827
Tabelecleucel (third party EBV specific T cells)	Atara	All ages	NCT03394365 NCT04554914
Multivalent third-party virus specific T-cells targeting multiple viruses including EBV	Cincinnati Children's Hospital Medical Center	Age > 1 day old	NCT02532452
EBV Specific T-cell Lines (Autologous)	Maisonneuve-Rosemont Hospital	18 and older	NCT02580539
Bendamustine and Subcutaneous Rituximab (DLBCL monomorphic subtype)	Asan Medical Center	19 and older	NCT02753062
Nanatinostat (selective class 1 HDAC inhibitor) and Valganciclovir	Viracta Therapeutics Inc	18 and older	NCT05011058
XmAb13676 (bispecific antibody that binds CD20 and CD3)	Xencor Inc	18 and older	NCT02924402

PTLD Policlinico di Milano

45 PTLD

Median age of 48 years (18-80)

Male 64%



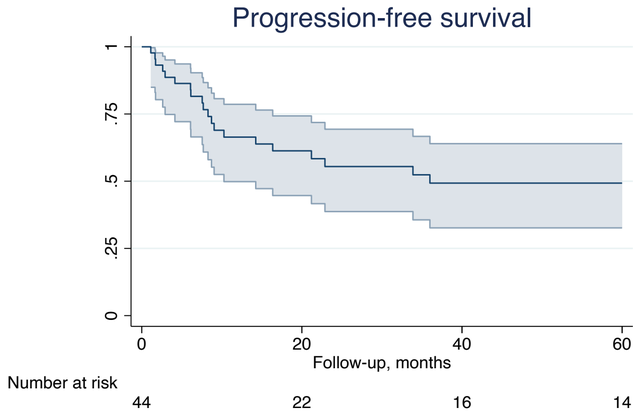
ORR 27/43 (63%)
CRR 22/43 (51%)

Histotype	N	N%
DLBCL	34	75.56
FL	1	2.22
HL	3	6.67
Polimoprfic PTLD	3	6.67
Plasmocytoma	1	2.22
TCL	3	6.67

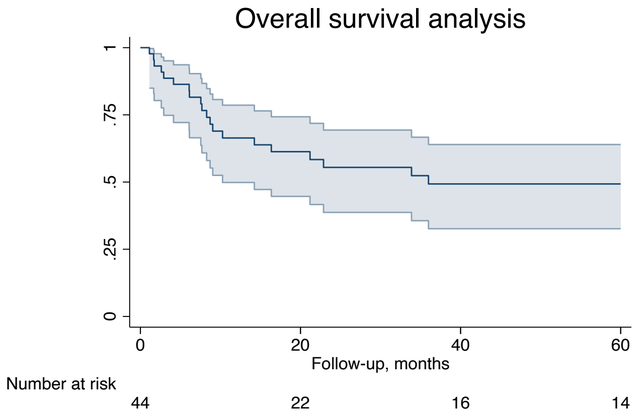
- 17/37 (46%) EBV-positive

Lung: 6/7 (86%)
Liver: 2/15 (13%)

Kidney: 6/12 (50%)
BMO: 3/3 (100%)



mPFS of 17 months (1-208)



mOS of 36 months (1-208)

Take Home Massages

» Multidisciplinar team work is essential

» Need to improve pre-emptive therapy, need to guidelines

» Need for large multi-institution prospective clinical trials dedicated to PTLDs, usually excluded from studies

» Optimal treatment strategy → response-adapted , risk stratified, low toxicities

» Adoptive immunotherapies has become a promising option for refractory disease but can be used as earlier lines of therapy